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STUDIES IN THE SYNTHETIC UTILITY OF THE DIANION OF β-KETOESTERS

by

STUART NICHOLAS HUCKIN

B.Sc. (Hons.), University of Sussex, 1968

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

in the Department of Chemistry

We accept this thesis as conforming to the required standard

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THE UNIVERSITY OF BRITISH COLUMBIA

April, 1973

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ABSTRACT.

Some of the reactions of the dianion of β-ketoesters were investigated. The dianion of methyl acetoacetate (132), prepared by sequential reaction of methyl acetoacetate with sodium hydride and n-butyllithium, was reacted with a variety of aldehydes and ketones to give δ-hydroxy-β-ketoesters (150) in moderate yield. The aldol products 150 derived from aromatic aldehydes and ketones were found to be thermally unstable and were converted to trimethylsilyl ether derivatives for characterisation purposes.

The acylation of dianion 132 was also investigated, and a modified procedure developed which allowed the preparation of β,δ-diketoesters in fair yield. When aromatic esters were employed as acylating agents, the product isolated was found to be a mixture of diketoester and diketoacid.

The reaction of dianion 132 with nitriles was briefly investigated, and shown to be a feasible method of producing γ-unsaturated δ-amino-β-ketoesters.

Finally, with dihaloalkanes, dianion 132 gave a mixture of cyclic alkylated products and bis-β-ketoesters. Procedures for the optimising of the yields of each of these classes of compounds were developed.

Tony Wilder

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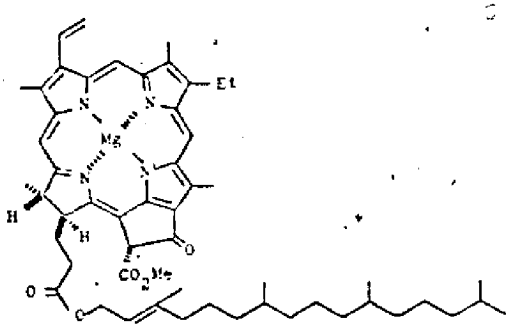
INTRODUCTION.

Organic compounds are synthesised for a great many reasons. Often, they are prepared because they are natural products, or because they possess a novel or unusual structure, and frequently, because their construction represents a challenge to the skill and ingenuity of the organic chemist.

Synthetic organic chemistry has now progressed to the extent that it is no longer sufficient for a synthesis to be merely successful, it should also be elegant and direct. An excellent example of a total synthesis of a natural product, which has achieved widespread recognition as possessing such qualities, is the synthesis of chlorophyll (1) accomplished by R.B. Woodward and coworkers.[1]



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Particulary in the synthesis of poly-functional natural products, such as chlorophyll, a high degree of selectivity is often required to perform the desired transformations, and it is only careful planning of the synthetic sequence that will produce an elegant and pleasing

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result. To be able to design such a synthesis, or even a simple, utilitarian method of producing a compound, it is necessary to scrutinise a large number of reactions as to their suitability in the synthetic sequence, and this requires a wide knowledge of both the scope and the limitations of each reaction.

Perhaps the most important, and certainly the most frequently used reactions in organic chemistry are those in which carbon-carbon bonds are formed. The subject of this dissertation is an outline of the attempts to delineate the scope of a reaction which allows the formation of a variety of carbon-carbon bonds, namely the reactions of the dianion of beta-ketoesters.

Although there are already documented a myriad ways of forming carbon-carbon bonds an additional method will surely find applicability, for without choice elegance becomes unattainable.

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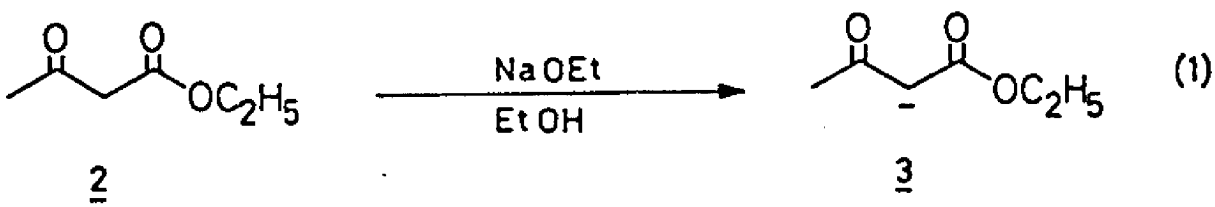
HISTORICAL BACKGROUND.

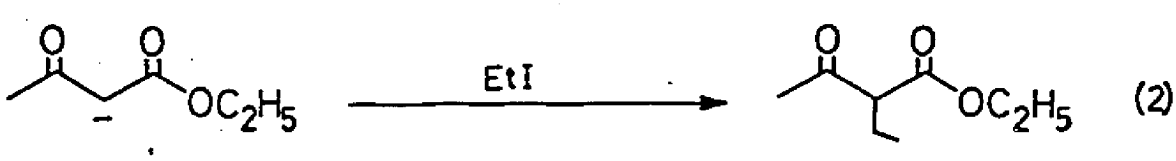
The Synthetic Value of β-Dicarbonyl Compounds.

It has long been known that the hydrogen atoms on the α-carbon atom of β-dicarbonyl compounds are relatively acidic. This was reported by Geuther[2] in 1863, who, whilst investigating the mechanism of the Claisen condensation of ethyl acetate, treated ethyl acetoacetate (2) with sodium ethoxide in anhydrous ethanol to form the sodium salt of ethyl acetoacetate (3), equation 1.



2 3 (1)

It was shortly after this, that Wislicenus reported in a lengthy paper[3] an extensive study of the properties of ethyl acetoacetate (2) which was significant in that not only was the nucleophilicity of ethyl sodioacetoacetate (3) first reported, namely its reaction with iodoethane to give ethyl 2-ethylacetoacetate (4), but the author foresaw the value of β-ketoesters as synthetic intermediates. The analagous



3 4 (2)

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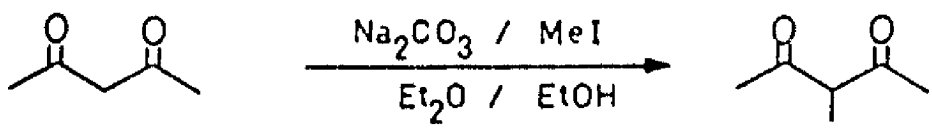
reactions of β-diketones were not reported until 1894 when Claisen[4] reported the synthesis of 2-methylpentanedione (6) from pentanedione (5) and methyl iodide in the presence of sodium carbonate, equation 3.



5 6 (3)

There then followed a period of over fifty years during which the reactions of β-dicarbonyl compounds were explored and rapidly utilised to a considerable extent, much as Wislecenus had predicted. A few examples of other nucleophilic reactions of ethyl sodioacetoacetate (3) are shown in scheme I; these reactions were chosen to provide a comparison with the analagous reactions of methyl lithiosodioacetoacetate, which will be discussed later.

It is difficult to appreciate the full significance of the synthetic applications of ethyl acetoacetate and other β-dicarbonyl compounds as their uses have been manifold, yet the literature pertaining to their reactions has not been reviewed (perhaps because of the daunting task such a review would present). This synthetic utility could be amply illustrated, almost ad infinitum, and may be demonstrated by two recent examples; the synthesis of marrubiin (15), a diterpene lactone from Marrubiin vulgare,[10] and of a trisporic

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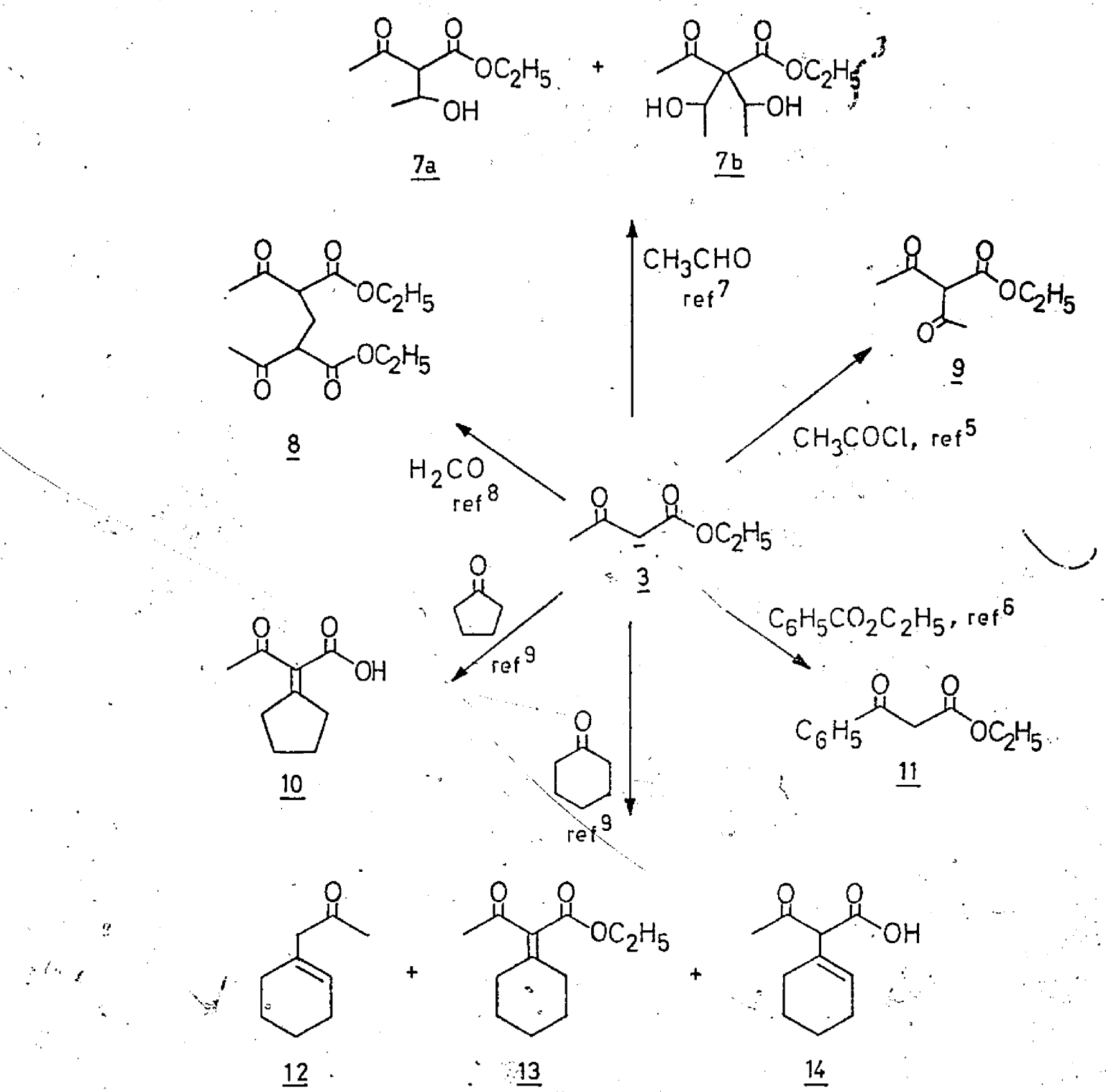
Scheme I



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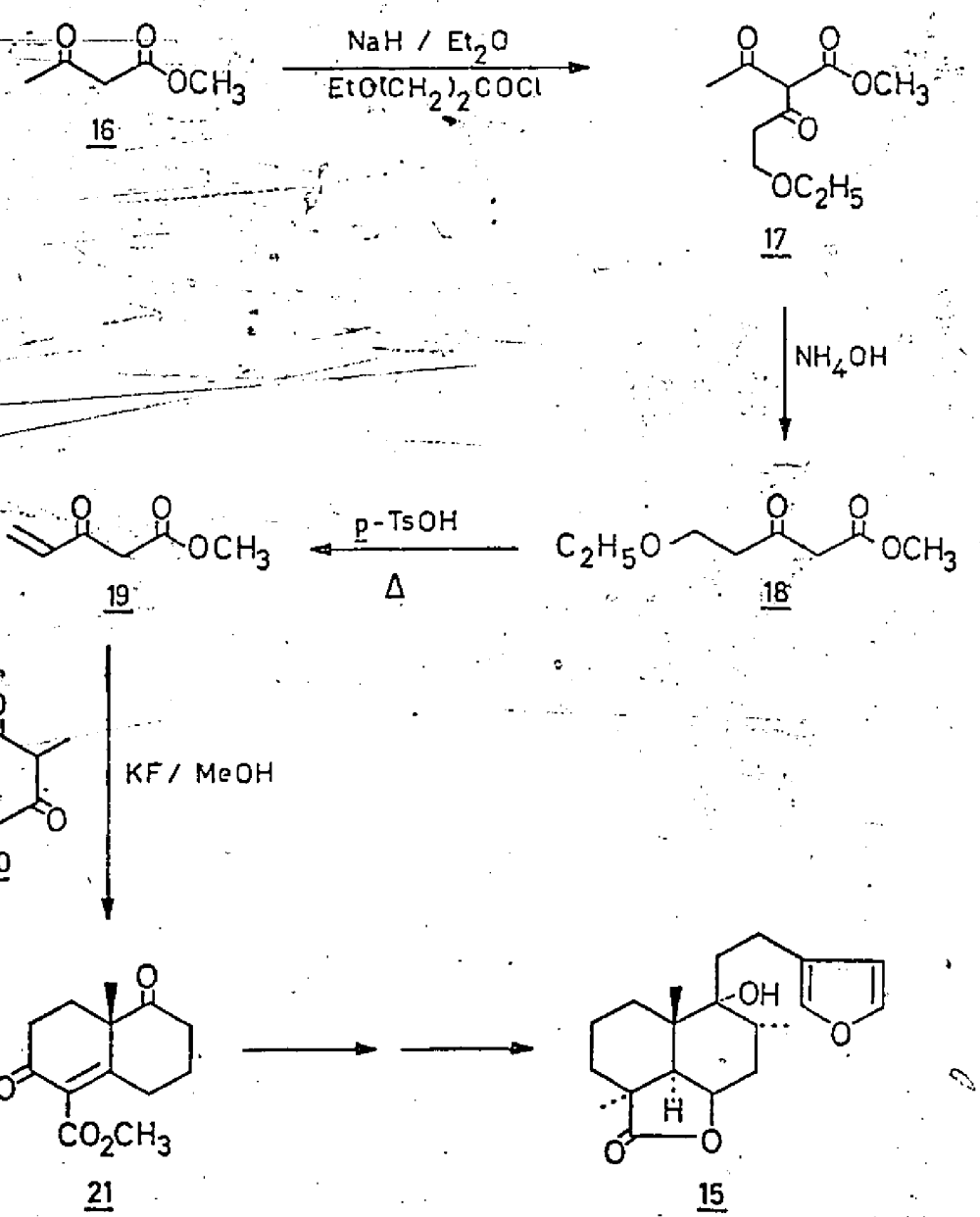
acid 24, the principal sex hormone of Mucor mucedo and Blakeslea trispora.[11] In the former synthesis, a key intermediate, enedione 21, was prepared by a modified Robinson annelation reaction[12] between 2-methylhexane-1,3-dione (20) and methyl 3-oxopent-4-enoate (19), which in turn had been derived from methyl acetoacetate (16) by the Nazarov procedure.[13]

Scheme II



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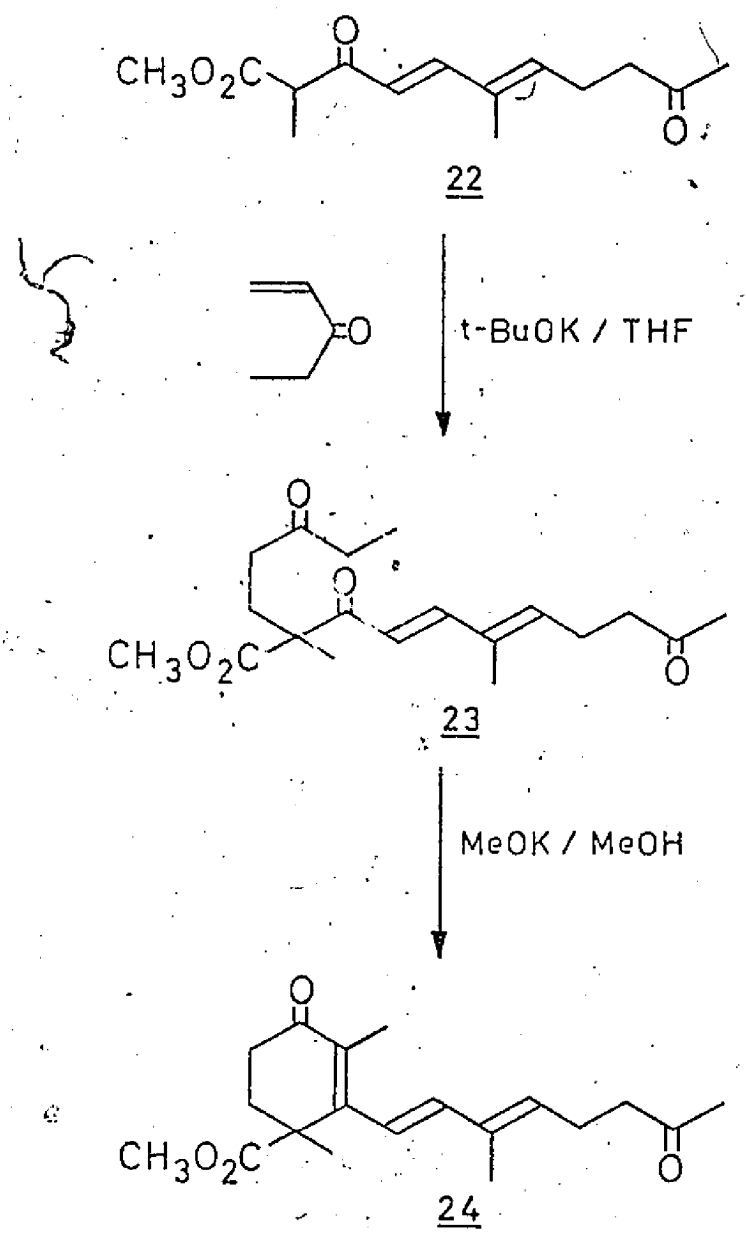
In the synthesis of (+)-7(t),9(t)-trisporic acid B (24), a Michael addition of diketoester 22 to ethyl vinyl ketone gave triketoester 23 which could be cyclised, via an aldol reaction with concomittant dehydration to trisporic acid 24.

Scheme III



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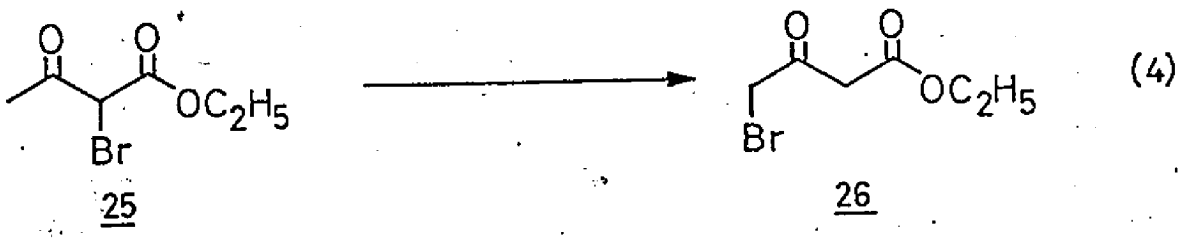
The Dianion of β-Dicarbonyl Compounds.

Until 1958, there was no generally applicable reaction which induced functionalisation at the γ-carbon atom of β-dicarbonyl compounds. One reaction of limited utility was the formation of ethyl 4-bromoacetoacetate (26) from ethyl 2-bromoacetate (25), when the latter was allowed to stand for a considerable time.[14]



25 → 26 (4)

This rearrangement has been shown to be induced by the presence of hydrogen bromide and air (oxygen),[15] and does not appear to be universal for γ-halo-β-dicarbonyl compounds; neither ethyl 2-chloroacetoacetate nor 3-bromopentanedione rearrange under similar conditions.[16]

It was observed by Hauser[17] that the dipotassio salts of two β-diketones, 1-phenylbutane-1,3-dione (29) and pentane-2,4-dione (30), could be obtained by treatment of the diketone with potassium amide in liquid ammonia. In the former case this was achieved by direct addition of solid 27 to the amide in liquid ammonia solution, whilst with the latter, the ammonium salt of pentanedione 28 was preformed and this added to the base.[18]

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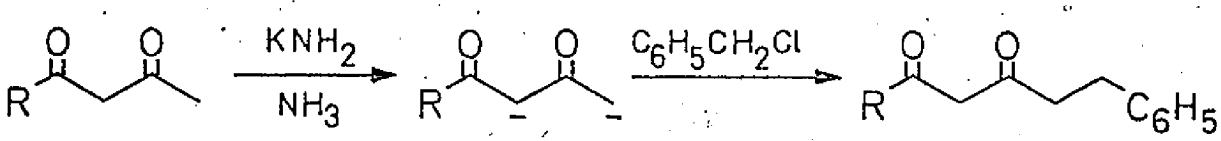


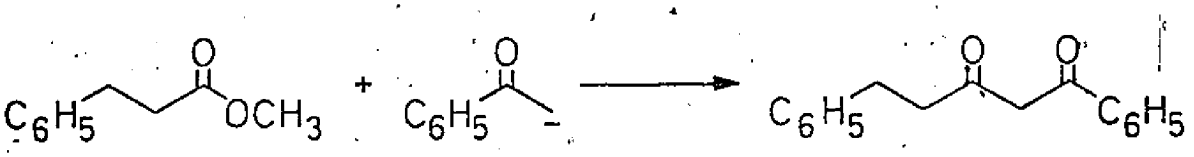
(5)

27; R=C_6H_5 29, R=C_6H_5 31, R=C_6H_5

28, R=CH_3 30, R=CH_3 32, R=CH_3

These dipotassio salts react rapidly with one equivalent of benzyl chloride to give only the compounds 31 and 32, alkylated at the γ position.

The structure of the product from the alkylation of 1-phenylbutane-1,3-dione was rigorously proven to be 31. Molecular weight determination showed it to be a mono-benzylated product, whilst a mixed melting point determination with 2-benzyl-1-phenylbutane-1,3-dione showed it not to be the α alkylated derivative. Independent synthesis of 31 was achieved via a Claisen type condensation of methyl hydrocinnamate (33) with the sodium salt of acetophenone (34), and a mixed melting point of the products from both sources was not depressed.



(6)

33 34 31

Additional data which confirmed the structure to be 31 was the

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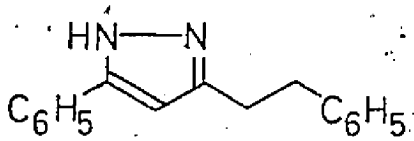
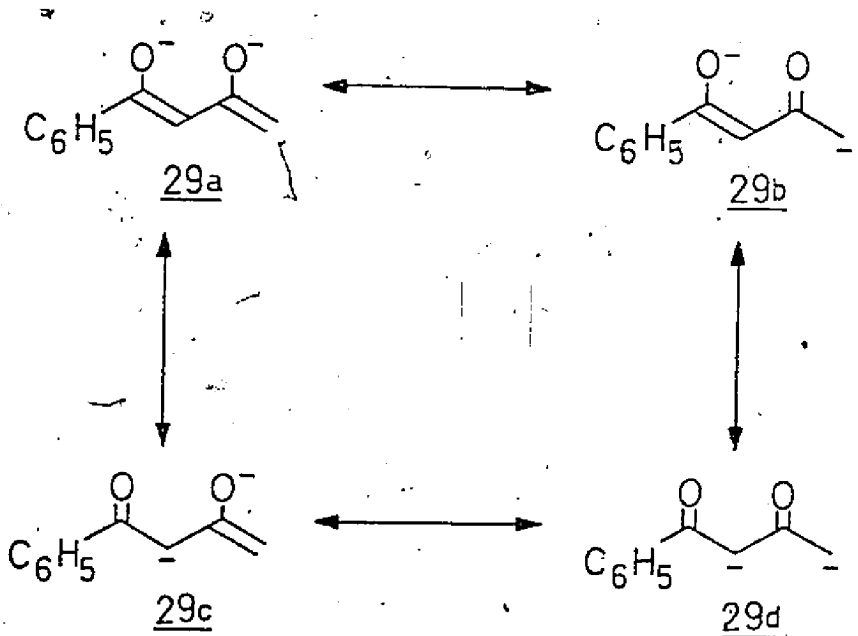
melting point of the copper chelate of the product and that of the pyrazole (35) derived from the product, which were in good agreement with the literature values of those derivatives of 31.



35

Although it was subsequently shown[19] by nmr that in solution most of the charge of dianion 29 resided on the oxygen atoms, which would indicate that 29a is the major contributor of the four possible canonical forms (29a-d), it is perhaps easiest to visualise the salt as a dicarbanion (29d), to emphasise the high reactivity of the γ-carbon atom.[20]

Scheme IV



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A measure of the reactivity of these dipotassio salts may be gained by comparing the rate of their alkylation to that of the alkylation of the simple monoanions of β-diketones; the latter often proceeds very slowly, even at elevated temperatures whilst rapid alkylation of the dipotassio salts occurs at low temperatures. So great is this difference in reactivity, that even when 29 is treated with an excess of alkylating agent no substitution at the α-position is observed.

In addition to this high degree of regio-specificity, the alkylation reaction exhibits a significant degree of stereo-selectivity; treatment of the dianion of 1-phenylpentane-2,4-dione with 1-chloro-1-phenylethane gave only the erythro product indicating a high degree of assymetric induction occurs during the reaction.[21]

Hauser also reported in this first communication,[17] the acylation of the dipotassio salts with methyl benzoate to give triketones 36 and 37, the phenylation of 30 with bromobenzene, in which benzyne is intermediate, to give 38, the carbonation of 29 to give diketoacid 39 and the aldol condensation of 29 with benzaldehyde, the resulting diketoalcohol 40 was subsequently dehydrated to the unsaturated diketone 41, scheme V. In all these reactions, substitution occurs only at the γ carbon atom.

The generality of this procedure of generating the dipotassio salt as a method of functionalising β-dicarbonyl compounds in the γ position has been demonstrated by its application to β-ketoaldehydedes,[22] β-ketoesters,[23]

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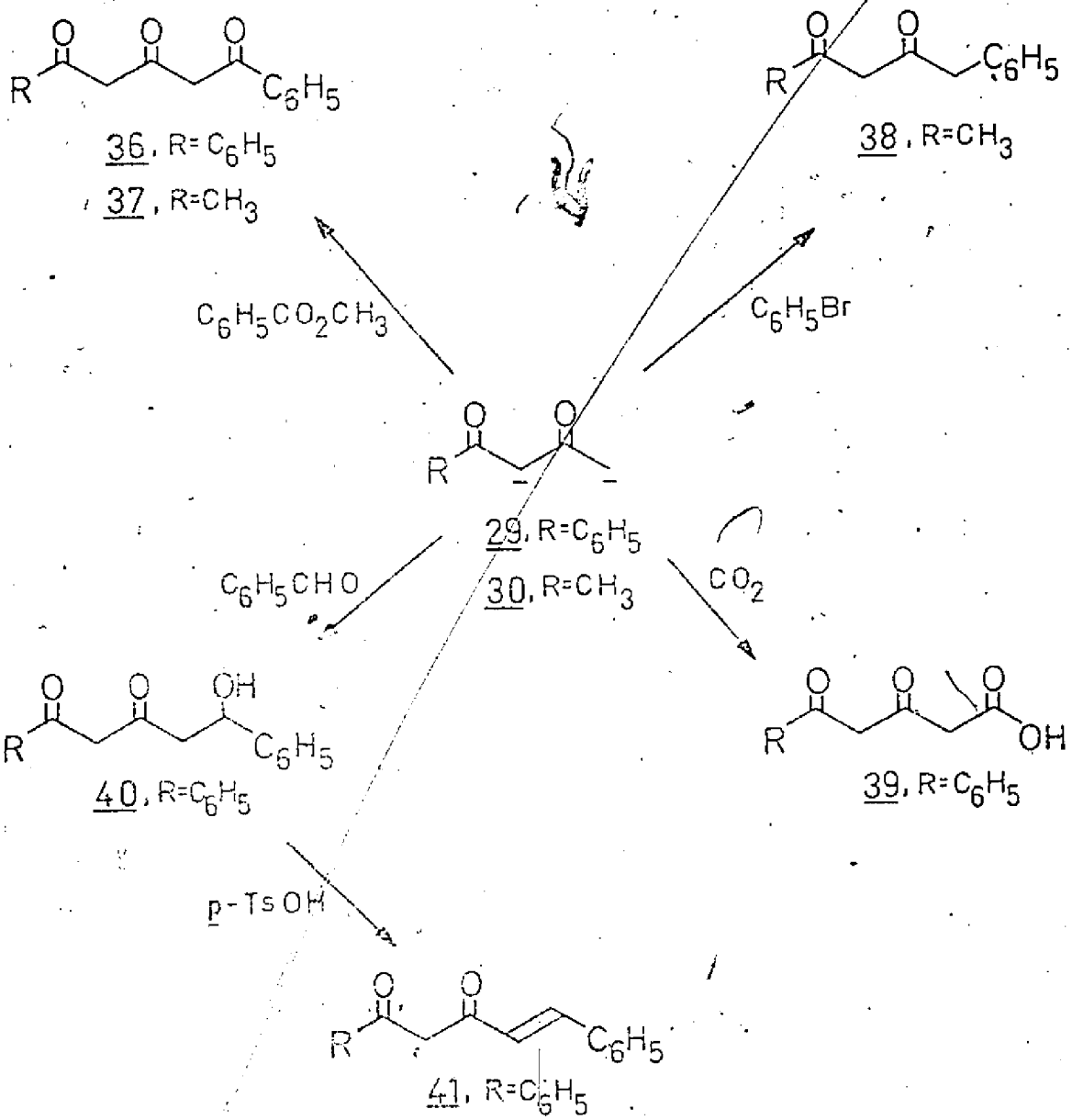
Scheme V



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β-ketolactones,[24] and other related carbonyl compounds, which have included β-iminoketones (in particular N-phenyl iminoketones),[25] β-ketosulphones,[26,27] and imides.[28]

The γ-alkylation of dicarbonyl compounds by this method has been fully investigated by Hauser and coworkers, and the relevant literature (until 1966) has been reviewed.[20]

The yields of alkylated β-diketones obtained via the dianion vary widely, but generally are fair to good. It was found, however, that the yields were dependent upon the nature of the alkali metal amide used to generate the dianion. In general, it was found that the dipotassio salt and the disodio salt gave comparable results[29] (with the exception of pentane-2,4-dione, whose disodio salt is much more soluble in liquid ammonia than its dipotassio salt.)[30] The dilithio salts have not been used extensively for alkylation, and those reactions which have been reported indicate a lower reactivity, and consequently lower yield, than either the dipotassio or disodio salts.[30a] This reduced reactivity, which is probably due to the higher covalent character of the lithium-carbon bond, appears to apply only for alkylation reactions as it has been reported that for Claisen and aldol condensations with enolisable esters and ketones, dilithium salts give better yields.[31,32]

The regio-specificity of the alkylation of β-diketones, in that reaction occurs only at the γ position, has already been mentioned, but it has been reported that the reaction is even more regio-selective. Where the two γ positions of a β-diketone are unequally substituted, as in the case of

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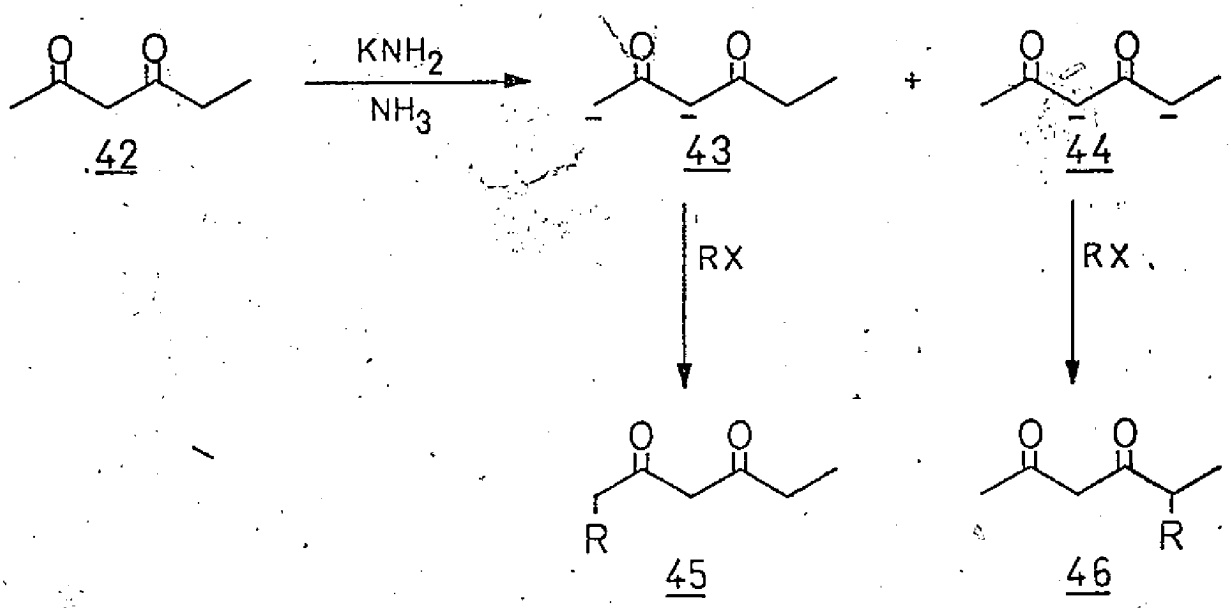
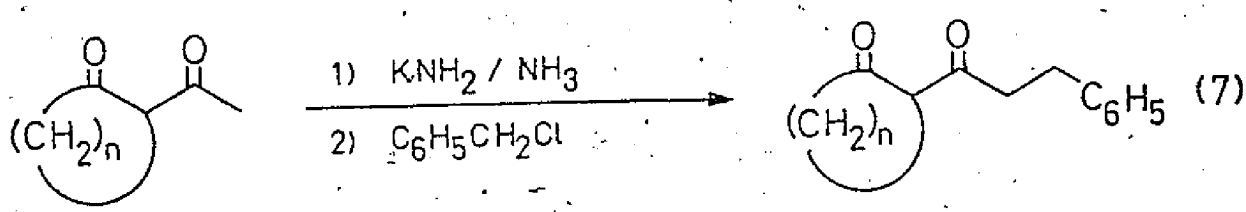
hexane-2,4-dione (42), two isomeric dianions are possible, 43 and 44, which in turn could lead to two different products upon alkylation 45 and 46. It has been found that generally

Scheme VI



42 43 44 45 46

alkylation at the least substituted γ position predominates. In the methylation of the disodio salt of hexane-2,4-dione (42), the product mixture, obtained in 56% yield, contains heptane-3,5-dione (45, R=Me) and 5-methylhexane-2,4-dione (46, R=Me) in the ratio 89:11.[33] Similarly, the benzylation of 2-acetyl cyclic ketones 47 gave only those products (48) in which alkylation had occurred at the methyl group.[34]



(7)

47, n=2 or 3 48, n=2 or 3

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The alkylations of β-ketoaldehydes have also been investigated,[22,24,35] and the yields, although generally lower than those obtained for β-diketones presumably because of the difficulty of isolating these more unstable dicarbonyl compounds, are still fair to good. To overcome this isolation difficulty, the alkylated ketoaldehydes have frequently been converted to more stable derivatives prior to isolation, and the inclusion of another step tends to lower the overall yield. The procedure has been slightly modified for β-ketoaldehydes; the substrate was usually added to the liquid ammonia-amide solution as the monosodio salt. This was necessary to avoid the reaction of the aldehyde with the ammonia, and other competing side reactions (e.g. aldol condensations of the monoanion with any unmetallated aldehyde).

However, the alkylation of β-ketoesters under these conditions of alkali metal amide in liquid ammonia give only poor yields of alkylated esters, Table I, presumably because of the low temperature of the reaction or because amidolysis of the ester function also occurs.

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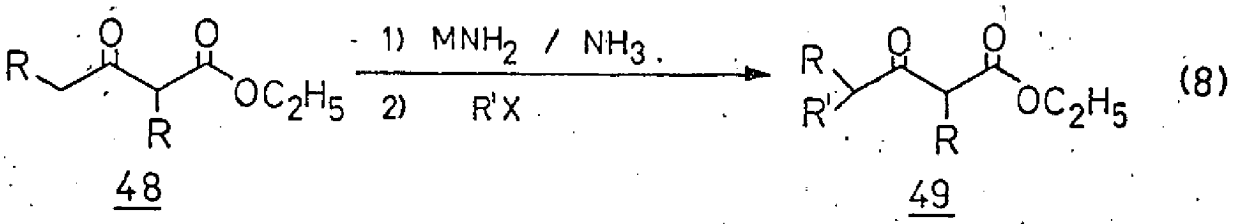
Table 1.

Alkylation of Dialkali β-Ketoesters in Liquid Ammonia.



48 49 (8)

M	R	R'-X	Yield(%)	Reference
Na	H	CH_3I	"Low"	36
K	H	CH_3I	36, 37	23
K	H	EtI	27, 29	23
Li	H	n-BuBr	0	36
Na	H	n-BuBr	0	23
K	H	n-BuBr	0	36
Na	H	$C_6H_5CH_2Cl$	41	36
K	H	$C_6H_5CH_2Cl$	0	23
K	C_6H_5	$C_6H_5CH_2Cl$	44	23
K	H	n-C_3H_7	63	77
K	H	$C_6H_5CH_2Br$	65	77

Only one instance has been reported in which the alkylation of a β-ketoester under these conditions has been observed to occur in high yield. The benzylation of β-ketolactone 51 has been reported to give 52 in 90% yield.[24] However, in the same communication it was also reported that under essentially the

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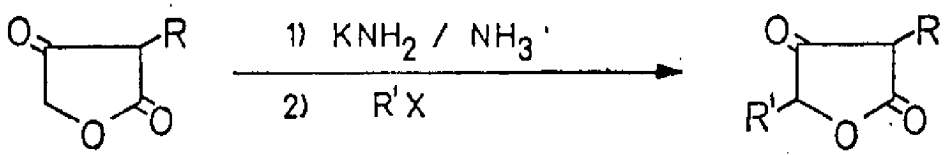

(9)

51, R=CH_3

54, R=C_2H_5

52, R=CH_3, R'=$C_6H_5CH_2$
53, R=CH_3, R'=CH_3
55, R=C_2H_5, R'=$C_6H_5CH_2$

same conditions methylation of the same lactone (51) to 53 could only be effected in 39% yield, and that the benzylation of its homolog 54 proceeds to give only 18% of the corresponding product 55.

The substitution of the β-diketones at the γ position via carboxylation, Claisen and aldol condensations of their dianions, initially reported by Hauser,[17] has since been thoroughly investigated. The dipotassio salts of β-diketones undergo aldol condensations with ketones and aldehydes having no hydrogen atoms on the carbon atom α to the carbonyls to give reasonable yields of the corresponding hydroxydiketone (Table II),[17,32,37] but with ketones and aldehydes that do possess such enolisable hydrogen atoms no aldol products could be isolated. The failure of these reactions was postulated to be due to proton transfer from the ketone or aldehyde to the dianion salt. Since lithio ethyl acetate,[38] and lithio t-butyl acetate,[39] but not sodio ethyl acetate,[40] had been reported to condense with acetophenone, substitution of the dilithio salt of the β-diketones was made, and the aldol

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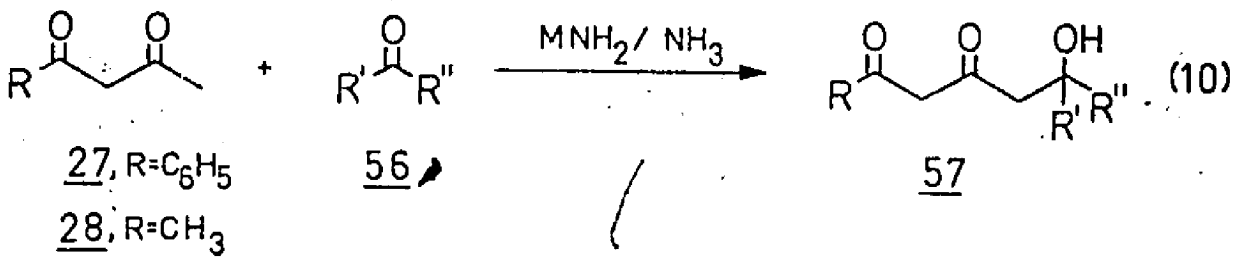
condensation with the enolisable ketones was found to proceed, albeit in lower yields than with the non-enolisable ketones.

Table II.

Aldol Condensations of Dialkali β-Diketones in Liquid Ammonia.



(10)

27, R=C_6H_5 28, R=CH_3 56 57

R	R'	R''	M	Yield(%)	Reference
C_6H_5	C_6H_5	H	K	28	17
C_6H_5	p-$MeOC_6H_4$	H	K	49	32
C_6H_5	C_6H_5	C_6H_5	K	73	32
C_6H_5	p-ClC_6H_4	C_6H_5	K	69	32
CH_3	C_6H_5	C_6H_5	K	73	32
CH_3	p-ClC_6H_4	C_6H_5	K	52	32
C_6H_5	C_6H_5	CH_3	Li	40	32
C_6H_5	$-(CH_2)_5-$		Li	34	32
C_6H_5	$C_6H_5CH=CH$	C_6H_5	K	66	37

It was apparent that the carboxylation of the dianions of β-diketones could not be performed in liquid ammonia solution, as carbon dioxide reacts with ammonia to form ammonium carbamate. Consequently, in the initial attempts to

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generate diketocarboxylic acids, the dipotassio salt of 1-phenylbutane-1,3-dione (29) was isolated from the ammonia solution, suspended in ether and treated with excess solid carbon dioxide.[17] Subsequent investigation[49] showed that the disodio salt gave superior yields, and all further carboxylations were performed using sodium salts. The significance of these communications,[17,49] aside from the synthetic value as a relatively efficient method of producing β,δ-diketoacids, is that they represent the first reaction of β-dicarbonyl dianions in solvents other than liquid ammonia.

Acylation of β-diketones has been the subject of more investigation than either of the two previous reactions.[17,31,41-45] This is probably due, at least in part, to the difficulties encountered during attempts to synthesise 1,3,5-triketones efficiently. These triketones are of considerable interest as postulated intermediates in the biosynthesis of phenolic compounds.[46]

The major difficulty, which occurs in any synthesis of poly-carbonyl compounds involving anions, i.e. acylation, arises from the fact that the initial condensation product (for example 61) possesses a more acidic hydrogen atom than the monoanion 59 of the starting dicarbonyl compound. Thus proton transfer occurs, equation 13, and one additional molecule of the dianion is quenched (protonated to give the monoanion) for each molecule of the product that is formed. Since the alkoxide ion that is formed during the condensation is not a sufficiently strong base to regenerate the dianion 60 from

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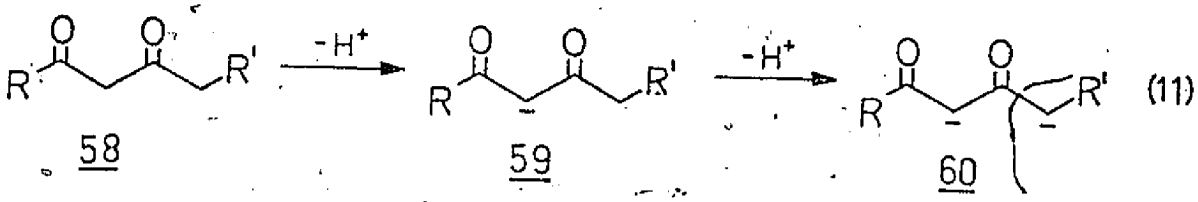
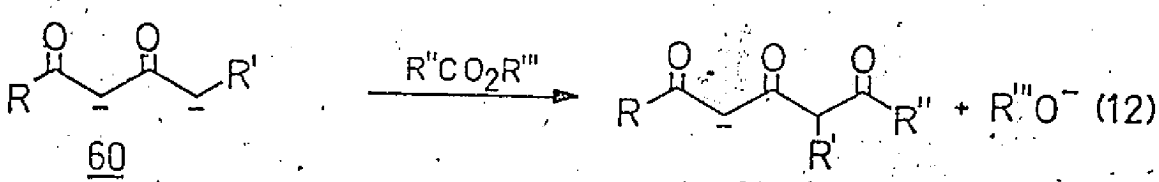
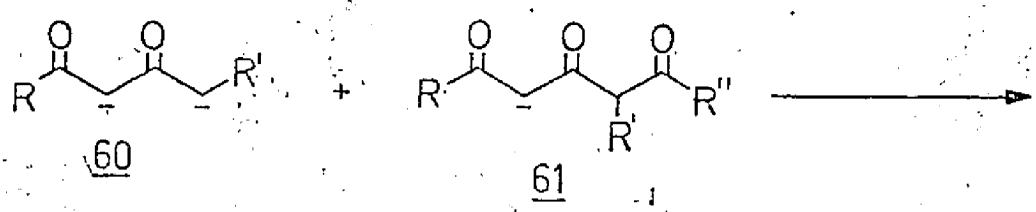
the monoanion 59, the maximum yield of product, based on the dicarbonyl component, is fifty percent.



58 59 60 (11)



60 61 (12)



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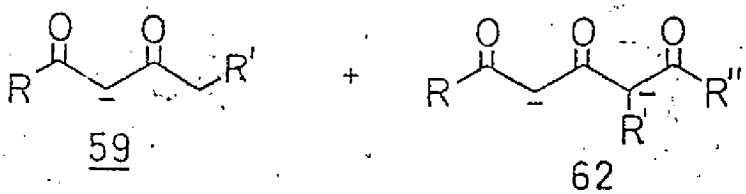

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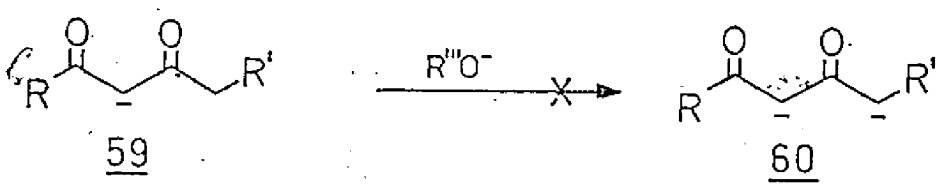

59 60 (14)

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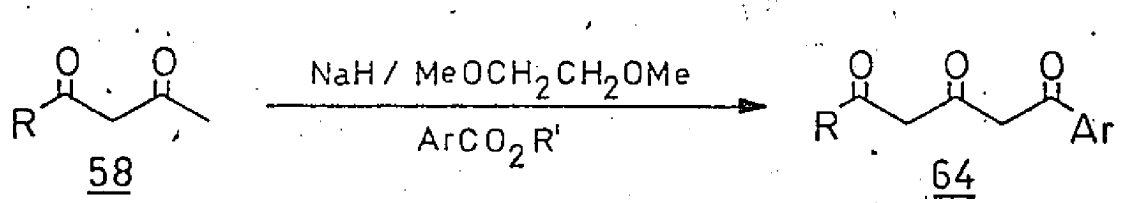
In the initial acylations,[17] a onefold excess of the dianion was employed, and the yield was based upon the degree of conversion of the ester, but this approach would be unsatisfactory in a synthetic sequence where the diketone is expensive or difficult to obtain.

Attempts to overcome this difficulty by addition of excess base have had only limited success during the condensation of methyl benzoate with 1-phenylbutane-1,3-dione (27) employing three equivalents of potassium amide, the excess base reacted mainly with the ester, converting it to benzamide. Whilst with esters which possess hydrogen atoms on the α carbon atom, excess potassium amide has been found to cause enolisation of the ester, and consequently gave no condensation.[41] In analogy with the aldol condensation results,[32] lithium amide was employed,[31] and found to be more satisfactory, but the yields of triketone were still rather poor (Table III).

A related reaction which was developed by Hauser and coworkers,[43] is the γ-aroylation of β-diketones employing an excess of sodium hydride in refluxing 1,2-dimethoxyethane as the condensing agent (equation 15).



58 64 (15)

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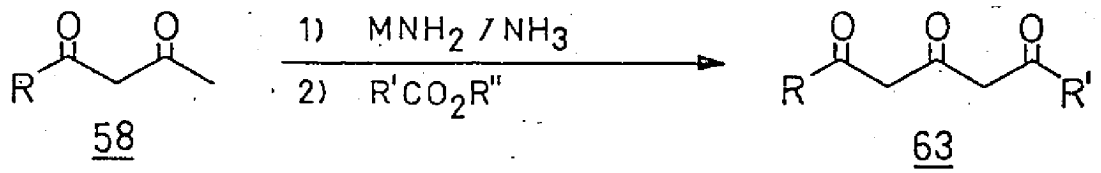
Table III.

Acylation of Dialkali ß-Diketones in Liquid Ammonia.



58 63 (16)

R	R'	R''	M	Yield(%)	Reference
$C_6H_5CH_2CH_2$	CH_3	CH_3CH_2	Li	17	44
CH_3	$n-C_7H_{15}$	CH_3	Li	41	44
$n-C_7H_{15}$	CH_3	CH_3	Li	17	44
CH_3	$n-C_5H_{11}$	CH_3	Li	38	44
CH_3	$n-C_3H_7$	CH_3	Li	42	44
CH_3	C_6H_5	CH_3	K	60[a], 53	17, 41
C_6H_5	C_6H_5	CH_3	K	58[a], 62, 80	17, 41, 42
C_6H_5	$p-CH_3OC_6H_4$	CH_3	K	61	41
C_6H_5	$p-ClC_6H_4$	CH_3	K	47	41
C_6H_5	3-pyridyl	CH_3	K	40	41
C_6H_5	CH_3	CH_3CH_2	Li	45, (66)[b]	31
C_6H_5	CH_3CH_2	CH_3	Li	42, (79)[b]	31
C_6H_5	$(CH_3)_2CH$	CH_3	Li	43, (88)[b]	31
C_6H_5	$n-C_9H_{19}$	CH_3	Li	40	31
CH_3	CH_3	CH_3CH_2	Li	45, (59)[b]	31
CH_3	CH_3CH_2	CH_3	Li	50	31

Notes a) a ratio of dianion to ester of 2:1 was used for these reactions and the yield is based on conversion of ester.
b) the yield in parentheses is based on conversion of dianion, allowing for recovered ß-diketone.

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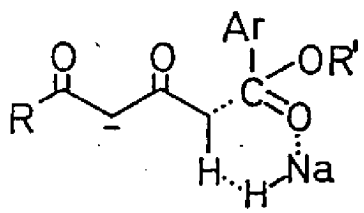
The mechanism of this reaction is uncertain but it is unlikely that sodium hydride forms the dianion directly, as only one equivalent of hydrogen is evolved on addition of the sodium hydride. A second equivalent of hydrogen is evolved on addition of the ester. One suggested mechanism[43] requires a second ionisation of the diketone to be induced via a termolecular transition state 65 occurring on the surface of the sodium hydride, with either a simultaneous or subsequent condensation of the dianion so generated.



65

The yields of triketone produced by this method are generally very good (Table IV), but this method as yet has only been applied to aroylations. Since it had been reported[47] that it was possible to form β-diketones from ketones and esters via a Claisen condensation under essentially these conditions (equation 17), it was deemed plausible that these two reactions could be combined, and aroylate a ketone twice to give linear triketone 68 (equation 18).

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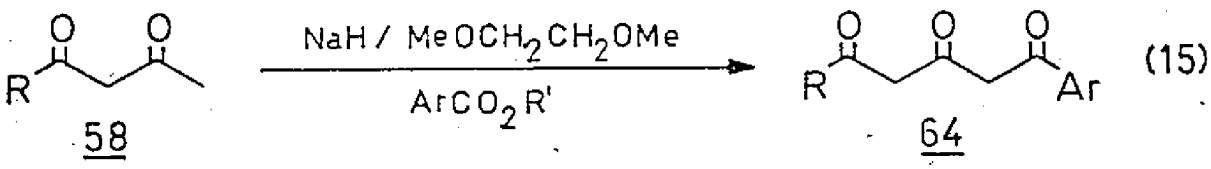
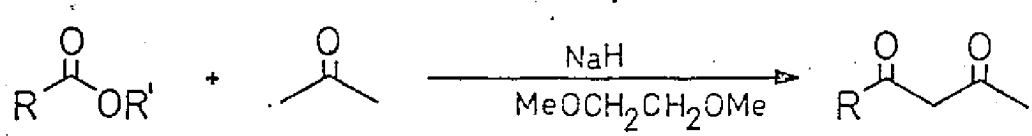
Table IV.

Aroylations of β-Diketones Employing Sodium Hydride in Refluxing 1,2-Dimethoxyethane.

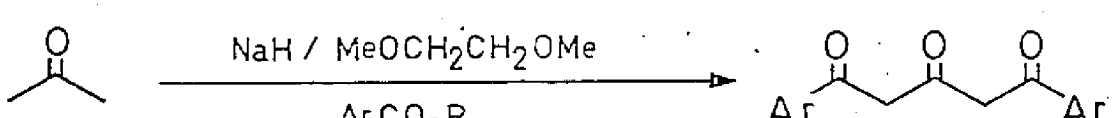


58 64 (15)

R	Ar	R'	Yield	Reference
C_6H_5	C_6H_5	CH_3	87	43
C_6H_5	p-$CH_3OC_6H_4$	CH_3	92	43
C_6H_5	p-ClC_6H_4	CH_3	78	43
C_6H_5	3-pyridyl	CH_3CH_2	69	43
CH_3	C_6H_5	CH_3	54, 55-60	43, 45
$C_6H_5(CH_2)_2$	C_6H_5	CH_3	61	45
CH_3	p-$CH_3OC_6H_4$	CH_3	72	45



66 + 67 → 58 (17)



67 → 68 (18)

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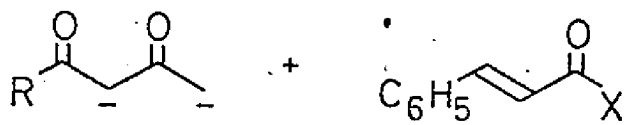
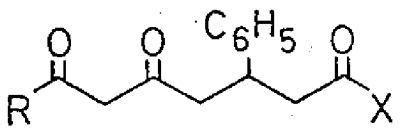
This method was found to give the desired triketone 68 in good yield,[43] but its application is obviously limited to the synthesis of symmetrical triketones.

The dianions of β-diketones have also been condensed with α, β-unsaturated carbonyl compounds in a Michael type reaction.



29, R=C_6H_5
30, R=CH_3

69



(19)

70, R=C_6H_5
71, R=CH_3

However, it was found that the reaction of dipotassio 1-phenylbutane-1,3-dione (29) with 1,3-diphenylprop-2-en-1-one (69, X=C_6H_5) gave no Michael addition product, but formed only the aldol product 72. When the unsaturated ketone was changed for the more sterically hindered chalcone, 3-phenyl-1-(2,4,6-trimethylphenyl)-prop-2-en-1-one (69, X=2,4,6-trimethoxyphenyl), the Michael product 70, X=2,4,6-trimethylphenyl, was formed in good yield.[37]

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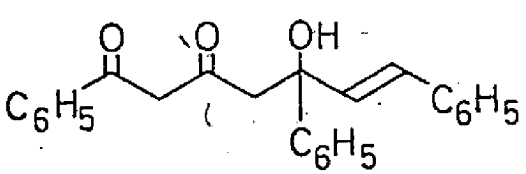
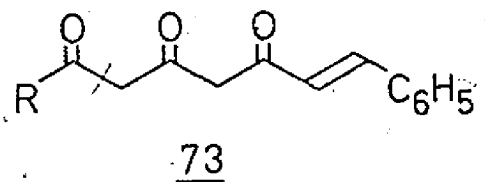
Dipotassio 1-phenylbutane-1,3-dione (29) also failed to give the Michael product with methyl cinnamate (69, $X=OCH_3$), attacking the carbonyl to give triketone 73, $R=C_6H_5$. The Michael addition was accomplished by making the carbonyl of the ester more sterically hindered, by using t-butyl cinammate (69, $X=OC(CH_3)_3$) in the reaction, to give 70, $X=OC(CH_3)_3$.[42]

Dipotassio pentane-2,4-dione (30) and methyl cinnamate (69, $X=OCH_3$) have been reported to give a mixture of products, both the Michael addition product 71, $X=OCH_3$, and the Claisen condensation product 73, $R=CH_3$.[42]



72



73

The Claisen and aldol condensations of the dianions of β-ketoaldehydes have also been investigated by Hauser and coworkers.[48] (The carboxylation of butane-1,3-dione has been reported to give no significant amounts of the expected product.[41])

These condensations are complicated by subsequent reactions of the anticipated products during work up. Frequently, the product isolated from the γ-aroylation of these ketoaldehydes is the pyrone 76.

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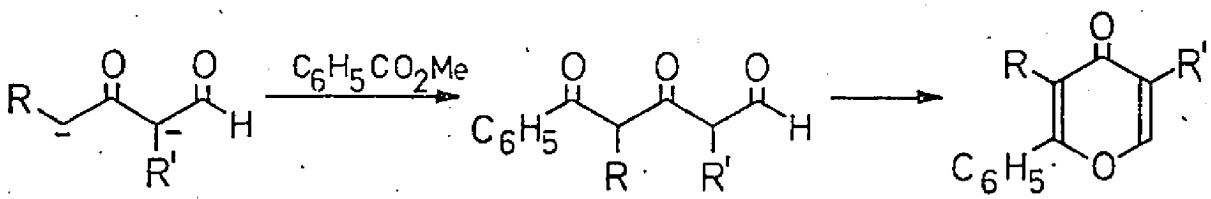
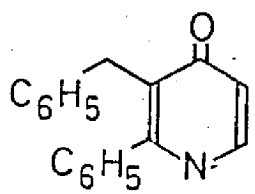
Scheme VII



74 75 76

But with 5-phenylpentane-1,3-dione (74, R=$C_6H_5CH_2$, R'=H) the reported product is the pyridone 77, formed by reaction of 75, R=$C_6H_5CH_2$, R'=H, or its mono- or dianion with ammonia.



77

The four Claisen condensations reported to this date are summarised below.

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Table V.

Claisen Condensations of Dialkali β-Ketoaldehydes.[48]

β-Ketoaldehyde 74 R	R'	Product	Yield(%)
H	H	aldehyde 75, R=H, R'=H	52
$C_6H_5CH_2$	H	pyridone 77	72
H	C_6H_5	pyrone 76, R=H, R'=C_6H_5	50 (53)[a]
H	$C_6H_5CH_2$	pyrone 76, R=H, R'=$C_6H_5CH_2$	60 (63)[a]

Note: a) the yields in parentheses are those obtained using sodium hydride in refluxing 1,2-dimethoxyethane as the condensing agent.

The γ-aroylation of β-ketoaldehydes has also been accomplished using sodium hydride in refluxing 1,2-dimethoxyethane; the products obtained are the corresponding pyrones 76. This reaction appears to give only marginally better yields than the liquid ammonia method.

The product from the aldol condensation of sodio potassio butane-1,3-dione (78) and benzophenone was isolated as its copper chelate 80 in 67% yield, but attempted hydrolysis of this chelate gave acetal 81 rather than the hydroxyaldehyde 79.

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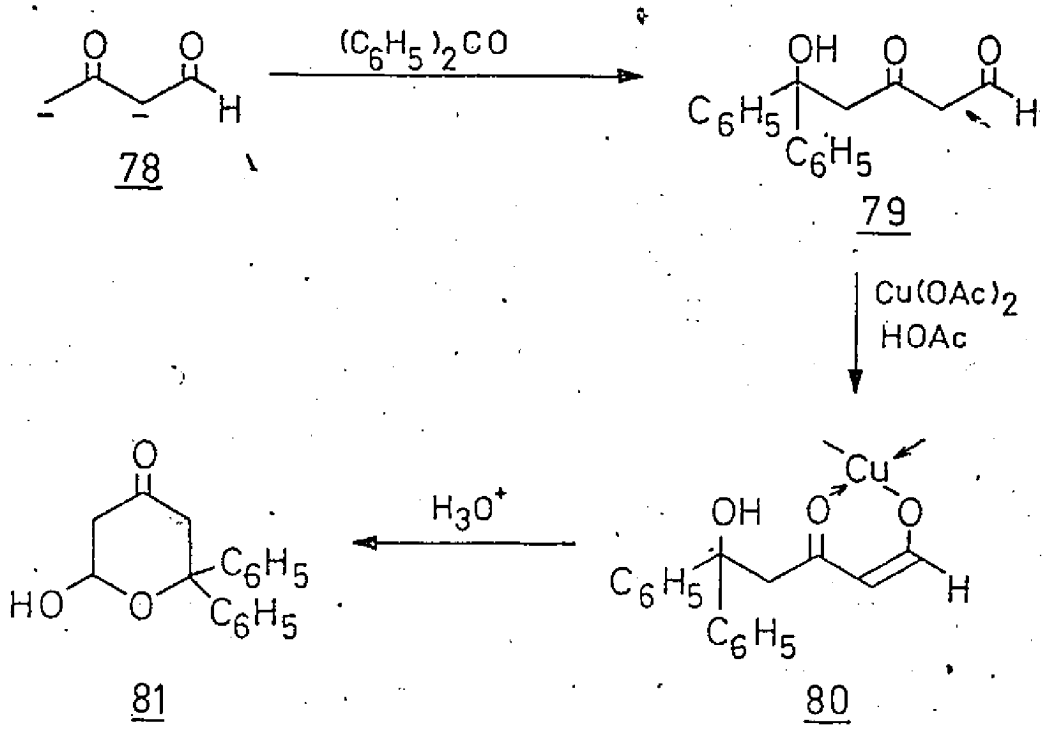
Scheme VIII



Reactions at the γ carbon atom of ethyl acetoacetate, induced via the dipotassio salt 82 in liquid ammonia, have been reported by Hauser,[23] but the yields have not been high.

The aldol condensation of benzophenone with 82 gave in 50% yield the expected hydroxyketoester 83, the carboxylation of 82 in ether gave acetonedicarboxylic acid monoethyl ester (84) in 55% yield,[49] but the Claisen condensation of methyl benzoate with 82 gave, after acid treatment, pyrone 86 in only 11% yield[23] (Scheme IX).

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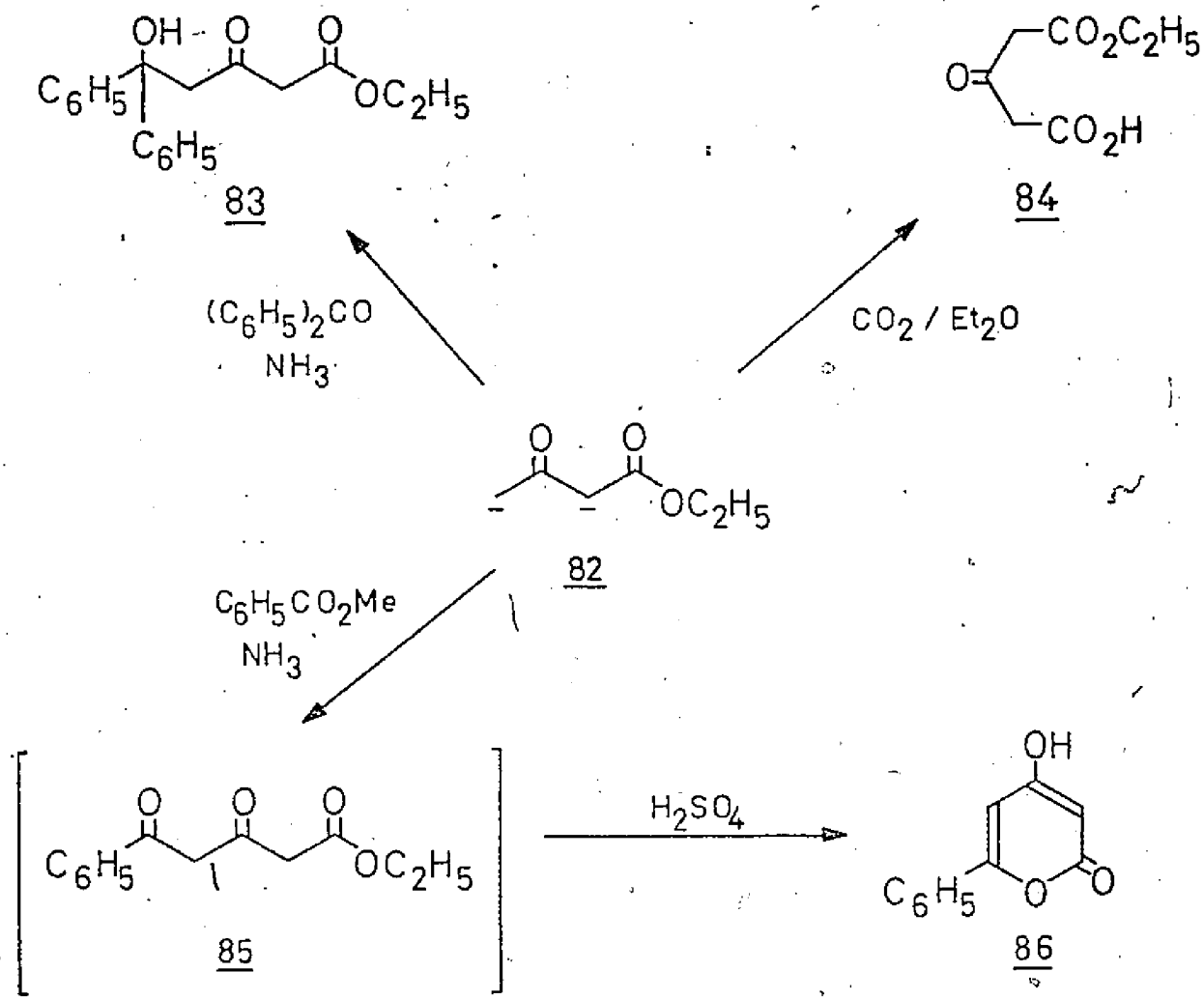
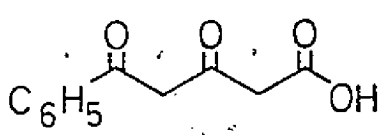
Scheme IX



The γ-aroylation of ethyl acetoacetate (2) has also been achieved with methyl benzoate, using sodium hydride in refluxing 1,2-dimethoxyethane, and under these conditions the isolated product is the diketoacid 87, obtained in 48% yield.



87

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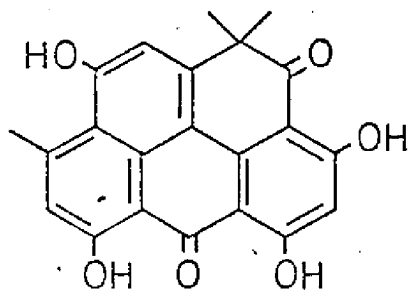
THE DEVELOPMENT OF A METHOD OF GENERATING THE DIANION OF β-KETOESTERS.

Choice of Reaction Conditions: A Review of Some Non-nucleophilic Bases.

It was recently required in our laboratory to functionalise β-ketoesters at the γ carbon atom in attempts to synthesise acetogenins, for example resistomycin (89).[111]



89

It appeared necessary to generate a dianionic intermediate if reaction at the γ carbon atom was to be obtained, (the sodium hydride - dimethoxyethane reaction may not proceed via the dianions, and that reaction seems limited to aroylations). It was felt that the use of liquid ammonia, as solvent, would not be appropriate for reactions of β-ketoesters, since its use would impose two intrinsic disadvantages; reactions would be limited to those which will proceed at a reasonable rate at low temperature (below -33°C), and the reactions might be complicated by condensation of the ammonia with reagents or products (vide ut supra). This

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decision not to use liquid ammonia as solvent, coupled with the requirement of a strong base that was also a poor nucleophile (necessary to generate the dianion), initially appeared to demand a very careful choice of reagents and possibly very stringent reaction conditions.

With regard to the choice of solvent, two other solvents, diethyl ether and 1,2-dimethoxyethane, had been employed for reactions of the dipotassio salt of ethyl acetoacetate (82)[23,49] but tetrahydrofuran has reportedly[50] better solvating ability for anionic species, and thus this latter solvent was selected.

Lithium salts, particularly enolates, have been found to be easily formed and are generally more soluble than the corresponding potassium or sodium salts,[38,39,51] and, since it was desired to have a homogeneous reaction, the initial investigations were designed to produce the dilithio salt of ethyl acetoacetate.

The addition of two equivalents of n-butyllithium to a solution of ethyl acetoacetate (2) in tetrahydrofuran failed to generate the desired dianion, but appeared to attack the carbonyl functions[52,80] (see also part IV), and hence a search for an alternative base possessing high proton abstracting ability yet low nucleophilicity was initiated. (A comparison of the utility of some bases which allegedly possess such ability has been very recently reported.[53])

It has been suggested that the condensation of an enolate of an ester, for example 91, with an acid chloride,

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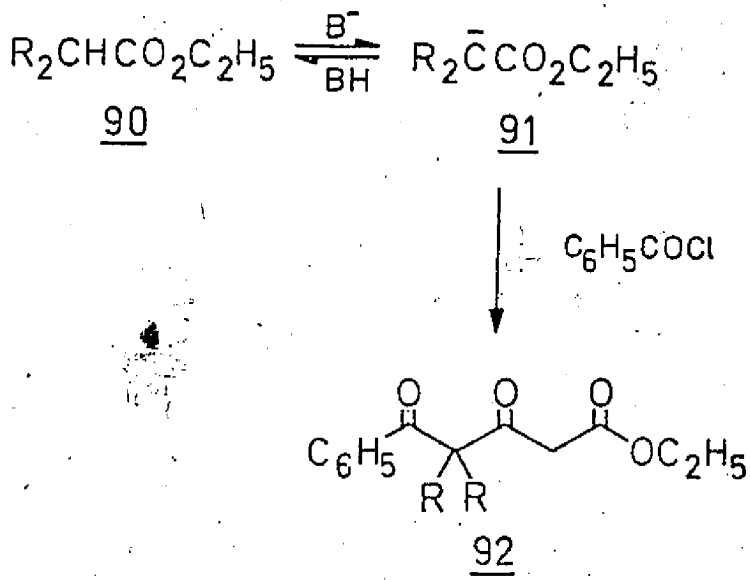
scheme (X), is one of the most stringent empirical measures of the strength and selective reactivity desired in a base (B^-) and of the inertness required in its conjugate acid, (BH).

Scheme X



Using this reaction as an assay, the failure of such bases as alkyl magnesium halides, alkyllithiums, sodium ethoxide, sodium hydride and sodium amide has been used to demonstrate the utility of alkali triphenyl methanes.[54] (These latter bases have recently been successfully employed in our laboratory to alkylate sterically hindered β-diketones in the γ position.[55])

Other bases of low nucleophilicity which have found recent applications are the lithium salts of dialkylamines, and include lithium diethylamide,[56] lithium diisopropylamide (93),[57] lithium N-isopropylcyclohexylamide (94),[58] lithium dicyclohexylamide (95),[53] lithium 2,2,6,6-tetramethylpiperide

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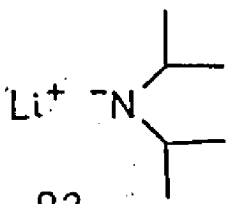
(96),[53,59] and lithium bis-(trimethylsilyl)amide.[60]



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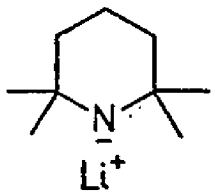

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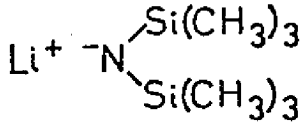
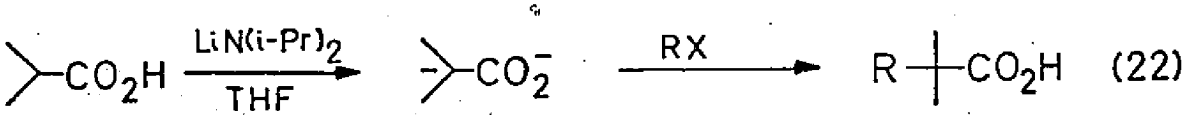


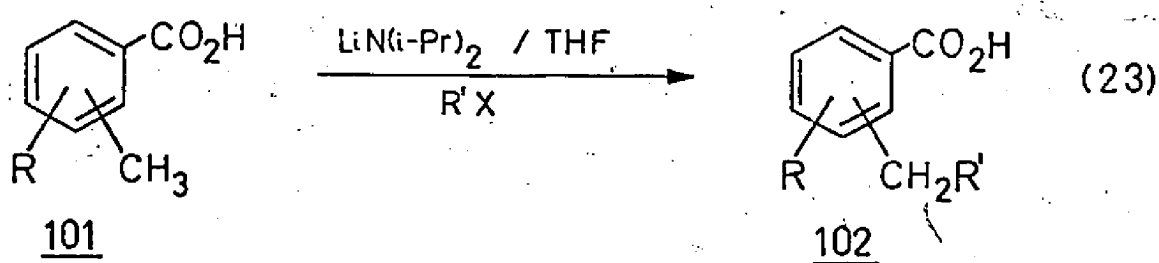
97

Of all these bases, only one 93 has been widely employed in a dianion reaction; it was used, initially by Creger,[57] to generate the dianion of 2-methylpropanoic acid (99) which could then be alkylated in high yields, providing the first efficient, one step synthesis of alkyldimethylacetic acids (100).



98 99 100 (22)

This dianion reaction has also been applied to toluic acids, and permits alkylation of the methyl group in moderate yields, equation (23).[61]



101 102 (23)

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It is interesting to note that ortho toluic acids give the highest yield of alkylated products, whilst the para isomers give better yields than the meta toluic acids, and there is a sufficient distinction between these positions that if there is more than methyl group on the phenyl ring, the o-methyl group is selectively alkylated in preference to either a m- or p- methyl group, and a p-methyl group is similarly selectively alkylated rather than a m-methyl group.

The dianion of alkylacetic acids, 103, R=H, have also been prepared, by means of this base (93), and have been shown to react with alkyl halides to give only the mono-α-alkylated product.[62] Other dilithio salts of carboxylic acids have been prepared, and condensed with aldehydes and ketones to give β-hydroxyacids,[63] condensed with formaldehyde to give, after dehydration, α-alkylacrylic acids,[64] condensed with epoxides,[57] and aminated with O-methylhydroxylamine in a one step synthesis of aminoacids,[65] (Scheme XI). In the last four reactions, hexamethylphosphoramide was used as a cosolvent to increase the solubility of the dianions. The use of this cosolvent has been investigated by Pfeffer and coworkers[66] and found to be very effective in increasing the rate of metalation of α-branched acids but it is deleterious in that it depressed the yield during alkylation.

Other studies by Pfeffer[67] indicate that the major contributing resonance structure of the dianion is 103a in which the change is localised on the oxygen atoms, (cf

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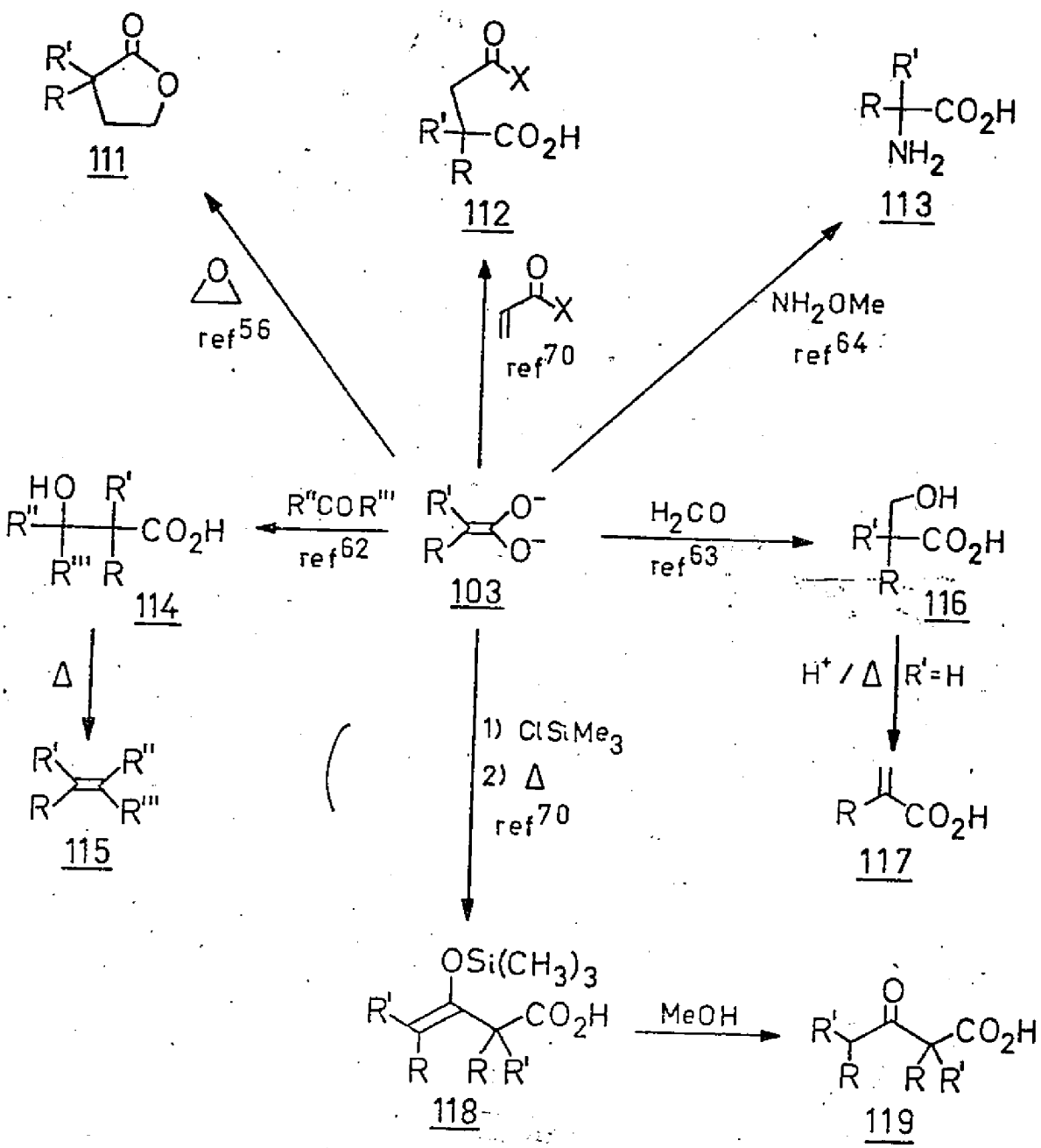
Scheme XI



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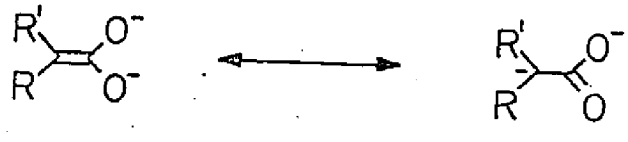
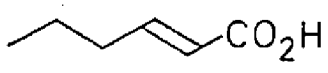
dipotassio-1-phenylbutane-1,3-dione (29)).



103a ⟷ 103b

This was indicated by the isomerisation of trans-2-hexanoic acid (104) which occurred under the conditions normally employed for dianion formation, whilst other unsaturated acids, in which the double bond is separated from the carboxylic acid by several methylene groups, are unaffected by this reaction.



104

1) $LiN(i\text{-}Pr)_2$ / THF
2) H_3O^+

(24)

105 + 106

That the dianion exists in the form of structure 103a was also indicated by the (unspecified) nmr spectrum of dilithio-2-methyl-3-phenylpropionate (103, R=CH_3, R'=$C_6H_5CH_2$),

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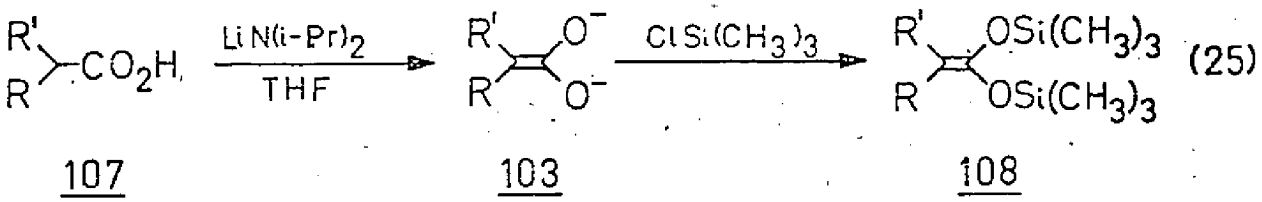
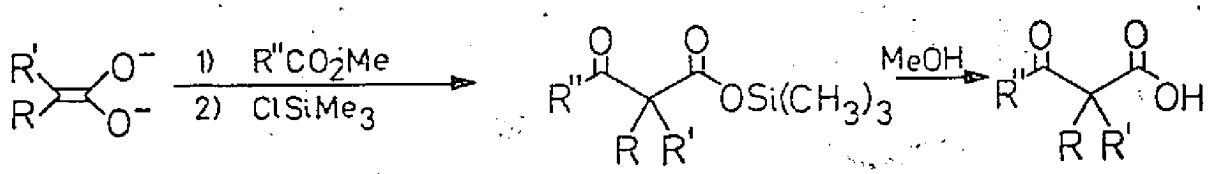
and further credibility for this structure arises from the report of Ainsworth[69] that the dianion from various carboxylic acids could be trapped by chlorotrimethylsilane as their bis-enol ethers 108.



(25)

107 103 108

This procedure of quenching the dianion with chlorotrimethylsilane was effectively employed to facilitate the isolation of the products from the Claisen condensation of dianion 103, which permitted β-ketoacids 110 to be prepared in high yield, the intermediate silyl esters 109 being easily and quantitatively hydrolysed in neutral conditions.[70]



(26)

103 109 110

A difficulty, similar to that of the nucleophilic attack upon the carbonyl groups of ethyl acetoacetate by n-butyllithium,[52] has been reported by Enders[71] during attempts to form an anion in the α position of

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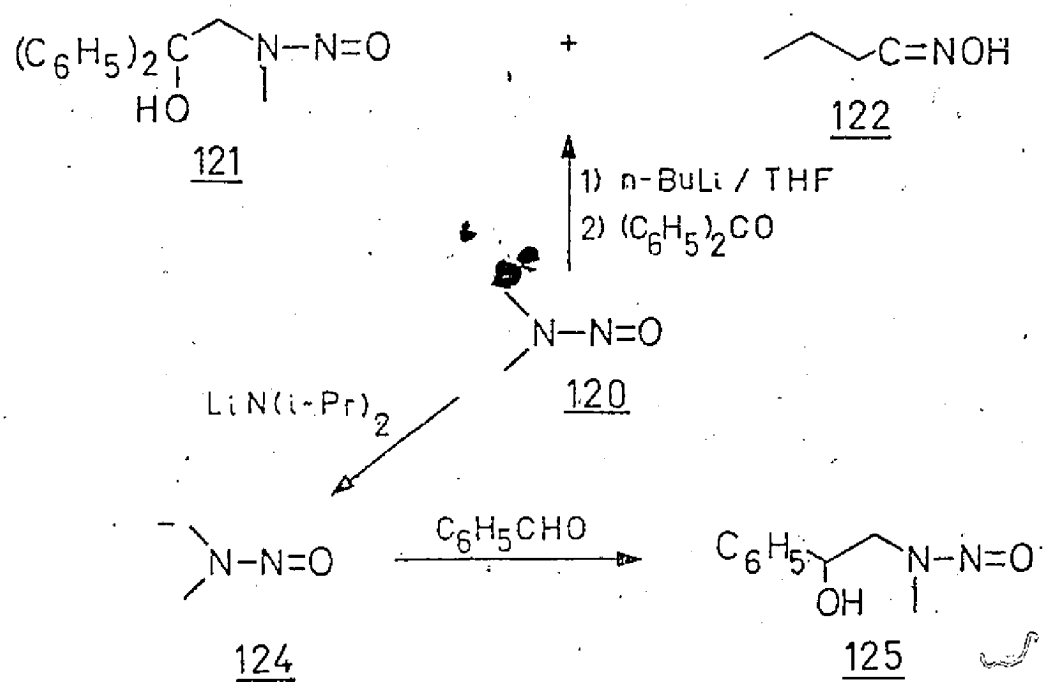
dimethylnitrosamine (120). The anion 124 could be formed by the addition of n-butyllithium to 120, as evidenced by its subsequent reaction with benzophenone, but the metalation competed with nucleophilic attack, and the product isolated (from sequential addition of n-butyllithium and benzophenone to 120) was a mixture of carbinol 121 and butanal oxime (122). However, when lithium diisopropylamide was employed as the base, very high yields of alkylated and aldol products could be obtained, indicating a very high conversion of the nitrosamine to its anion.

Scheme XII



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Hence it would appear that lithium diisopropylamide (93) might well obviate the difficulty encountered in the prior attempt to generate the dianion of β-ketoesters, (see part IV, for discussion of use of this base).

Lithium bis-(trimethylsilyl)amide (97) was briefly employed to form lithio ethyl acetate (91, R=H) from the ester.[60] However, it was necessary to use this base at very low temperature (-78°C), and whilst the yields of aldol condensation products from lithio ethyl acetate were good, it was subsequently found[58] that the use of this base could not be extended to form other ester enolates.

An investigation of various alkyl-substituted lithium amides, including lithium diisopropylamide, showed that lithium N-isopropylcyclohexylamide (94) was superior to the other bases in forming the enolate of ethyl hexanoate. The ester enolates, prepared by means of this base 94, were found to be unique in that they could be warmed to room temperature without undergoing substantial self-condensation, (if the reaction mixture derived from any of the other bases, including 93 or 97, was allowed to warm substantially above -78°C, a rapid and irreversible disappearance of the ester occurred, which was ascribed to self-condensation).

Quenching the solution with deuterium oxide under a variety of conditions, gave a maximum deuterium incorporation when lithium N-isopropylcyclohexylamide was employed, but the level of deuterium incorporation never exceeded seventy-five percent. This low level of incorporation was postulated to

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arise from an (unspecified) unusual protonation mechanism, and not from partial enolisation. The latter explanation was eliminated by the results of an additional experiment; the addition of excess ester to the base, which rapidly gave self-condensation products, showing that an equilibrium between the ester and the enolate was impossible. (Similar low deuterium incorporations have been reported by Creger,[61] when employing lithium diisopropylamide to form dilithio toluic acid salts). The lithio ethyl esters of substituted acetic acids could be alkylated, at room temperature, in good yield, but lithio ethyl acetate apparently undergoes self-condensation at a rate comparable to that of alkylation and it was found that t-butyl acetate was more satisfactory for alkylation.

The use of lithio enol esters, formed by the procedure of Rathke,[58] has been extended as a method of preparing α-iodo esters,[72] and of preparing symmetrically substituted succinate esters.[73] The latter conversion was achieved by the addition of copper (II) salts to a solution of the enolate, analogous, oxidative dimerisations of aldehyde and ketone enolates have also been reported.[74]

The Preparation and Alkylation of the Dianion of β-Ketoesters.

It is well known that a ketone may be protected from nucleophilic attack during a reaction by conversion to its enolate, for example, a selective conversion of the ester functionality of β-ketoester 126 to an alcohol was achieved by sequential treatment of 126 with sodium hydride and excess

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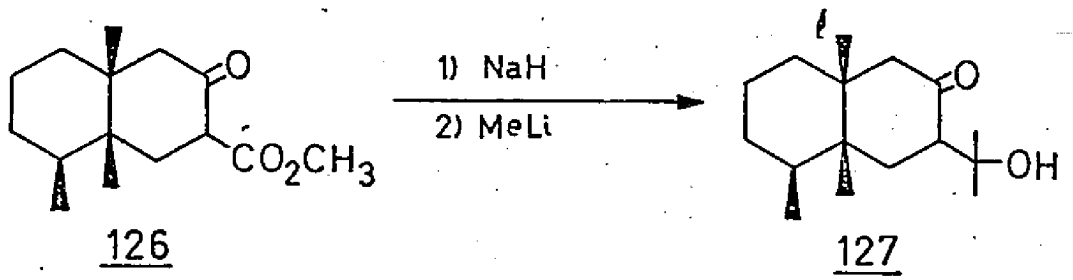
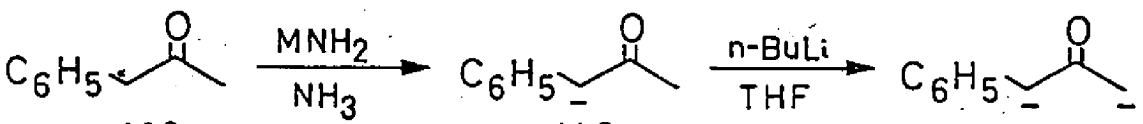
methyllithium.[75]



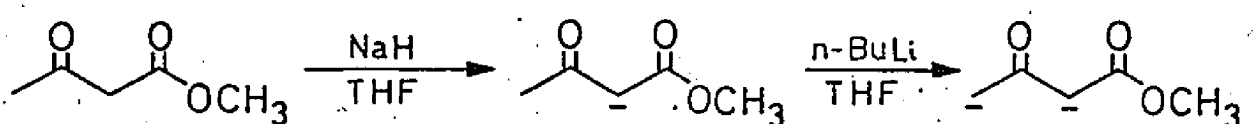
126 127 (27)

Similarly, Hauser has prevented condensation of β-ketoaldehydes with ammonia by preforming their sodium salts.[22,24,35] The formation of the dianion of these ketoaldehydes must perforce proceed via the monoanion. Also, the dianion of phenylpropanone (130) has been prepared via the monoanion 129.[76]



128 129 130 (28)

Hence it was expected that metalation of the monoanion of methyl acetoacetate (131) would give the dianion 132, and it was found[78] that treatment of methyl acetoacetate (16) with sodium hydride and n-butyllithium did produce the dianion 132.



16 131 132 (29)

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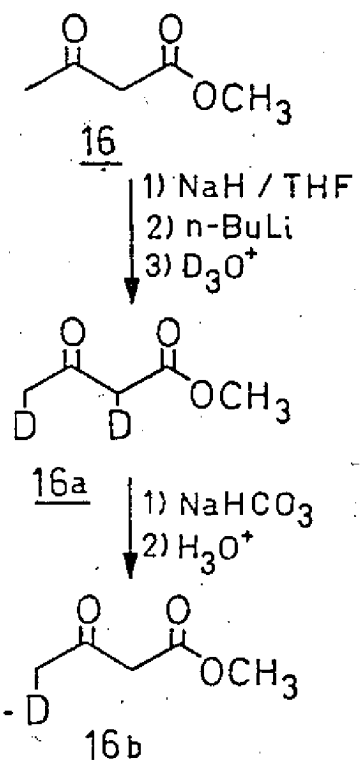
Formation of the dianion was confirmed by quenching the reaction with a solution of deuterated trifluoroacetic acid in deuterium oxide, which gave incorporation of deuterium at both the α and γ positions. The deuterium at the former position was removed by extraction of the isolated product into a solution of sodium hydrogen carbonate, followed by acidification and re-isolation of the β-ketoester. After this treatment, it was found, by nmr and mass spectroscopy, that the methyl acetoacetate contained 0.96 ± 0.03 deuterium atoms per molecule and this deuterium was located only in the γ position.



The dianion 132 could be monoalkylated in the γ position rapidly and in high yield at 0°C (Table VI), but

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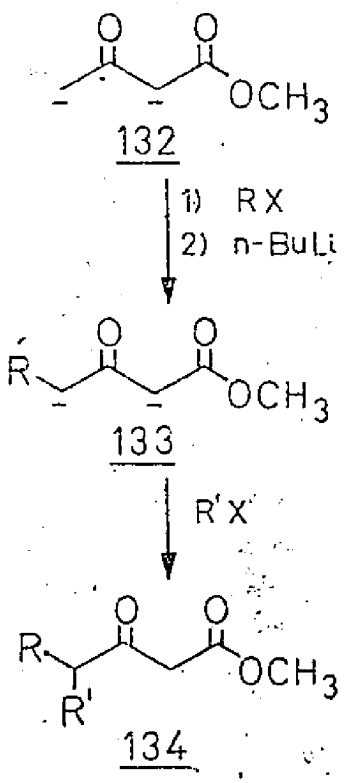
at lower temperatures the rate of alkylation decreased sharply (indicating one of the reasons for the low yields obtained by the liquid ammonia - amide method). The nmr and mass spectra of the isolated, alkylated products indicated that reaction had occurred exclusively at the γ position, and furthermore, nmr spectral analysis of the crude reaction mixtures failed to show any evidence for dialkylated or O-alkylated products.

This procedure also permitted alkylation of substituted β-ketoesters. Thus it was possible, starting with methylacetoacetate (16) to generate the dianion 132, alkylate, generate the dianion of this alkylated ketoester 133 by addition of a second equivalent of n-butyllithium and alkylate a second time with a different alkylating agent to give a γ,γ-disubstituted β-ketoester 134.



(30)

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However, it was found that higher yields were obtained if the intermediate monoalkylated product was isolated and purified prior to performing the second alkylation (Table VI).

This procedure is not limited to methyl esters, the dianion of ethyl acetoacetate (82) was alkylated with 3-chloropropene to give ethyl 3-oxohept-6-enoate in 77% yield. The presence of an α alkyl substitutent does not appear to affect the reaction, ethyl 2-ethylacetoacetate has also been alkylated in good yield,[52] (see also part IV for the alkylation of methyl 2-oxocyclohexanecarboxylate).

Much effort has been expended in optimising conditions for the preparation of β-ketoesters by a variety of methods, but nearly all the previously employed methods of preparing simple γ substituted β-ketoesters suffer disadvantages.[79] For instance, the Claisen condensation of an ester with ethyl acetate, except in a few instances, usually gives four products, two self-condensation and two mixed condensation products which are often difficult to separate. Whilst the acylation of methyl ketones with dimethyl carbonate occasionally gives substitution at the methylene position rather than the methyl group.

The alkylation of the dianion of β-ketoesters appears to be a superior method of preparing γ substituted ketoesters, and comparison of Tables I and VI indicates very clearly that, of the two procedures for alkylating the dianion, the sodium hydride - n-butyllithium method gives the better yield.

The γ-alkylation of β-ketoesters using the sodium

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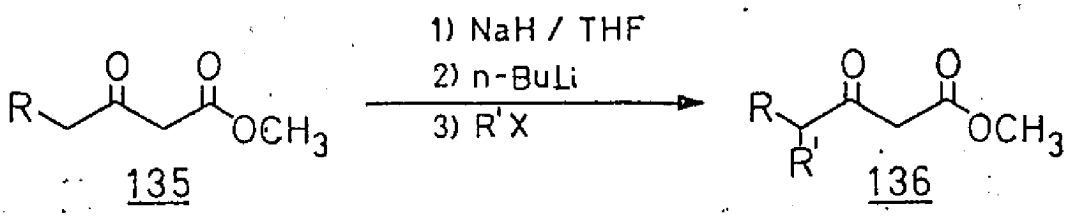
Table VI.

Alkylation of Sodio Lithio Methyl Acetoacetate in Tetrahydrofuran.[78]



(31)

R	R'	X	Yield(%)
H	CH_3	I	81
H	C_2H_5	Br	84
H	$(CH_3)_2CH$	I	73
H	$n-C_4H_9$	Br	72
H	$CH_2=CHCH_2$	Br	83
H	$C_6H_5CH_2$	Cl	81
$n-C_4H_9$	$CH_2=CHCH_2$	Br	77
$n-C_4H_9$	$C_6H_5CH_2$	Cl	62 (48)[a]
CH_3	$C_6H_5CH_2$	Cl	76
$C_6H_5CH_2$	CH_3	I	86

Note: a) the yield in parentheses refers to that obtained by successive alkylation of methyl acetoacetate with n-butyl bromide and benzyl chloride, without isolation of the intermediate monoalkylated product.

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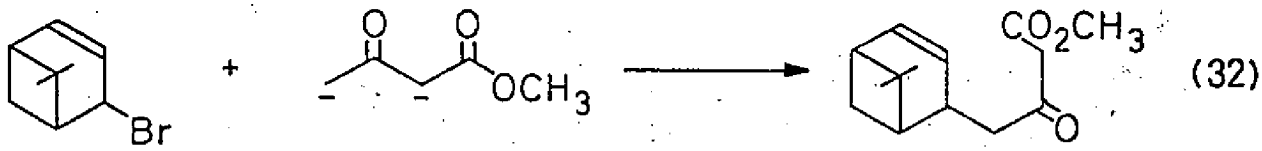
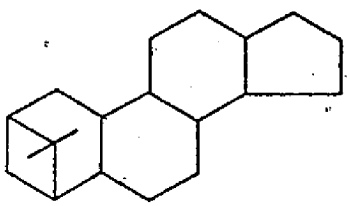
hydride - n-butyllithium procedure has recently been applied to the synthesis of 4-substituted apopinene derivatives. Trans-4-bromoapopinene (137) was successfully converted by this method to ketoester 138 which is a key intermediate in the synthesis of polycyclic compounds of type 139.[112]



137 132 138 (32)



139

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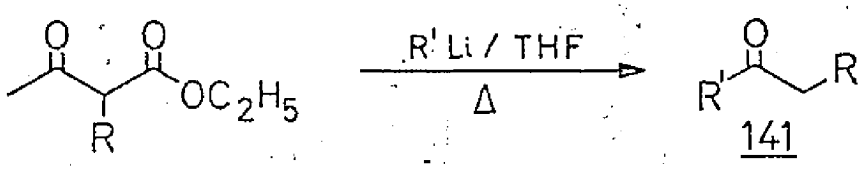
RESULTS AND DISCUSSION.

The aims, at the commencement of this work, were to explore the possibility of functionalising β-ketoesters at the γ carbon atom, and investigate the scope of the reactions of the dianion of β-ketoesters. In particular, it was desired to develop the aldol and Claisen reactions of the dianion, as possible synthetic routes to acetogenins.

The Reaction of Alkyllithium Compounds with Sodio Methyl Acetoacetate.

However, a recent report[80] has indicated that the treatment of β-ketoesters with excess alkyllithium reagents at elevated temperatures lead to cleavage of the ester functionality from the molecule resulting in the formation of ketones.



140 141 (33)

Although it had been clearly demonstrated[78] that the action of n-butyllithium on the monoanion of methyl acetoacetate (131) formed the dianion 132, it was felt advisable to reinvestigate this reaction using other alkyllithium reagents, in case the reaction of n-butyllithium was fortuitously anamolous. Hence the monoanion of methyl acetoacetate was prepared by the reaction of sodium hydride

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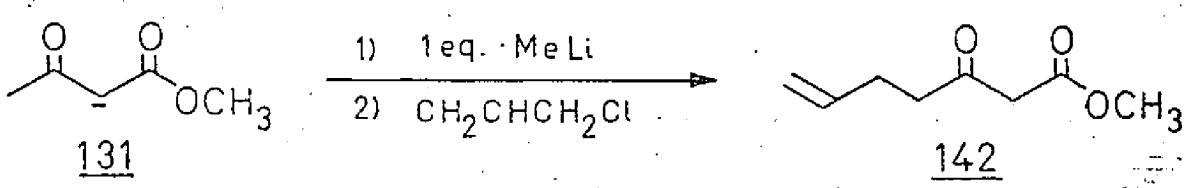
with the β-ketoester at 0°C and treated with methyllithium. Methyllithium was selected because of its known tendency to undergo nucleophilic additions.[81] When sodio methyl acetoacetate (131) was treated with one equivalent of methyllithium the dianion 132 was formed, as evidenced by its subsequent alkylation with 3-chloropropene. The product from this alkylation was shown to be methyl 3-oxohept-6-enoate (142) by glpc comparison with authentic material, but the yield of the alkylated ketoester 142 was slightly lower than that obtained using n-butyllithium.[78] No evidence for addition products of methyllithium to the ketoester could be detected by glpc, and hence the lower yield was ascribed to the technical difficulty of handling the more reactive methyllithium.



131 142 (34)

However, addition of more than one equivalent of methyllithium to 131 did result in nucleophilic attack on the carbonyl of the ester. When two equivalents of methyllithium were allowed to react with 131 for a slightly longer period of time (30 min) than usually allowed during alkylation reactions (10 min), and the reaction quenched with acid, the major product was found to be pentane-2,4-dione (5) contaminated with some methyl acetoacetate and diacetone

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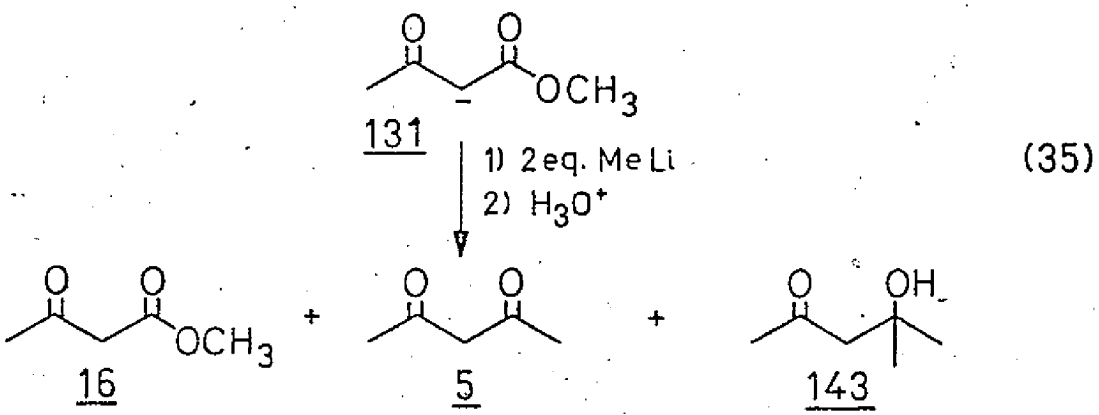
alcohol (143). The relative amounts of the products were determined by glpc analysis, using commerically available pentane-2,4-dione and diacetone alcohol as standards, to be 90:5:5 for 5:16:143 respectively.



(35)

The presence of pentane-2,4-dione was further demonstrated by treatment of the crude product mixture with a solution of 2,4-dinitrophenylhydrazine and isolating, by crystallisation, the resulting hydrazone. The solid from this derivatisation reaction had a melting point of 207 - 209°C which is in good agreement with the literature[82] value of 209°C for the melting point of the 2,4-dinitrophenylhydrazone of pentane-2,4-dione. Furthermore, a mixed melting point of this material with a sample of the hydrazone of authentic pentane-2,4-dione showed no depression. The yield of pentane-2,4-dione, based on its derivative, was 80%, indicating that most of the starting material was accounted for.

Similarly, when a larger excess (3 equivalents) of methyllithium was added to sodio methyl acetoacetate (131)

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and the reaction quenched, the major product was found to be diacetone alcohol (143) with only a little pentanedione 5 and less than 0.1% (the minimum limit of detection) methyl acetoacetate present. The ratio of the products was found to be 96:4 (143:5), by glpc, and the yield of the diacetone alcohol, isolated as its 2,4-dinitrophenylhydrazone, was 82%. The melting point of this derivative was 201-203°C (literature[82] mp 203°C), and a mixed melting point with the 2,4-dinitrophenylhydrazone of authentic diacetone alcohol showed no depression.

When an even larger excess of methyllithium (6 equivalents) was employed, the reaction products showed no detectable pentane-2,4-dione or methyl acetoacetate but the yield of diacetone alcohol, again isolated as its hydrazone, was substantially lower (44%). Since glpc analysis of the crude reaction mixture failed to show significant amounts of any product other than the diacetone alcohol, the low yield could be explained by further nucleophilic attack of the methyllithium on the hydroxyketone 143 followed by fragmentation of the resulting diol.

The results of these experiments and others performed in our laboratory,[52,78] indicate that the addition of the first equivalent of an alkyllithium to the sodium salt of acetoacetic esters does indeed abstract a proton from the γ carbon atom, whilst the second and third equivalents appear to attack the ester functionality to give a diketone and a hydroxyketone respectively. The generality of this procedure

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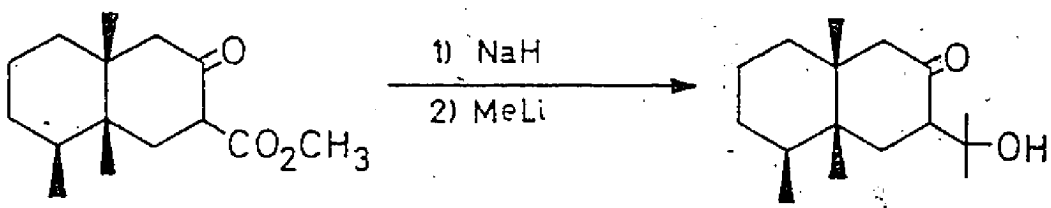
as a synthetic method of preparing β-diketones and β,β-dialkyl β-hydroxyketones has yet to be investigated. However, addition of alkyllithium in excess of three equivalents should be avoided, not only because of possible decomposition of the hydroxyketone, but excess alkyllithium reagents have been reported[83] to cleave ether solvents of the type used in these reactions.

These results are also in agreement with the reported conversion of β-ketoester 126 to 127,[75] and are not in dissent with those of Spencer.[80]



126 127 (27)

It was also felt that the generality of this method (sodium hydride - n-butyllithium) of generating the dianion would be enhanced if it could be shown to be applicable to cyclic β-ketoesters. Analogous dianions have been formed from cyclic β-diketones and β-ketoaldehydes by Hauser,[17,35b] using amide bases in liquid ammonia. Alkylation of the dianion derived from 2-acetylcyclohexanone (144, R=CH_3) was shown to occur at the exocyclic methyl group, whilst for the ketoaldehyde 144, R=H alkylation was observed at the C_3 position of the cyclohexane ring.

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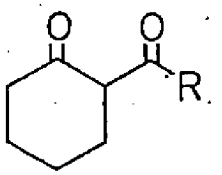
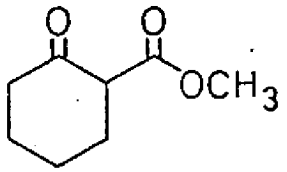


144



145

Accordingly, methyl 2-oxocyclohexanecarboxylate (145) was prepared in an analogous manner to the method of Rhoads,[84] and reacted sequentially with sodium hydride, n-butyllithium and 3-chloropropene. The product, isolated in 67% yield, was shown to be homogeneous by glpc and tlc analysis, and exhibited spectral properties consistent with the expected product, methyl 2-oxo-3-(prop-2-enyl)-cyclohexanecarboxylate (146).

Elemental analysis of this product was in agreement with the proposed structure, as was the molecular weight derived from the low resolution mass spectrum. Further evidence for the presence in the product of an allyl group were the characteristic absorptions in the nmr spectrum, centered at δ5.75 and δ4.93 ppm, typical of the vinyl protons of an allyl group.[86] The ir spectrum showed the product to exist as a mixture of enol and keto forms in chloroform solution. It would be unlikely that the product arising from α-alkylation (alkylation at C_1 of the cyclohexane ring), 147, would exist in the enol form to any substantial degree. The presence of an absorption in the ir spectrum at 1650 cm^{-1}, which would arise from an α,β-unsaturated carbonyl

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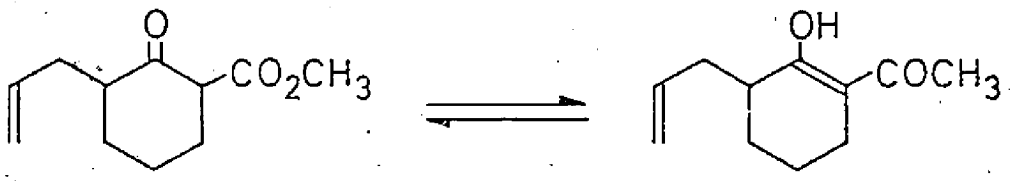
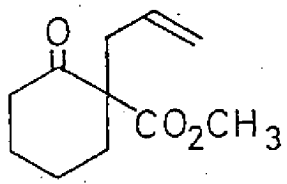
functionality, such as the ester carbonyl of enol 146b, excludes the possibility of α-alkylation.[87]



146a ⇌ 146b



147

Nor could the product be derived from alkylation upon oxygen, as there was an absorption, characteristic of a saturated ketone, at 1715 cm^{-1} in the ir spectrum of the product, and the nmr spectrum contained an absorption at δ14.23 ppm, arising from an enol hydrogen atom. Neither of these absorptions would be observed if O-alkylation had occurred.

It is highly unlikely that alkylation would take place at C_4, C_5 or C_6, and the products arising from these possibilities were excluded on the basis of an analysis of their probable nmr and mass spectra.

The reported[88] major fragmentation pathway of cyclohexanones involves α-cleavage, followed by proton

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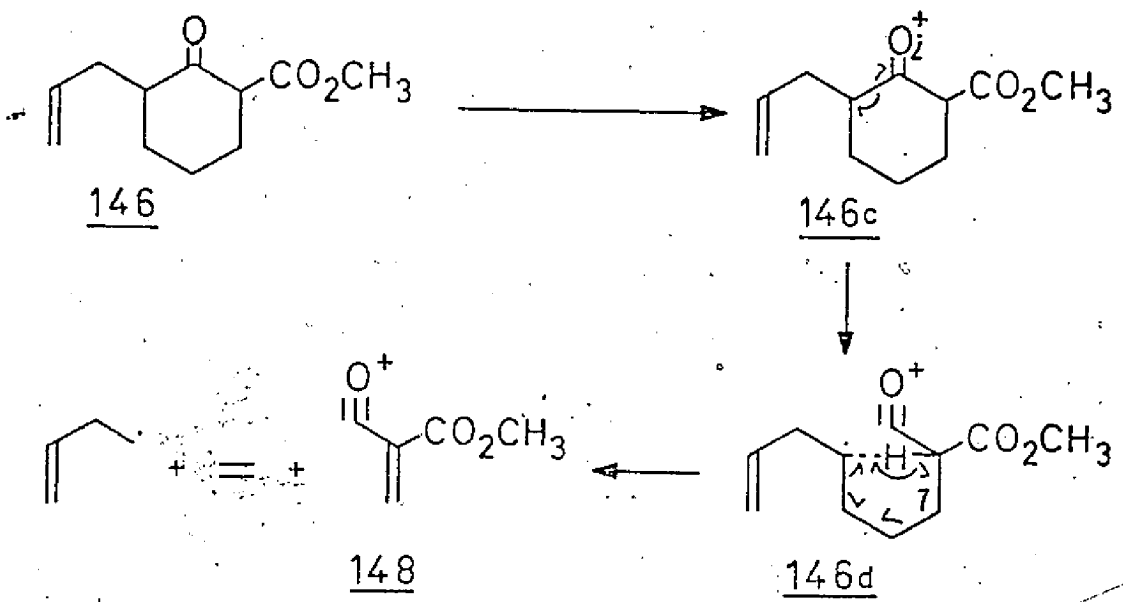
transfer from C_1 to C_3, loss of C_3 as a radical, and loss of C_4 and C_5 as a neutral ethylene moiety, for example scheme XIII.

Scheme XIII



This fragmentation pathway would only give a peak at 123 $\frac{m}{e}$, the base peak in the mass spectrum of the product, if the allyl group was on C_3, C_4 or C_5. The C_6 alkylated product would be expected to show a base peak at 163 $\frac{m}{e}$, and the product from the reaction shows no significant peak at this mass/charge value.

The nmr spectrum of the product is only consistent with a fully enolised β-ketoester in which alkylation occurred at C_3, and this is consistent with the results of Hauser[35b] for cyclic β-ketcaldehydes, and the results obtained in our

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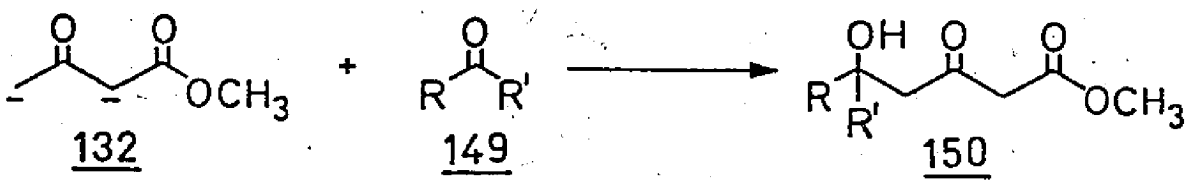
laboratory with acyclic β-ketoesters.[78]

Aldol Reactions of the Dianion of β-Ketoesters:

One of the initial aims in developing the sodium hydride - n-butyllithium method of generating the dianion of β-ketoesters was to functionalise the γ carbon atom, and in accordance with this initial aim an investigation of the aldol condensation of these dianions was initiated.

It was found that the dianion of methyl acetoacetate (132) reacted rapidly with a wide variety of aldehydes and ketones to give, as the only product, δ-hydroxy-β-ketoesters 150, equation 36. The results of this investigation are summarised in Table VII.



132 149 150 (36)

All the products from these aldol condensations showed spectral properties in accord with their assigned structures, and in view of the similarity between these products, the structural assignment will not be discussed in detail for each individual compound. The reactions summarised in Table VII may be divided into two broad classes; the condensations of aliphatic aldehydes and ketones, and those of the aromatic aldehydes and ketones. The evidence

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for the structural assignment of one representative product from each of these classes will be presented in detail, and the conclusions applied to the other members of the class.

The aldol condensation of propanal with dianion 132 is typical of the reactions of the aliphatic aldehydes and ketones, in that it gave a single distillable product. This product was found to be homogeneous by glpc and tlc analysis, and elemental analysis of the distilled material was in agreement with the proposed structure 150b, R'=C_2H_5, R"=H. The molecular weight, determined by mass spectroscopy, indicated the product was a one to one adduct of the aldehyde and ketoester. The ir spectrum of the product showed absorptions at 2500, 1740 and 1705 cm^{-1} indicating the presence in the molecule of a hydroxyl, a saturated ester and a saturated ketone respectively.[87]

Evidence that the condensation had occurred at the γ carbon atom was manifest in the nmr spectrum of the product, which showed an absorption at δ3.52 ppm in the form of a singlet, the integral value of which corresponded to two protons. This absorption was assigned to the methylene group at C_2 of 150b, by analogy to the nmr spectrum of methyl acetoacetate. (The latter compound shows only three signals in the nmr spectrum; δ3.74 (s, 3H, OCH_3), 3.48 (s, 2H, CH_2) and 2.27 ppm (s, 3H, CCH_3).) The absence of a three proton singlet at ca. δ2.3 ppm in the nmr spectrum of the product was further evidence that the condensation had occurred at the γ carbon atom.

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With some of the aromatic aldehydes and ketones, difficulty was encountered when attempts were made to purify the products by distillation. These products, 150e, f, g, m and n, were all liquids and they decomposed to some extent on distillation, and consequently were not obtained in sufficient purity for elemental analysis. These compounds were isolated by tlc or column chromatography, and their molecular formulae were determined by high resolution mass spectrometry. In addition to their spectral properties being in accord with their proposed structures, they were converted to their trimethylsilyl ether derivatives, and the spectral properties and composition of these derivatives scrutinised for consistency with the proposed structure.

Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n, R'=2-$CH_3OC_6H_4$, R"=CH_3) is representative of these thermally unstable products. The molecular formula of the product was established as $C_{14}H_{18}O_5$ by high resolution mass spectroscopy. The presence of the aromatic ring in the compound was demonstrated by bands in the ir spectrum of the product at ca. 1600 cm^{-1}, an absorption in the uv spectrum in the region of 270 nm[89] and a complex absorption in the nmr spectrum centred at δ7.2 ppm, all of which are characteristic of a 2-methoxyphenyl ring.

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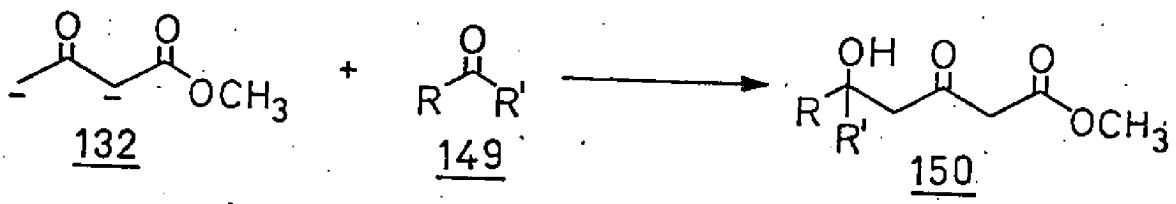
Table VII.

Aldol Reactions of Sodio Lithio Methyl Acetoacetate in Tetrahydrofuran



(36)

Product 150 identification letter	R'	R	Yield (%)
a	CH_3	H	26
b	CH_3CH_2	H	73
c	$CH_3(CH_2)_2CH_2$	H	36
d	$(CH_3)_3C$	H	82
e	C_6H_5	H	89
f	o-$CH_3OC_6H_4$	H	73
g	2,3-$(CH_3O)_2C_6H_3$	H	68
h	2-Furyl	H	68
i	CH_3	CH_3	70
j	CH_3CH_2	CH_3	56
k	$-(CH_2)_5-$		63
l	$-(CH_2)_4-$		25
m	C_6H_5	CH_3	77
n	o-$CH_3OC_6H_4$	CH_3	79
p	C_6H_5	C_6H_5	93

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The absorptions at 3500, 1740 and 1705 cm^{-1} in the ir spectrum of the product indicated, as previously the presence of hydroxyl, saturated ester and ketone functionalities in the molecule. The absence of an absorption at ca. δ2.3 ppm in the nmr spectrum of the product was taken as evidence for the aldol condensation to have occurred at the γ position. The expected two proton singlet at ca. δ3.5 ppm for the protons on C_2 of the proposed product was not observed in the nmr spectrum, and initially, this absence caused a little concern.

There was, however, a multiplet absorption centred at δ3.1 ppm and another multiplet at δ2.0 ppm, together these absorptions accounted for four protons. It was then realised that during the aldol condensation, with ketones 149 where R'≠R", and with all aldehydes, a chiral carbon atom (C_5) is introduced into the molecule. Since there no longer exists a plane of symmetry in the molecule (150, R'≠R"), the two protons on C_4 are no longer magnetically equivalent but are diastereotopic, and consequently the spin-spin splitting between them will become observable in the nmr spectrum. (Similarly, the protons on C_2 are diastereotopic.)

It is interesting to note that the mere presence of a chiral atom at C_5 is not sufficient for the splitting of the methylene protons at C_2 and C_4 to become observable. There must also be a considerable amount of steric crowding at C_5 for the assymetric environment to extend as far as C_2. Thus in the products derived from the aldehydes, no spin-spin

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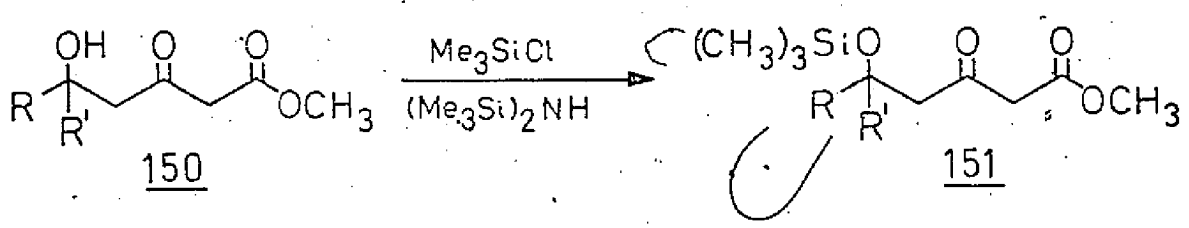
splitting is observed for the protons on C_2 (the splitting of the protons at C_4 is due to the presence of the proton on C_5). Similarly for the one compound derived from an aliphatic ketone, with a chiral centre at C_5 no splitting is observed for the protons at either C_2 or C_4. Only with the products derived from the aromatic ketones, and their silyl derivatives, do the protons at both C_2 and C_4 show spin-spin splitting. Similar long range effects of aromatic rings are well known.[88a]

The trimethylsilyl ether of the product from the reaction of o-methoxyacetophenone (149, R'=o-$CH_3OC_6H_4$, R=CH_3) and dianion 132 was prepared by the method of Sweeley.[91]



150 151 (37)

This derivative, as were all the trimethylsilyl ethers, was a colourless, distillable liquid, the homogeneity of which was checked by glpc and tlc analysis. Elemental analysis was in agreement with the proposed structure (157n, R'= o-$CH_3OC_6H_4$, R"=CH_3), and the molecular weight confirmed by mass spectroscopy. The major spectral changes accompanying this derivatisation were the expected ones; loss of the band at 3500 cm^{-1} in the ir spectrum, accompanied by the appearance of a band at 1075 cm^{-1}, this latter band being assigned to the trimethylsilyl ether functionality. The presence of a singlet at δ0.0 ppm in the nmr of spectrum and the loss of the absorption at δ4.10 ppm

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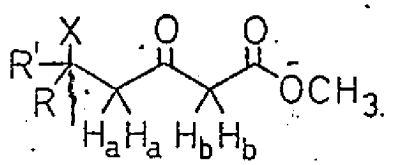
Table VIII.

Multiplicity of the nmr Absorptions of the α and γ Protons of some Substituted δ-Hydroxy-β-Ketoesters.



150. X=OH

151. X=OSi$(CH_3)_3$

Compound Identification X=OH, X=OSi$(CH_3)_3$	R'	R''	Multiplicity of Proton Resonance X=OH H_a	X=OH H_b	X=OSi$(CH_3)_3$ H_a	X=OSi$(CH_3)_3$ H_b
150a	CH_3	H	d	s	-	-
150b	CH_3CH_2	H	m[1]	s	-	-
150c	$CH_3(CH_2)_2$	H	m[1]	s	-	-
150d	$(CH_3)_3C$	H	m[1]	s	-	-
150e, 151e	C_6H_5	H	m[1]	s	m	s
150f, 151f	o-$CH_3OC_6H_4$	H	m[1]	s	m	s
150g, 151g	2,4-$(CH_3O)_2C_6H_3$	H	m[1]	s	m	s
150h	Furyl	H	m[1]	s	m	s
150j	CH_3CH_2	CH_3	s	s	s	s
150m, 151m	C_6H_5	CH_3	m	s	m	m
150n, 151n	o-$CH_3OC_6H_4$	CH_3	m	m	m	m

Note: Abbreviations for multiplicity, m=multiplet, s=singlet, d=doublet

1) Multiplicity is not just due to proton on C_5, splitting pattern is of form arising from ABX type three nuclei system[90]

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further confirmed the conversion of the alcohol to the trimethylsilyl ether. The remaining absorptions in the ir and nmr spectra of this derivative were essentially unchanged from those in the original reaction product. As a check to ensure no molecular rearrangement had occurred on derivatisation (none was apparent from a comparison of the spectra of 150n and 151n), the trimethylsilyl ether was subjected to hydrolysis in refluxing methanol, and the resulting alcohol compared with the original reaction product. These two compounds appeared identical in all respects (superimposible ir and nmr spectra and identical R_f in two tlc systems). Consequently, it was felt that the structure of the product from the aldol condensation was firmly established as 150n (R'=o-$CH_3OC_6H_4$; R"=CH_3).

No difficulty was encountered during isolation and purification of the products from the attempted aldol condensation of sodio lithio methyl acetoacetate (132) with 2-furfuraldehyde and benzophenone. The product from the former reaction was a distillable liquid, and the latter a crystalline solid. The significant spectral properties of these compounds were similar to those outlined for 150n, and elemental analysis and molecular weight determinations being in accord, the products were assigned structures 150h and 150p respectively.

From the results in Table VII, it is apparent that the sodium hydride - n-butyllithium procedure of generating the dianion 132 is applicable to the aldol reaction, and gives

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δ-hydroxy-β-ketoesters in reasonable yield.

The yield is low for products 150 a, c and 1, and this is probably due to proton transfer from the aldehyde or ketone to the dianion, as much methyl acetoacetate is recovered in these reactions. (The yields in Table VII do not allow for this recovery.) It is believed that these yields could be increased by variation of the reaction conditions, as no significant effort has been expended to optimise the yields. Similar difficulties involving proton transfer have been reported by Hauser[31,32] during the aldol condensation of β-diketones. (This work has already been discussed in part II.) It is possible, by analogy to the work of Hauser, that the use of dilithio salts would increase the yields of these reactions.

In order to make a more direct comparison with the amide - liquid ammonia conditions, the dianion of ethyl acetoacetate was prepared employing sodium hydride and n-butyllithium, and condensed with benzophenone. The product, isolated in 81% yield, exhibited spectral properties in accord with the expected structure, ethyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate (152), and had a melting point of 68 - 69°C, which agrees closely with the literature[23] value of 68.5 - 69.5°C for 152. A comparison of the yield obtained by Hauser, 50%,[23] to the above value indicates the superiority of the sodium hydride - n-butyllithium procedure.

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A brief study of the temperature dependence of the aldol condensation was made, employing the reaction of propanal with sodio lithio methyl acetoacetate (132) as a model.

At temperatures below 0°C, the reaction became very sluggish, and at -78°C only 11% of the desired product was obtained, and much methyl acetoacetate and propanal were recovered. At temperatures higher than 0°C, the yield also decreased, and at 25°C, the product was only isolated in 53% yield, and very little propanal was recovered. Presumably, at lower temperatures the rate of the aldol reaction slows sufficiently for proton transfer to become a major competing reaction, whilst at the higher temperature, the rate of self-condensation of the aldehyde becomes significant.

Attempts to make use of some of the newer non-nucleophilic bases (discussed in part III) had only minor success. When the dilithio salt of methyl acetoacetate was generated using two equivalents of lithium diisopropylamide (93), the base having been produced *in situ* by prior reaction of diisopropylamine and n-butyllithium, and condensed with propanal, a slightly lower yield (62%) of the δ-hydroxy-β-ketoester 150b was obtained. Whilst use of lithium bis-(trimethylsilyl)amide (97) did not appear to generate the dianion. No evidence of any product was obtained from an attempted aldol condensation of methyl acetoacetate and propanal when this base (97) was employed. At first this failure was attributed to the possibility that the base had not been generated, but analysis of this base, prepared by

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the method of Shaw,[92] by means of an acid-base titration indicated it to be essentially pure. Additionally, the boiling point of the pure base was very similar to the literature value, and in tetrahydrofuran solution, the base gave a purple colouration with 2,2-bipyridyl, which is indicative of the amide bases.[93] When 2,2-bipyridyl was employed as an indicator in the aldol reaction, the solution remained coloured throughout the reaction period, implying that there was still lithium amide present. From these results it was presumed that lithium bis-(trimethylsilyl)amide was not a sufficiently strong base to completely form the dianion. The lower basicity of lithium bis-(trimethylsilyl)amide as compared to other lithium dialkylamides is not exceptional; similar lower basicity for silylamines, as compared to their isostructural alkylamines, has been reported.[113] For example, trisilylamine exhibits no basic properties, whilst trimethylamine is a strong base. The lower basicity of these silylamines has been postulated to arise from the delocalisation of the lone pair of electrons of the nitrogen atom onto the silicon atoms, via $d\pi - p\pi$ bonding. A similar reason could be invoked to account for the apparent low base strength of lithium bis-(trimethylsilyl)amide.

It was also desired to investigate the possibility of converting the aldol products, for example 150, to unsaturated ketoesters. Accordingly, attempts were made employing the usual methods of dehydrating β-ketols. Phosphorus oxychloride in pyridine, p-toluenesulfonic acid in refluxing benzene and

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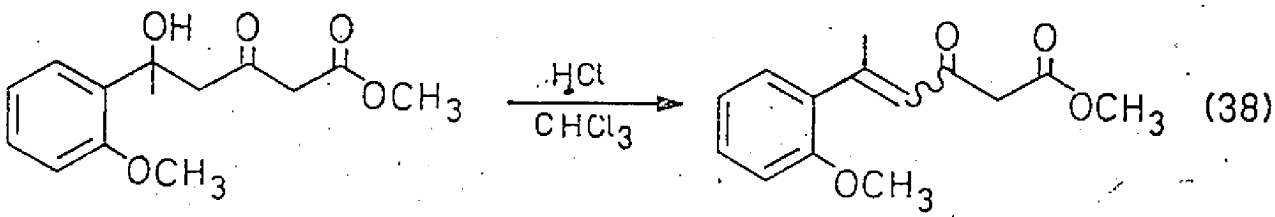
refluxing sulphuric acid (10% aqueous solution) were all tried, but these reagents led to complex mixtures of products. Eventually it was found that treatment of aldol product 150n with anhydrous hydrogen chloride in chloroform gave smooth conversion to the unsaturated ketoester 152.



(38)

150n 152

The formula of the product of this acid treatment was established by high resolution mass spectroscopy as $C_{14}H_{16}O_4$. The presence, in the ir spectrum of the product, of bands at 1740 and 1680 cm^{-1} implied that the molecule contained a saturated ester and an α,β-unsaturated ketone functionality. This data, coupled with the disappearance of the absorption at 3500 cm^{-1} of the starting material suggested strongly that the desired transformation had occurred. Confirmation of the structure of the product was supplied by the presence in the nmr spectrum of absorptions at δ6.20 and 6.10 ppm indicative of vinyl protons. The signal due to the methyl group on C_5 of the starting material also changed, from a sharp singlet to two doublets which appeared at δ2.43 and 2.12 ppm and were consistent with those arising from vinyl methyl groups. From a comparison of the nmr spectra of other styrenes (Table IX) and from the Pascual additivity rule, it

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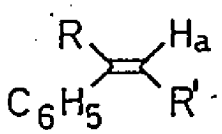
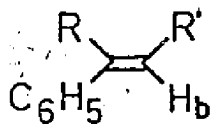
is apparent that in styrenes a proton which is cis to the aromatic ring appears at lower field in the nmr spectrum than a proton which is trans to the aromatic ring. Accordingly, the signal at δ6.20 ppm was assigned to the vinyl proton of the E isomer of 152, and hence the isomer ratio of the product was found to be 2.3:1, E:Z.

Table IX.

The Chemical Shifts of the β-Protons of Some Substituted Styrenes



195a



195b

Compound	R	R'	Chemical Shift of H_a	Chemical Shift of H_b
195	H	H	5.05	5.55
195	CH_3	H	5.08	5.28
195a	CH_3	CH_3	5.85	-
195b	CH_3	CH_3	-	6.15

Note: The chemical shifts are of solutions in carbon tetrachloride extrapolated to infinite dilution and are given in ppm on the δ scale, relative to TMS.[90]

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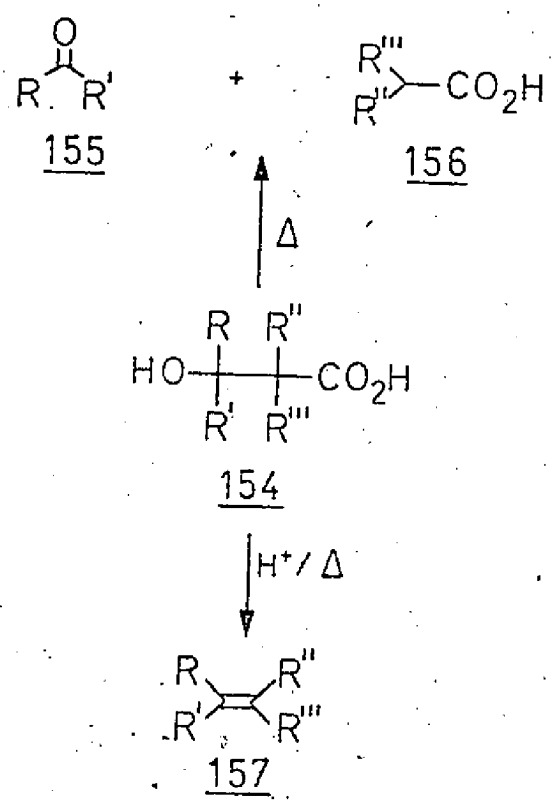
The ready thermal decomposition of most of the aldol products derived from aromatic aldehydes and ketones was, for some time, a subject of concern. Examination of the literature, however, showed several similar examples of the instability of aldol products.[63,94] Tetrasubstituted aldol products, for example 154, have been reported to undergo a retro-aldol reaction on heating, and in the presence of acid, lose water and carbon dioxide to give alkene 157.[63]

Scheme XIV



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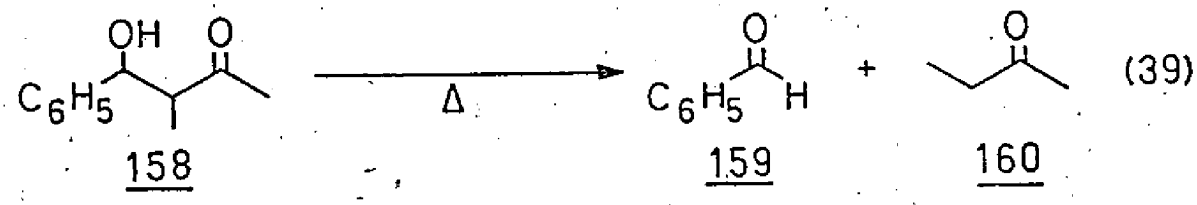
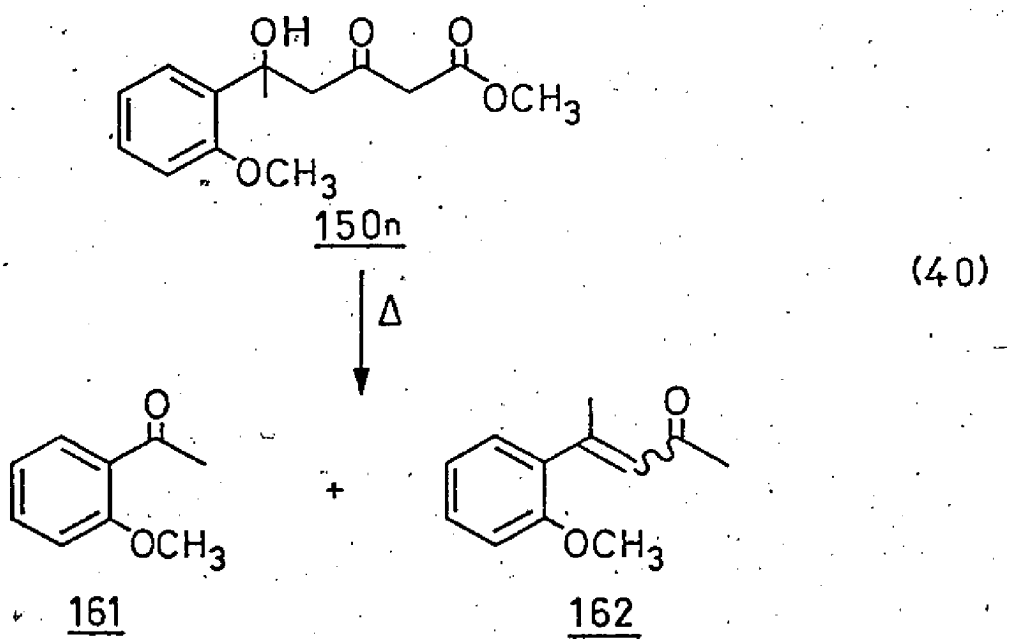
Less sterically crowded aldol products, for example β-ketol 158, have also been reported as undergoing a similar retro-aldol reaction. Particularly prone to decomposition are those β-hydroxy carbonyl compounds which also have a β-aromatic substituent.[94a]



158 159 160 (39)

An investigation of the decomposition products of one of the aldol products 150n, showed that both a retro-aldol reaction and a dehydration - decarboxymethylation were occurring.



150n (40)

161 162

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Distillation of 150n under high vacuum gave a colourless distillate, which was shown to be a mixture of three components by glpc analysis. The three components were identified as o-methoxyacetophenone and the two isomers of 4-(2-methoxyphenyl)-pent-3-en-2-one (162).

The first component was identified as 161 by comparison of its ir and nmr spectra and glpc retention time with authentic o-methoxyacetophenone. In addition, its melting point was very close to the literature[62] value for that of 161, and the melting point of a mixture of this component with authentic material was not depressed. Indications that the structures of the two other products were very similar was obtained from their ir and uv spectra; the latter being identical and the former differing only in the "fingerprint" region. The uv spectra of these compounds featured bands in the region 272 and 295 nm, indicative of a more extended conjugated system than a simple phenyl ring. The presence of an absorption at 1675 cm^{-1} in the ir spectra, indicative of an α,β-unsaturated ketone, and the absence of a band at ca. 3500 cm^{-1}, suggested dehydration had occurred. The molecular weight, established by mass spectroscopy, was found to be the same for both compounds, and implied the loss of the elements of water and ketene from the starting material 150n. The nmr spectrum of the major of these two components (the other product was not isolated in sufficient amounts to permit its nmr spectrum to be recorded) showed the presence of only one

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methoxy group, and together with the lack of an ester absorption in the ir spectrum, this suggested the structure of these compounds to be 162. Elemental analysis of these compounds was consistent with this proposed structure, and all other signals in the nmr spectrum were in accord with this structure. Additionally, the long range coupling of the resonances of the methoxy group and the vinyl hydrogen in the nmr spectrum of the major component permitted its identification as the Z isomer.

Attempts to condense formaldehyde with the dianion 132 did not lead to any identifiable product. A variety of conditions were employed in these attempts, but in all of these reactions, only intractable tars were obtained. This result is not unexceptional, as it has been reported[7,95] that nucleophilic additions to formaldehyde by enolates of carbonyl compounds, such as acetone and ethyl acetoacetate, often lead to polymeric materials.

Attempted Michael Reactions of the Dianion of β-Ketoesters.

Attempts were also made to add dianion 132 conjugately to α,β-unsaturated ketones in a Michael type reaction. However, addition of both methyl vinyl ketone and cyclohex-2-enone to a solution of sodio lithio methyl acetoacetate led only to the aldol products 163 and 164 respectively.

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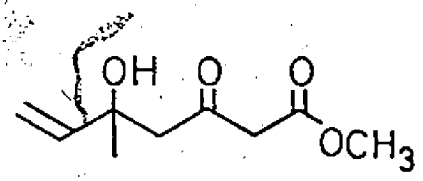
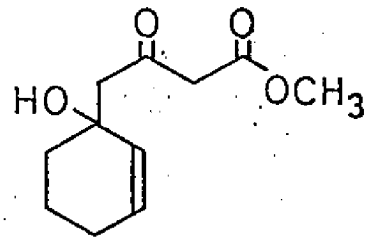


163



164

The presence of a band at ca. 3500 cm^{-1} in the ir spectra of both of these products was indicative of addition to the carbonyl of the unsaturated ketones, rather than the desired Michael reaction. The spectral properties of these products were consistent with their proposed structures, and these compounds were identified by similar criteria to the aldol products 150 previously described.

It has long been known that Michael additions of Grignard reagents are catalysed by copper (I) salts,[96] and more recently, dialkyl copper lithium reagents have been successfully added in a conjugate manner to α,β-unsaturated ketones.[97] Accordingly, in an attempt to promote a Michael reaction, anhydrous cuprous iodide was added to a solution of the dianion 132, prior to the addition of cyclohex-2-enone. Although it is believed some form of copper - dianion complex was obtained, as evidenced by the dissolution of the copper salt and formation of a brown solution, no products arising from a Michael reaction were isolated. A variety of stoichiometries of cuprous iodide to dianion 132 were employed, but all these reactions gave negative results.

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Since it had been reported[96] that the product from Michael reactions could be decomposed if direct addition of acid was employed in the work-up of the reaction, the cuprous iodide reaction was repeated and quenched by an inverse procedure in which the reaction mixture was added to dilute acid. (Formerly, concentrated acid had been directly injected into the reaction mixture.) From this procedure a new product was isolated, as well as the previously mentioned aldol product 164. This compound also showed a band in the ir spectrum at 3500 cm^{-1}, and so could not be a Michael reaction product. The molecular formula of this new compound was established by high resolution mass spectroscopy as $C_{11}H_{16}O_4$, the same as that of 164. The spectral properties of this new compound and 164 were similar in that their ir spectra indicated the presence of the same functional groups. However, a comparison of these ir spectra showed a significant difference in the region between 3000 and 4000 cm^{-1}. The "normal" aldol product 164, like all the previously prepared aldol products, showed only one broad absorption due to the hydroxyl functionality. Presumably because the compound exists exclusively in the form in which the hydroxyl group is strongly hydrogen bonded to the ketone. The new product showed two bands in this region, one sharp, assignable to non-hydrogen bonded hydroxyl, and the other broad band due to associated hydroxyl. This evidence suggested that the hydroxyl was no longer in a position where strong hydrogen bonding was possible. Inspection of the nmr spectra of this

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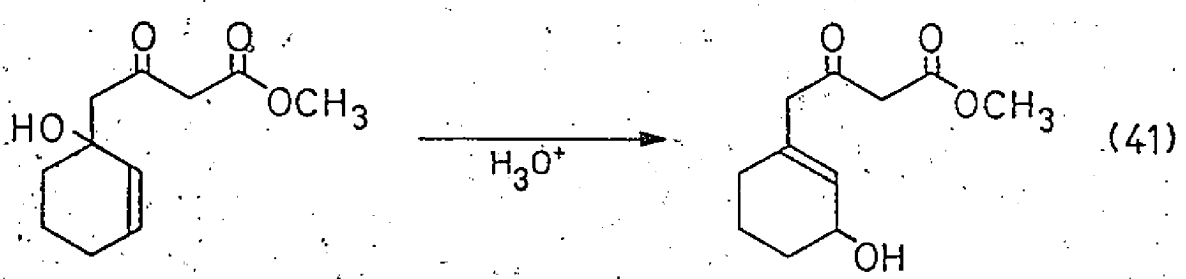
compound revealed a resonance at δ6.67 ppm corresponding to only one hydrogen atom, and no other signals which could be assigned to vinyl protons. Hence the double bond present in the molecule must be trisubstituted. One feasible reaction which would produce such a trisubstituted double bond is the allylic rearrangement of 164, equation 41.



(41)

164 165

The structure of the product 165 from this allylic rearrangement is in accord with all of the observed spectral properties of the new product, and hence this product was assigned structure 165. An additional experiment, in which the addition of cyclohex-2-enone to sodio lithio methyl acetoacetate was followed by the inverse quenching procedure, established the presence of cuprous iodide was not necessary for the formation of the allylically rearranged product.

The failure of these Michael reactions was attributed to the high reactivity of the dianion. Although similar Michael reactions, for example the addition of dipotassio butane-1,3-dione (30) to methyl cinnamate previously mentioned, do occur, it has been generally found that the more reactive the nucleophile employed, the less conjugate addition is observed.[98]

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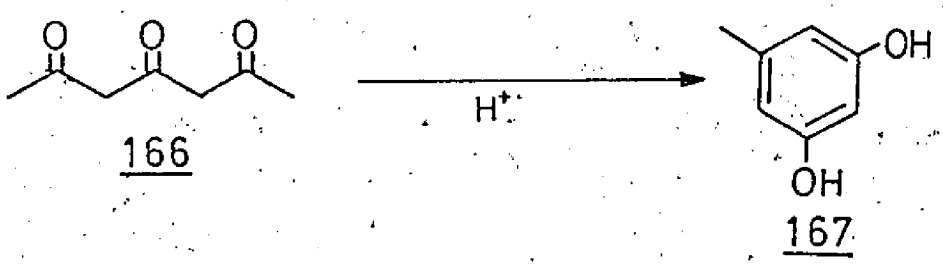
Claisen Condensations of The Dianion of β-Ketoesters.

It was also desired to investigate the possibility of acylating the dianion prepared by the sodium hydride - n-butyllithium procedure as a method of preparing tricarbonyl compounds. It has been previously mentioned that one of the main reasons for the interest in polycarbonyl compounds is their postulated intermediacy in the biosynthesis of phenolic compounds. As it is anticipated that some of the future applications of the acylations of polycarbonyl compounds may be directed towards biogenetic type synthesis of these acetogenins, a brief digression will be made to amplify this connection between polycarbonyl and phenolic compounds.

The initial report which indicated the polycarbonyl origin of some phenolic compounds was the observation, by Collie,[99] of the acid catalysed conversion of heptane-2,4,6-trione (166) to orcinol (167) and other dimeric products.



166 167 (42)

It was these observations, later confirmed by Birch[101] and Bethel,[102] which led to the formulation of the polyacetate

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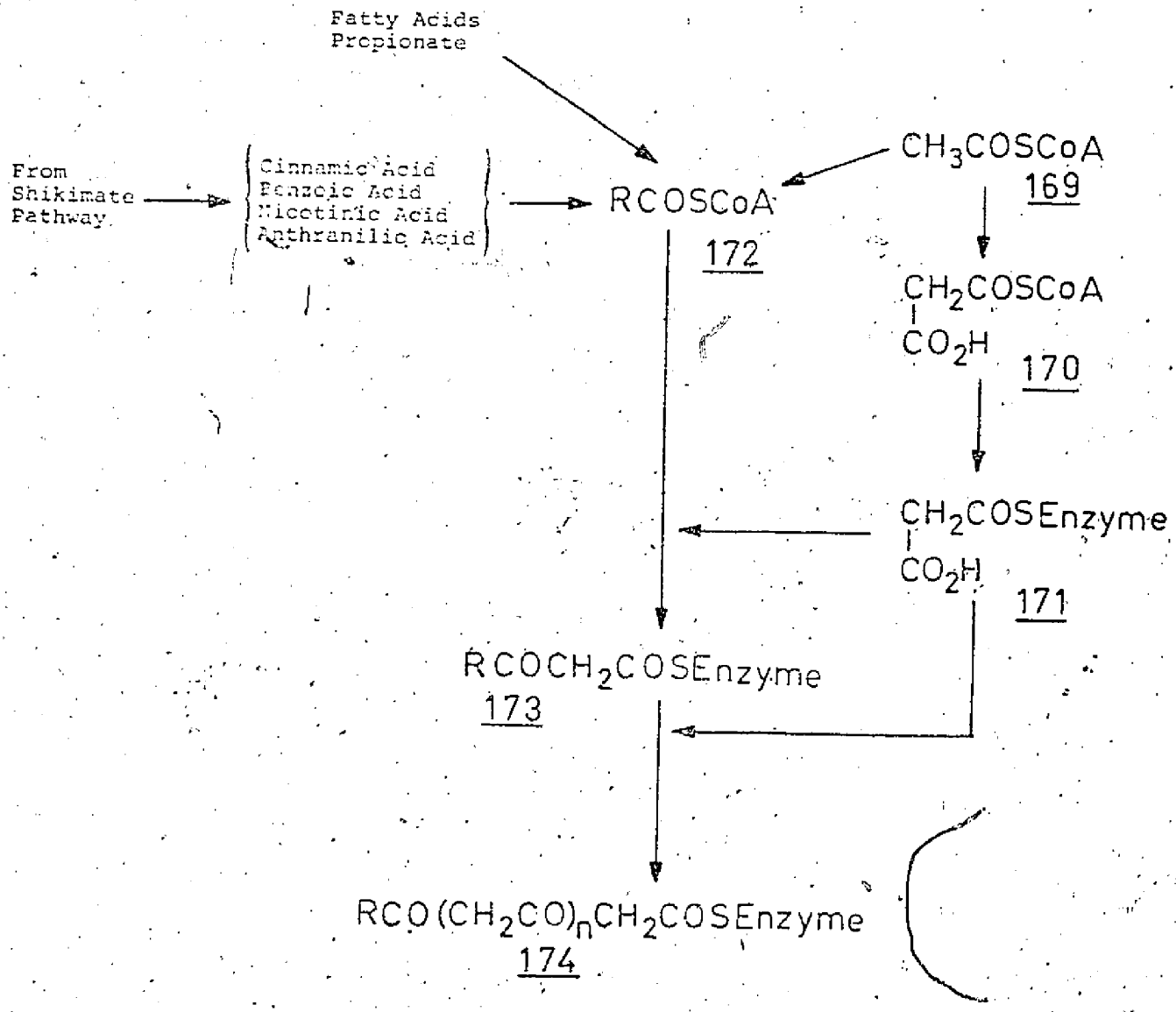
route to phenolic compounds.

The major biosynthetic pathway leading to phenolic compounds is now believed to be the acyl polymalonate route. This pathway has been described in detail in a number of reviews and is supported by a considerable amount of evidence.[103] The portion of this pathway which is relevant to the biosynthesis of phenolic compounds is outlined below, scheme XV.

Scheme XV



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The main steps in this sequence are the conversion of acetyl coenzyme A (169) to malonyl coenzyme A (170), which is essentially a carboxylation, followed by repeated condensation of malonyl coenzyme A units on to an α substituted acetyl coenzyme complex (172), the "starter" unit, and decarboxylation. This results in the formation of a linear polyacyl chain (174) which is then postulated to undergo intramolecular cyclisation to give phenolic compounds.

The laboratory synthesis of analogs of the polyacyl intermediate 174, n=2 has developed along two separate lines; the synthesis of protected carbonyl compounds employed by Money, Scott and coworkers,[104] and the direct synthesis of polycarbonyl compounds reported by Harris.[45,105] The observations of both of these groups indicate that the conversion of these analogs to phenolic compounds is possible. The literature pertaining to these biogenetic type conversions has recently been reviewed.[106]

In the initial attempts to acylate sodio lithio methyl acetoacetate, only one half equivalent of acylating agent was employed, since it was realised that due to the quenching of the dianion by the initial product via proton transfer (previously discussed in part II), a larger amount of this reagent would be an excess. It was found that the reaction of dianion 132 with acyl halides was violently exothermic, and even when performed at very low temperature (-78°C), the reaction gave a complex mixture of products. Accordingly, less reactive acylating agents were investigated,

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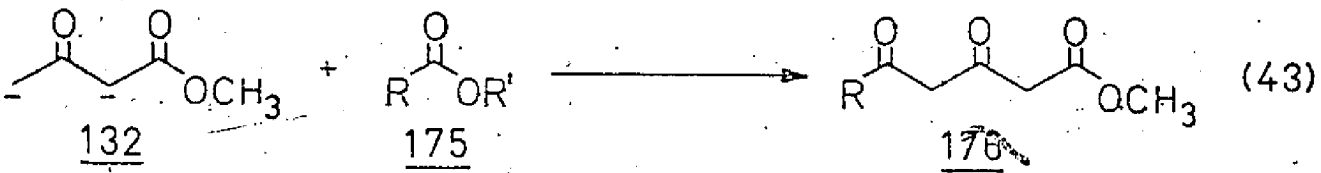
and it was found that the reaction of dianion 132 with esters proceeded smoothly at 0°C to give the desired diketoester, equation 43.



132 175 176 (43)

This procedure, although affording a simple synthesis of diketoesters, was not entirely satisfactory, as the yield of the Claisen condensation product, based on the starting ketoester were low. For example, condensation of methyl acetate (175, R=CH_3, R'=CH_3) with dianion 132, gave only 37% conversion of the ketoester.

Attempts to overcome this difficulty be employing an additional equivalent of base in the reaction were not successful, as any base strong enough to form the dianion was also sufficiently nucleophilic to attack the ester. Even use of the non-nucleophilic bases, lithium diisopropylamide (93) and lithium N-isopropylcyclohexylamide (94), did not obviate this difficulty. In a series of experiments, in which dilithio methyl acetoacetate was prepared by the addition of the ketoester 16 to three equivalents of lithium diisopropylamide, no evidence of reaction was observed from the condensation of methyl acetate and the dianion. Whilst with methyl benzoate,

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again using lithium diisopropylamide as base, the major product isolated was N,N-diisopropylbenzamide. This latter compound exhibited spectral properties in accord with the assigned structure and possessed a melting point that was in agreement with the literature value for diisopropylbenzamide. Similar experiments in this series, using lithium N-isopropylcyclohexylamide were slightly more promising, giving small amounts of the desired diketoester, 4 and 8% from the methyl esters of acetic and benzoic acids respectively. However, again with the aromatic ester, substantial amounts of the corresponding benzamide were obtained. This N-isopropylcyclohexylbenzamide (196) was characterized by its unexceptional spectral properties, and by high resolution mass spectroscopy. The formation of these carboxamides is not without precedent, similar reactions of non-enolisable esters with lithium amides have been reported as a convenient method for the preparation of carboxamides.[107]

It was then envisaged that the degree of the conversion of dianion 131 to the diketoester could be raised, if, after the addition of half an equivalent of the ester, the dianion was regenerated by addition of more base before adding further ester. The stoichiometry of the Claisen condensation of dianions, for example 132, demands that three equivalents of base are needed if complete conversion of the dianion to product is to be obtained. But, after addition of one half equivalent of ester, only one half of an

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equivalent of base is needed to completely regenerate the dianion. Such an addition, of half an equivalent of base, would raise the maximum theoretical yield to 75%, whereupon addition of one quarter of an equivalent of base would regenerate the dianion completely. Whilst it is possible that alternate additions of ester and base in ever decreasing amounts would eventually give complete conversion of the dianion to diketoester, such a procedure would be very tedious and time consuming. It was found that generation of dianion 132, by the sodium hydride - n-butyllithium procedure, followed sequentially by addition of one half equivalent of ester, a second half equivalent of base, and finally by a further half equivalent of ester, did give yields in excess of 50%. For example, the condensation of methyl acetate with dianion 132 gave a 56% yield of product by this method.

It was adventitiously discovered that addition of a full equivalent of base, after addition of the first portion of ester, gave even higher yields, and the most convenient procedure which provided the maximum conversion was established as: generation of the dianion by the sodium hydride - n-butyllithium procedure, addition of one half equivalent of ester, addition of one full equivalent of n-butyllithium and finally, addition of the remaining half equivalent of ester. In this manner it was possible to condense methyl acetate with methyl acetoacetate to give methyl 3,5-dioxohexanoate (176, R=CH_3) in 71% yield.

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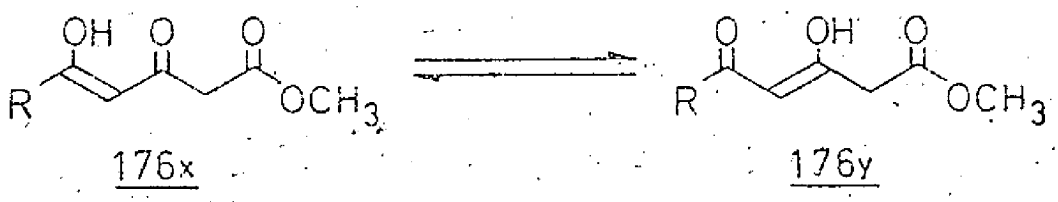
The product from this reaction was characterised by an elemental analysis which was consistent with the assigned structure. The molecular weight, determined by mass spectroscopy, indicated the product was a monoacylated derivative of methyl acetoacetate, and the ir spectrum of the product exhibited a broad band at 1600 cm^{-1} indicative of the enol form of a β-diketone functionality. The presence in the nmr spectrum of a two proton singlet at δ3.57 ppm, assignable to a methylene group bearing two carbonyl groups, excluded the possibility of the product being derived from α acylation. The remaining signals in the nmr spectrum were in accord with the proposed structure and indicated that the compound existed in solution mainly as the enol form 176x or 176y.



176x ⇌ 176y (44)

This procedure was applied to the Claisen condensation of methyl acetoacetate with several other esters and the results of these investigations are summarised below, Table X.

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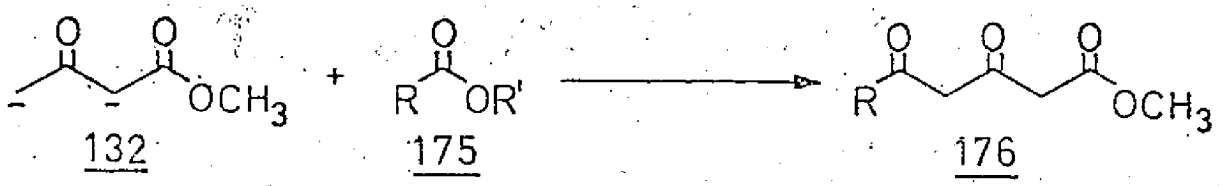
Table X.

Claisen Condensations of Sodio Lithio Methyl Acetoacetate.



132 175 176 (43)

Compound Identification	R	R'	Yield (%)
176a	CH_3	CH_3	71
176b	H	CH_3	69
176c	$CH_3CH_2CH_2$	CH_3	67
176c	$CH_3CH_2CH_2$	CH_3CH_2	33 (11)[1]
176d	C_6H_5	CH_3	37 (30)[2]
176e	p-$CH_3OC_6H_4$	CH_3	42 (29)[2]

Note: [1] Yield in parentheses refers to ethyl 3,5-dioxooctanoate (177) also isolated from the reaction.
[2] Yields in parentheses refers to the diketoacids 178, also isolated from the reaction.

The product 176b arising from the Claisen condensation of methyl formate and dianion 132 decomposed on all attempts to purify it by distillation and was consequently never obtained in analytical purity. The molecular formula of this compound was established by high resolution mass spectroscopy, and it exhibited spectral properties in accord with its

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assigned structure. All other diketoesters were fully characterised employing the criteria previously outlined for methyl dioxohexanoate 176a.

When the Claisen condensation of dianion 132 with ethyl butanoate was performed, the product isolated was a mixture of methyl and ethyl esters of 3,5-dioxooctanoic acid, the latter arising from transesterification during the reaction. The two esters were separable only with difficulty, and to avoid this complication all subsequent reactions were performed with methyl esters.

It was found that the yield of the diketoesters from the condensation of aromatic esters with dianion 132 were low. Reinvestigation of the crude product from these reactions revealed one additional product in each reaction. These additional products were soluble in sodium hydrogen carbonate solution, and their ir spectra exhibited a very broad absorption in the region 3500 to 3000 cm^{-1}. Both of these data were indicative of carboxylic acids. Both of these additional products, (one from each aromatic ester investigated) were solids. After recrystallisation the product from the reaction of methyl benzoate possessed a melting point very similar to that reported by Hauser[23] for 3,5-dioxo-5-phenylpentanoic acid (178d, R=H). All the spectral properties of this product were consistent with the structure 178d. Similarly the spectral properties of the product, derived from the reaction of the dianion with methyl p-anisate

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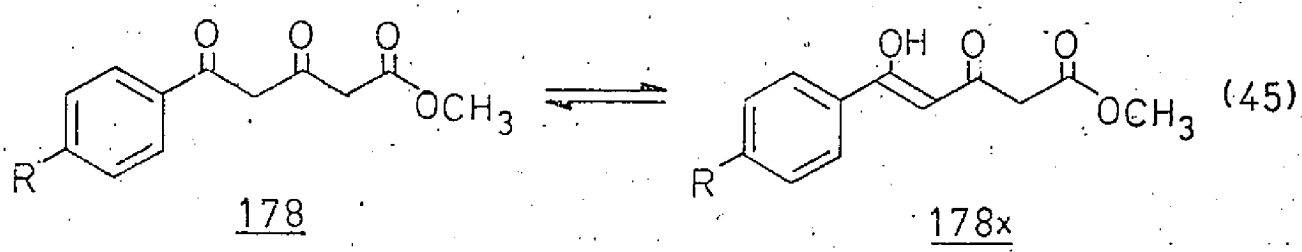
(175, R=$CH_3OC_6H_4$), were in accord with the structure 178e, R=OCH_3. In addition, elemental analysis and molecular weight determination of this latter product were also consistent with this structure.



178 ⇌ 178x (45)

A re-examination of the crude reaction products from all the above Claisen condensations showed that the formation of diketoacids was a phenomenon produced only when aromatic esters were used. It is interesting to note that from the aroylation of ethyl acetoacetate with methyl benzoate employing sodium hydride in refluxing 1,2-dimethoxyethane, Hauser reports only the isolation of the diketoacid.[24] The mechanism of the hydrolysis, in both the work of Hauser and that reported here, remains obscure.

One interesting acylation that has recently been reported is the condensation of enolate anions of β-ketoesters with very powerful nucleophiles, such as di- and tri-anions.[108] For example, it was possible to condense the dianion of 1-phenylbutane-1,3-dione (29) with the monoanion of ethyl benzoylacetate (179) and with the monoanion of ethyl acetoacetate (3), to produce tetraketones 180 and 181 respectively.

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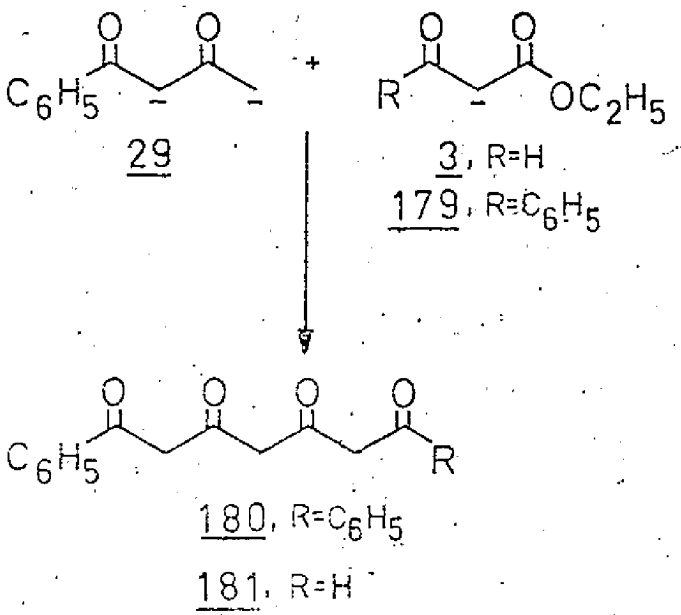

29 + 3, R=H; 179, R=C_6H_5 → 180, R=C_6H_5; 181, R=H (46)

Possible mechanisms for this reaction involve either direct condensation of the monoanion of the ketoester with the dianion, such a reaction would have a considerable electrostatic barrier to overcome, or elimination of ethoxide from the ketoester and condensation of the resulting acylketene with the dianion. This latter mechanism has considerable support from studies of the hydrolysis of β-ketoesters where evidence of the intermediacy of acylketenes has been found.[109]

It has been found that a similar acylation of methyl acetoacetate may be achieved. If, upon generation of the dianion of methyl acetoacetate, only one half equivalent of n-butyllithium is added, and the reaction left at room

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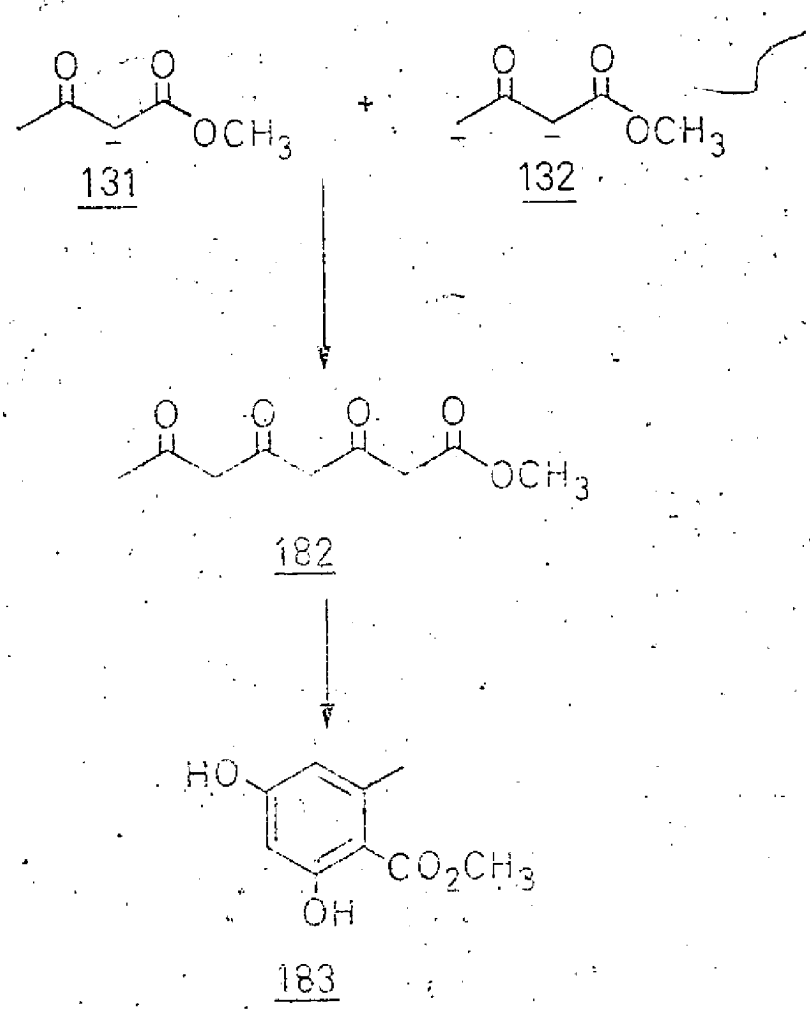
temperature for a considerable time (five days) before quenching, the methyl acetoacetate undergoes self-condensation and a significant amount of methyl orsellinate (183) is obtained. The reaction time may be considerably shortened by raising the temperature, but as yet the maximum yield obtained is only 24%.

Scheme XVI



The product was characterised as methyl orsellinate by comparison of its ir and nmr spectra with those of an authentic sample,[110] and, in addition, a mixed melting

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point with the authentic material was undepressed. It was also possible to isolate the intermediate triketoester 182 by quenching the reaction very carefully. The optimum procedure for this quenching process appears to be an inverse addition of the reaction to mixture of phosphate buffer (pH 6.5) and ether. Chromatography permitted the separation of an unstable oil, whose spectral properties were consistent with triketoester 182, but this product was not sufficiently stable to permit elemental analysis, nor did it show a parent peak in the mass spectrum corresponding to 182. This compound underwent spontaneous conversion to methyl orsellinate on standing at 0°C for twelve hours.

The nmr spectra of all the acylated β-ketoesters indicated that they existed, in solution at least, with the β-diketone functionality mainly in the enol form, i.e. 176x or 176y, 178x and 182x or 182y. The nmr spectra did not permit distinction to be made between the enol forms of type 176x and 176y or 182x and 182y, but in the products from aromatic esters the enol forms where the enol double bond is in conjugation with the aromatic ring (176x and 178x) should be substantially favoured over the other possible enol. The enol content of these acylation products is considerably higher than that of the aldol products which exist mainly in the keto form (as determined by nmr spectroscopy), and this is to be expected as it is widely known that β-diketones exist in the enol form to a far greater extent than β-ketoesters.[98a]

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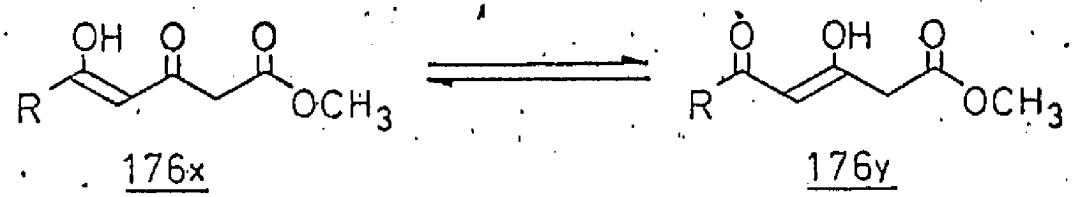
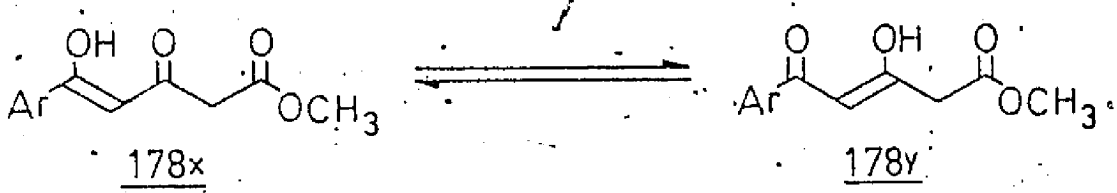
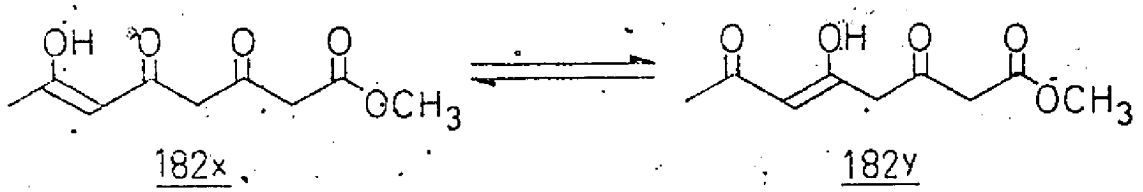


176x 176y (44)



178x 178y (45)



182x 182y (47)

Alkylation of the Dianion of β-Ketoesters with Dihaloalkanes.

The alkylation of sodio lithio methyl acetoacetate with dihaloalkanes was also investigated. In such reactions there is a possibility of two products being formed, depending upon the mode of reaction of the initially formed, halogen containing product 185. This intermediate may either undergo an intramolecular reaction to give a cyclic β-ketoester (186), or may alkylate a second molecule of dianion 132, producing a bis-β-ketoester (187), scheme XVII.

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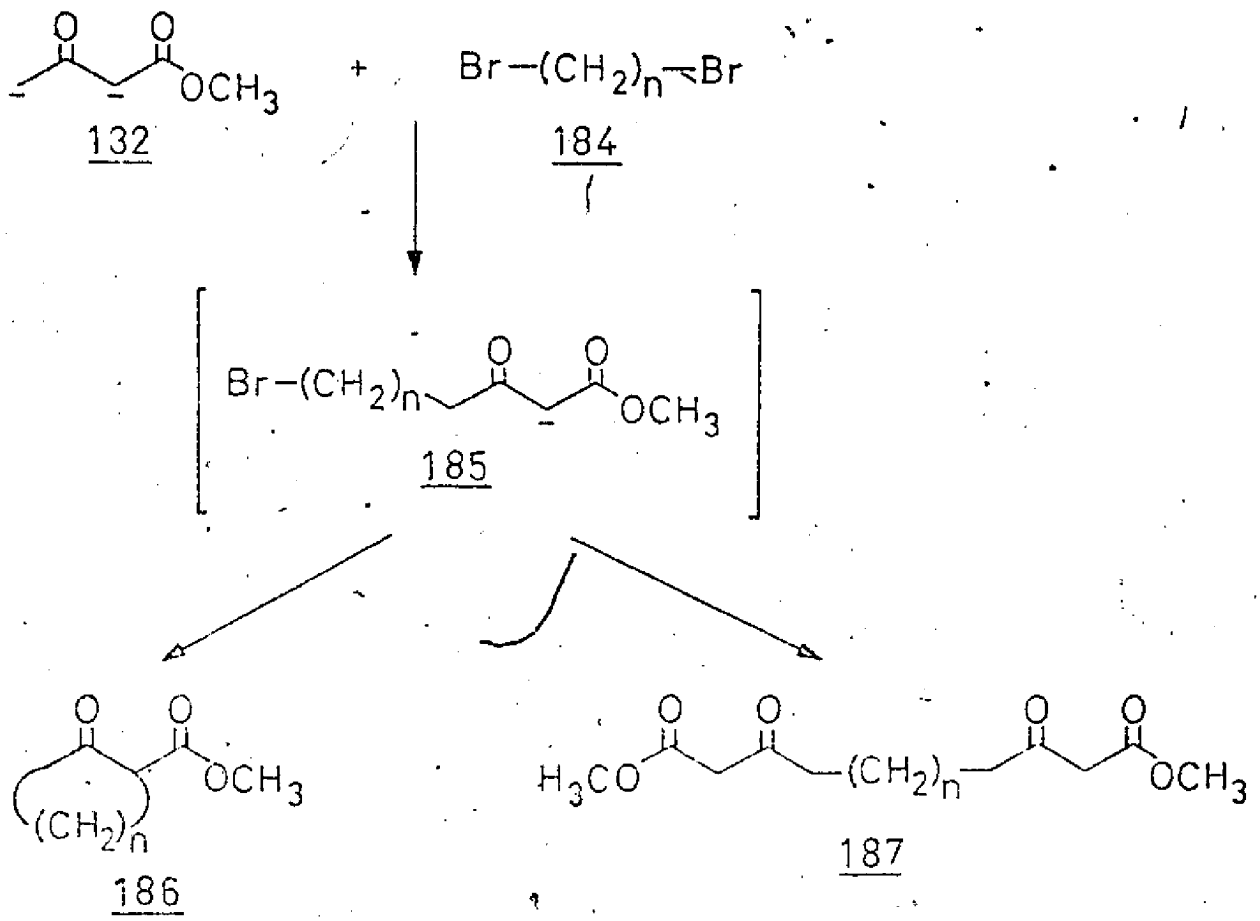
Scheme XVII



It was found that when one equivalent of 1,3-dibromopropane was added to a solution of dianion 132, two products were obtained in approximately equal amounts. These products could be separated by chromatography, and were identified as methyl 2-oxocyclohexanecarboxylate (186a, n=3) and dimethyl 3,9-dioxoundecanedioate (187a, n=3). The former product was characterised by comparison of its ir and nmr spectra with those of authentic material, prepared by the

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method of Rhoads.[84] This product also exhibited identical R_f values to that of the authentic material on two different tlc systems. The second product was characterised as bis-β-ketoester 187a by an elemental analysis which was in agreement with the proposed structure, and molecular weight determination indicated a two to one adduct of methyl acetoacetate and dibromopropane. All other spectral properties of this product were also in accord with its proposed structure.

That the reactivity of the dianion of β-ketoesters is considerably greater than that of the monoanion is manifest when the rates of alkylation of the two species is compared. As has been previously mentioned, the monoanion often requires prolonged periods at elevated temperatures for alkylation, whilst the same reaction for the dianion is essentially instantaneous at 0°C.

In view of this difference in reactivity, formation of the bis-β-ketoester 187 should be favoured by an excess of dianion 132 in the reaction mixture. In fact, when only one half equivalent of 1,3-dibromopropane was added to a solution of the dianion, the only product isolated in 77% yield was the bis-β-ketoester 187a.

Conversely, if the reaction to form the cyclic product is to be favored, all excess dianion must be avoided. There are two procedures which would achieve this end,

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addition of the dianion to a large excess of alkylating agent or reaction in very dilute solution. Although it was found that the addition of a moderately dilute solution of dianion 132 to a large excess (10 equivalents) of 1,3-dibromopropane did give mostly the cyclic product, this procedure would not be convenient if the dihaloalkane was difficult to obtain or costly. This procedure also gave low yields and apparently involved many side reactions. A double dilution experiment in which the initial reaction was performed separately from both reagents and the second cyclisation step, was found to give both reasonable yield and mainly the desired product. In this way it was possible to effect a 68% conversion of methyl acetoacetate to methyl 2-oxocyclohexanecarboxylate.

When dibromomethane was employed as the alkylating agent, no evidence for either the cyclic product or the bis-β-ketoester was obtained. When one equivalent of dibromomethane was reacted with sodio lithio methyl acetoacetate, much dibromomethane but only a little methyl acetoacetate was recovered. In addition there was a new compound whose spectral properties could not be reconciled with either of the expected products. The ir spectrum of this product showed two carbonyl bands at 1740 and 1680 cm^{-1} in the ratio of ca. 2:1. There also appeared to be a shoulder at 1735 cm^{-1} on the more intense band. This compound also exhibited an absorbtion at 228 nm in the uv spectrum, which together with the band in the ir spectrum at 1680 cm^{-1},

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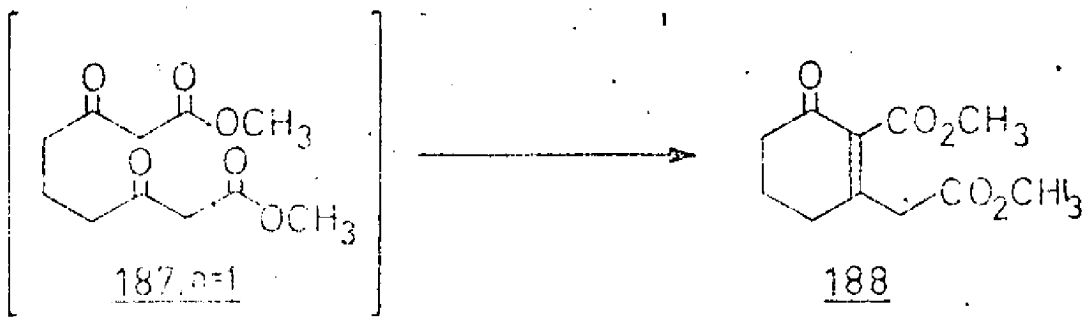
indicated an α,β-unsaturated ketone. The mass spectrum of this compound showed a parent peak at 226 m/e which is eighteen mass units lower than that expected for the bis-β-ketoester. This datum suggested that the new compound had arisen from dehydration of the bis-β-ketoester 187, n=1. However, the only structure which would also possess an α,β-unsaturated ketone is 188.



187, n=1 → 188 (48)

Elemental analysis of this product was consistent with this structure, as was the nmr spectrum. Such cyclisations of β-ketoesters are not unknown, for instance, a previously employed example, the synthesis of trisporic acid 24 employs a similar cyclisation.

It was subsequently found that 188 could be formed in good yield (62%) from dibromomethane and dianion 132, if only one half equivalent of the alkylating agent is added very slowly to the dianion solution.

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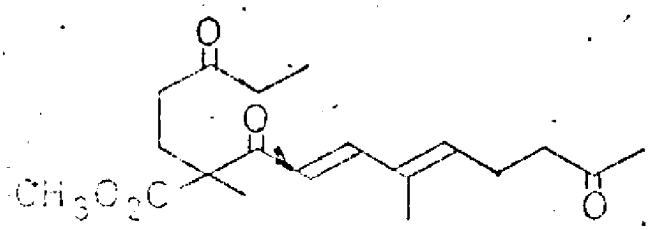
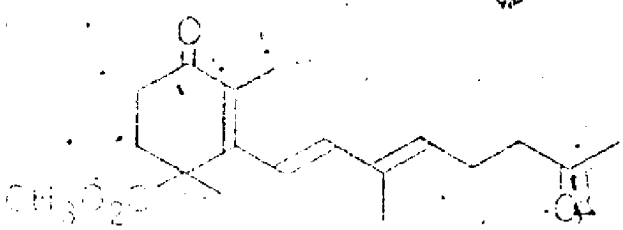
Scheme XVIII



23

MeOK / MeOH



24

The generality of alkylation of dianion 132 with dihaloalkanes as a simple and efficient method of synthesising dialkylacetoacetates was further demonstrated by the reaction of one half equivalent of 1,10-dibromodecane with sodio lithio methyl dihydroacetate, which gave an almost quantitative yield of dimethyl 2,16-dioxocetadecanedioate 187b, n=10. This latter compound was fully characterised by elemental analysis and its unexceptional spectral properties.

Reaction of Nitriles with the Dianion of β-Ketoesters.

It has recently been reported[114] that ethyl acetoacetate may be condensed at the γ carbon atom with benzonitrile by employing two equivalents of sodium amide

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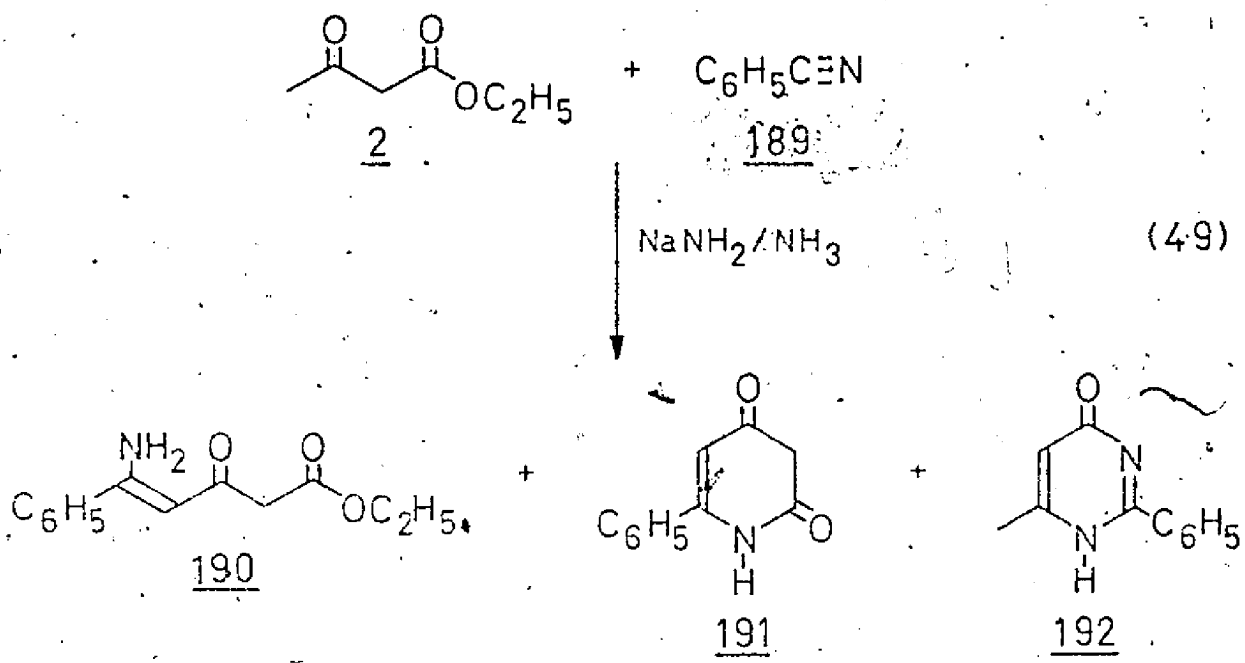
in liquid ammonia. The major product from this reaction is enamine 190, but the reaction is complicated by nucleophilic attack of the amide ion on the nitrile, and subsequent condensation of the benzamidine so formed with the ketoester to give pyrimidone 192. A minor product also isolated from this reaction is pyridinedione 191, which arises from cyclisation of enamine 190.



Generation of the dianion of the β-ketoester by the sodium hydride - n-butyllithium procedure should avoid the complication of pyrimidone formation, and since pyridine-2,4-diones are of some significance as therapeutic agents (as analgesics[115]), the reaction of nitriles with the dianion of methyl acetoacetate was briefly investigated.

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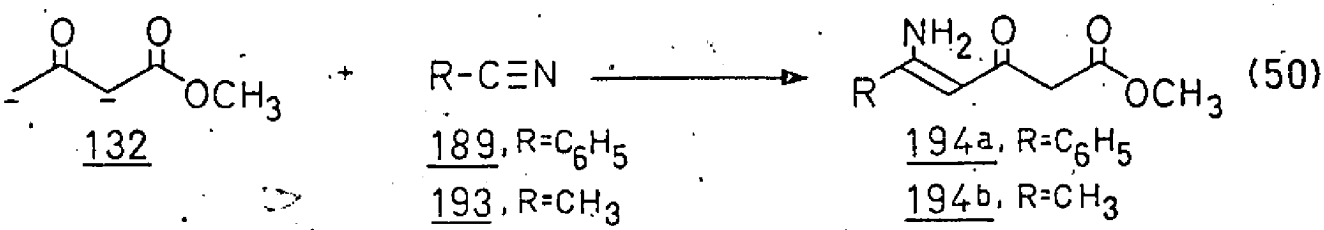
It was found that the reaction between dianion 132 and benzonitrile was sluggish, and extended reaction times were necessary to produce reasonable amounts of condensation products. A reaction period of twelve hours at room temperature was found to give a good yield (66%) of methyl 5-amino-3-oxo-5-phenylpent-4-enoate (194a, R=C_6H_5) and some (29%) pyridinedione 191.



132 + 189, R=C_6H_5 / 193, R=CH_3 → 194a, R=C_6H_5 / 194b, R=CH_3 (50)

The enamine 194a was isolated by chromatography as a pale yellow liquid which was not thermally stable. Attempted distillation of 194a gave quantitative conversion to a crystalline compound later identified as pyridinedione 191, (the analagous thermal conversion of enamine 190 to 191 has been reported by Sugiyama[114]). Consequently, enamine 194a was not obtained in analytical purity. The molecular formula of this compound was established by high resolution mass spectroscopy and characterisation was effected by the spectral properties of 193a, all of which were very similar to those reported[114] for its ethyl homolog 190.

Pyridinedione 191, both that isolated from the reaction mixture directly and that derived from the

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thermolysis of enamine 194a, exhibited a melting point very similar to that reported by Sugiyama, and additionally its ir and uv spectra were in accord with those previously reported.[114,116]

Extension of this reaction to the condensation of acetonitrile with dianion 132 gave in high yield (86%) the analogous enamine 193b, R=CH_3, but no evidence for the formation of the corresponding pyridinedione was observed. Thermal conversion of enamine 193b to a pyridinedione could not be accomplished; the enamine sublimed unchanged, under a variety of pyrolytic conditions. (No attempts were made to perform this conversion by other means, for example, by base treatment, which converts the analagous enamine 190 to the pyridindione[114].) Enamine 194b was fully characterised, elemental analysis, molecular weight as determined by mass spectroscopy and all other spectral properties were in accord with the proposed structure.

Although the results of these two experiments are not as promising as desired, they do indicate the possibility of synthesising pyridine-2,4-diones via the dianion of β-ketoesters.

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Summary

It would appear, from the results so far obtained, that the sodium hydride - n-butyllithium procedure of generating the dianion represents a more advantageous method of functionalising β-ketoesters at the γ position than the alkali amide - liquid ammonia procedure. It appears to be applicable to a wide range of anionic condensations, generally giving at least moderate yields of the desired product.

The initial aim of this work, as previously outlined, was to investigate the aldol and Claisen condensations of the dianion of β-ketoesters, and the results obtained (Tables VII and X) indicate the feasibility of these two reactions.

It is hoped that the reactions outlined in this work will be of some synthetic utility in the future.

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EXPERIMENTAL.

General.

Melting points, which were determined on a Kofler hot stage microscope, and boiling points are uncorrected. All ir, uv and nmr spectra were recorded in solution, the solvent used is reported in parentheses at the beginning of each spectrum. The ir spectra were recorded using a Perkin-Elmer model 700 spectrophotometer, and were calibrated with the 1601 cm^{-1} band of polystyrene. The assignment of each absorption is indicated in parentheses after each band. The uv spectra were recorded using either a Unicam model SP 800 or a Carey model 14 spectrophotometer. The molar extinction coefficient, where applicable, is reported in parentheses after each absorption. The ^1H nmr spectra were recorded on either a Varian model T-60 or HA-100 spectrophotometer. The signal positions are reported using the δ scale with tetramethylsilane as internal standard, except where indicated. The multiplicity, coupling constants, integrated peak areas and proton assignments are indicated in parentheses after each signal. The mass spectra were obtained using an Atlas CH-4b mass spectrometer, and high resolution determinations were obtained using an AEI MS-902 mass spectrometer. Both instruments were operated at an ionising potential of 70 volts. Elemental microanalyses were performed by Mr. Peter Borda, University of British Columbia.

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Gas liquid partition chromatography (glpc) was performed using a Varian-Aerograph model 90P3 chromatograph. The columns employed were:

column A, 20 ft. x 3/8 in. column of 10% carbowax on 60-80 mesh Chromosorb W,

column B, 5 ft. x 1/4 in. column of 3% SE 30 on 60-80 mesh Chromosorb W,

column C, 5 ft. x 1/4 in. column of 5% QF-1 on 60-80 mesh Chromosorb W, and,

column D, 5 ft. x 1/4 in. column of 20% DEGS on 60-80 mesh Chromosrob W.

The carrier gas that was employed was helium with a flow rate of 50 ml/min. The specific column used, along with the column temperature are indicated in parentheses. Silica gel was obtained from E. Merck, and that used for column chromatography was the grade finer than 200 mesh ASTM, whilst that used for thin layer chromatography (tlc) was the grade PF_{254}.

Tetrahydrofuran was dried by refluxing over lithium aluminium hydride for a minimum of two hours prior to use.

Reaction of Alkyllithiums with the Sodium Salt of β-Ketoesters.

Methyl 3-oxohept-6-enoate (142)

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mole) was weighed into an oven dried 50 ml flash, and tetrahydrofuran (ca. 25 ml) was distilled directly into this flash, from lithium aluminium hydride. The flask

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was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry, and after the addition was complete, the reaction was allowed to stand for ten minutes. Methyllithium, as a 2 1M solution in hexane (5.0 ml, 10.5 mmole) was added dropwise to the reaction and the reaction allowed to stand a further ten minutes after this addition. 3-Bromopropene (1.332 g, 11.0 mmole) was added in one portion to the reaction and after a final ten minute period, the reaction was quenched with concentrated hydrochloric acid (ca. 2 ml). The reaction was worked up by the addition of ether (35 ml) and water (5 ml). The aqueous phase was separated, and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure, and the resulting oil distilled to give 1.170 g (75%) of 142, bp 99-101°C (14 mm), (lit.[78] bp 99-100°C (14 mm)), which had identical glpc retention times (col. B, 130°C and col. E, 140°C) as previously prepared methyl 3-oxohept-6-enoate (142).[117]

Methyl 2-oxocyclohexanecarboxylate (145).

Sodium hydride, as a 57% mineral oil dispersion, (0.933 g, 22.0 mmole) was weighed into an over dried 100 ml

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two-necked flash and, p-dioxane (ca. 50 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, a dropping funnel with a nitrogen inlet and a reflux condenser carrying a calcium chloride drying tube. Dimethyl carbonate (1.803 g, 20.0 mmole) was added to the flask and the assembly flushed with nitrogen. A solution of cyclohexanone (1.963 g, 20.0 mmole) in p-dioxane (10 ml) was added dropwise over a period of one hour to the flask and after completion of the addition the flask was heated until a moderate rate of reflux was attained and this continued for three hours. The flask was allowed to cool to room temperature and the solvents removed by evaporation under reduced pressure. Ether (50 ml) was then added and the reaction neutralised by the addition of glacial acetic acid (2 ml), and water (15 ml) added to dissolve the solids produced. The aqueous phase was separated and further extracted with ether (2 x 25 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 20 ml), dried over anhydrous sodium sulphate and filtered. The ether was removed by evaporation under reduced pressure, and the resulting oil distilled under reduced pressure to give 1.269 g (83%) of 145, bp 97-100°C (14 mm) (lit.[84] bp 94-95°C (19 mm)).

ir ($CHCl_3$) 3600 (enol OH), 1745 (ester C=O, keto form), 1720 (C=O), 1650 (ester C=O, enol form) and 1610 cm^{-1} (C=C, enol form);

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nmr ($CDCl_3$) δ14.3 (broad s, exchangeable D_2O, 1, enol OH), 3.76 (s, 3, OCH_3) and 2.60 - 1.74 ppm (m, 8, cyclohexyl protons).

Methyl 2-oxo-3-(prop-2-enyl)-cyclohexanecarboxylate (146).

This compound was prepared by the same procedure as that employed in the preparation of methyl 3-oxohept-6-enoate (142). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.075 g, 1.65 mmole), methyl 2-oxocyclohexanecarboxylate (0.233 g, 1.50 mmole) n-butyllithium, as a 2.3M solution in hexane (0.7 ml, 1.61 mmole) and 3-bromopropene (0.198 g, 1.65 mmole), which gave 0.197 g (67%) of 146, bp 110-112°C (14 mm).

ir ($CHCl_3$) 3600 (enol OH), 1740 (ester C=O, keto form), 1715 (C=O), 1650 (ester C=O, enol form), and 1610 cm^{-1} (C=C);

nmr (CCl_4) δ14.23 (broad s, exchangeable D_2O, 1, enol OH), 6.00-5.50 (m, 1, C=CH), 5.16-4.86 (m, 2, $C=CH_2$), 3.70 (s, 3, OCH_3) and 2.70-1.10 ppm (m, 9, cyclohexyl protons and CH of propenyl group);

mass spectrum m/e (rel intensity) 196(55), 183(6), 178(9), 165(37), 164(60), 155(24), 154(51), 137(36), 136(49), 125(32), 123(100), 122(30), 119(49), 109(24), 108(77), 95(70), 94(48), 93(47), 87(54), 79(77), 68(65), 55(90), and 41(100);

analysis calcd. for $C_{11}H_{16}O_3$: C 67.32, H 8.22:

found : C 67.31, H 8.35.

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Reaction of Methyllithium with the Sodium Salt of Methyl Acetoacetate.

General Procedure.

Sodium hydride, as a 57% mineral oil dispersion (0.465 g, 11.0 mmoles) was weighed into an oven dried flask and tetrahydrofuran distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry, and the reaction allowed to stand for ten minutes after the addition was complete. Various quantities of methyllithium were then added and the reaction allowed to stand for thirty minutes before being quenched with a slight excess of concentrated hydrochloric acid. The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated, saturated with sodium chloride and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure. The resulting oils were then subjected to glpc analysis and treated with 2,4-dinitrophenylhydrazine (2.200 g, 11.0 mmole) dissolved in methanol, acidified with concentrated sulphuric acid, to convert any ketonic compound

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to its 2,4-dinitrophenylhydrazone.

a) With two equivalents of methyllithium.

The general procedure was performed using 10 ml of a 2.1M solution of methyllithium in hexane. The glpc analysis (column D, 140°C) showed the product to contain mainly pentane-2,4-dione with a little methyl acetoacetate and diacetone alcohol (rel proportions, 90:5:5). The solid from the derivitisation reaction was washed with ether and recrystallised from ethanol to give 2.301 g (80%) of the 2,4-dinitrophenylhydrazone of pentane-2,4-dione, mp 207 - 209°C, mixed mp 207 - 209°C.

b) With three equivalents of methyllithium.

The general procedure was performed using 15 ml of a 2.1M solution of methyllithium in hexane. The glpc analysis (column D, 140°C), showed the product to contain mainly diacetone alcohol with only a little pentane-2,4-dione present, (rel proportions, 96:4). The solid from the derivatisation reaction was recrystallised from methanol-water (9:1, v/v) to give 2.419 g (82%) of the 2,4-dinitrophenylhydrazone of diacetone alcohol, mp 201 - 203°C mixed mp 201 - 203°C.

c) Wtih six equivalents of methyllithium.

The general procedure was performed using 35 ml of a 2.1M solution of methyllithium in hexane. The glpc analysis (column D, 140°C) showed the major product to be diacetone alcohol, with no pentane-2,4-dione or methyl acetoacetate

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present. However, the solid from the derivatisation reaction was isolated in smaller amounts; and after recrystallisation from methanol-water (9:1 v/v) only 1.294 g (44%) of the 2,4-dinitrophenylhydrazone of diacetone alcohol, mp 201-203°C, was isolated.

Aldol Reactions of The Dianion of β-Ketoesters.

Methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i)

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven-dried 50 ml flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0°C and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. A solution of n-butyllithium (5 ml 2.1M in hexane, 10.5 mmole) was added dropwise to the solution and the reaction allowed to stir for a further ten minutes. Acetone (0.638 g, 11.0 mmole) was added in one portion and the reaction allowed to stir for ten minutes before being quenched with concentrated hydrochloric acid (ca. 2 ml). The reaction was worked up by the addition of water (10 ml) and diethyl ether (35 ml). The aqueous layer was separated and further extracted with ether (2 x 35 ml). The organic extracts were combined, washed

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with saturated sodium chloride solution (6 x 15 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and distillation of the resulting oil gave 1.162 g (72%) of 150i, bp 51-52° (14 mm).

ir ($CHCl_3$) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr ($CDCl_3$) δ3.76 (s, 3, OCH_3), 3.48 (s, 2, $COCH_2CO_2Me$), 3.27 (broad s, 1, exchangeable D_2O, OH), 2.70 (s, 2, $HOCCH_2CO$) and 1.30 ppm (s, 6, $C(CH_3)_2$);

mass spectrum m/e (rel intensity) 174(4), 159(48), 128(71), 116(100), 85(62), 59(87) and 43(87);

analysis calcd for $C_8H_{14}O_4$: C 55.16, H 8.10:
found: C 54.97, H 8.32.

Methyl 5-hydroxy-5-methyl-3-oxoheptanoate (150j)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150j). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.467 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) and 3-butanone (0.792 g, 11.0 mmole), which gave 1.052 g (56%) of 150j, bp 88-89° (14 mm).

ir (neat film) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

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nmr ($CDCl_3$) δ3.77 (s, 3, OCH_3); 3.51 (s, 2, $COCH_2CO_2Me$), 3.15 (broad s, 1, exchangeable D_2O, OH), 2.71 (s, 2, $HOCCH_2CO$), 1.60 (distorted q, 2, J = 8Hz, $MeCH_2COH$), 1.27 (s, 3, CH_3COH) and 0.92 ppm (distorted t, 3, J = 8Hz, CH_3CH_2);

mass spectrum m/e (rel intensity) 188(0.2), 170(10), 159(49) 128(75), 116(50), 85(47), 73(47) and 43(100);

analysis calcd for $C_9H_{16}O_4$: C 57.43 H 8.57:

found : C 57.27 H 8.71

Methyl 4-(1-hydroxycyclohexyl)-3-oxobutanoate (150k).

This compound was also prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) and cyclohexanone (1.078 g, 11.0 mmole), which gave 1.348 g (63%) of 150k, bp 95-96° (0.3 mm).

ir (neat film) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr ($CDCl_3$) δ3.75 (s, 3, OCH_3), 3.50 (s, 2, $COCH_2CO_2Me$), 3.11 (broad s, 1, exchangeable D_2O, OH), (s, 2, $HOCCH_2CO$) and 1.52 ppm (m, 10, cyclohexyl protons);

mass spectrum m/e (rel intensity) 214(3), 196(18), 182(12), 138(61), 123(40), 122(47), 116(44), 98(63), 95(60), 80(53), 69(69), 55(84), and 43(100);

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analysis calcd for $C_{11}H_{18}O_4$: C 61.66 H. 8.47

found: C 61.84 H 8.47

Methyl 4-(1-hydroxycyclopentyl)-3-oxobutanoate (150l)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole); methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) and cyclopentanone (0.924 g, 11.0 mmole), which gave 0.502 g (25%) of 150l, bp 67-68° (0.3 mm).

ir (neat film) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr ($CDCl_3$) δ3.77 (s, 3, OCH_3), 3.52 (s, 2, $COCH_2CO_2Me$), 3.10 (broad s, 1, exchangeable D_2O, OH), 2.90 (s, 2, $HOCCH_2CO$) and 1.72 ppm (m, 8, cyclopentyl protons).

mass spectrum m/e (rel intensity) 200(4), 182(12), 159(89), 126(62), 116(89), 109(51), 198(65), 101(84), 85(89), 84(98), 67(62), 59(62), 55(100) and 43(100);

analysis calcd for $C_{10}H_{16}O_4$: C 59.98 H 8.05

found: C 60.14 H 7.94

Methyl 5-hydroxy-3-oxoheptanoate (150b)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the

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preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5.0 ml, 10.5 mmole) and propanal (0.639 g, 11.0 mmole), which gave 1.270 g (73%) of 150b, bp 86-87° (0.5 mm).

ir (neat film) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr ($CDCl_3$) δ4.00 (m, 1, CHOH), 3.76 (s, 3, OCH_3), 3.52 (s, 2, $COCH_2CO_2Me$), 2.66 (m, 2, $HOCCH_2CO$), 2.43 (broad s, 1, exchangeable D_2O, OH), 1.45 (m, 2, $HOCCH_2CH_3$) and 0.95 ppm (m, 3, CH_2CH_3);

mass spectrum m/e (rel intensity) 174(1), 156(6), 145(17), 116(16), 114(38), 101(32), 83(59), 71(49), 69(53), 59(52), and 43(100);

analysis calcd for $C_8H_{14}O_4$: C 55.16 H 8.10

found: C 54.95 H 8.09

Methyl 5-hydroxy-3-oxononanoate (150c)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) and pentanal (0.946 g, 11.0 mmole), which gave 0.727 g (36%) of 150c, bp 55-56° (0.2 mm).

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ir (neat film) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr ($CDCl_3$) δ4.00 (m, 1, HOC<u>H</u>), 3.76 (s, 3, OC<u>H</u>$_3$), 3.50 (s, 2, COC<u>H</u>$_2$CO$_2$Me), 2.66 (m, 2, HOCC<u>H</u>$_2$CO), 2.42 (broad s, 1, exchangeable D_2O, O<u>H</u>) and 1.52-0.77 ppm (m, 9, C<u>H</u>$_3$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$COH);

mass spectrum m/e (rel intensity) 202(1), 184(9), 145(38), 127(9), 116(36), 113(35), 101(23), 97(14), 85(27), 84(19), 58(32) and 43(100);

analysis calcd for $C_{10}H_{18}O_4$: C 59.39 H 8.97

found: C 59.19 H 8.96

Methyl 5-hydroxy-3-oxohexanoate (<u>150a</u>)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (<u>150i</u>). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole), and acetaldehyde (0.484 g, 11.0 mmole), which gave 0.416 g (26%) of <u>150a</u>, bp 42-43° (0.3 mm).

ir ($CHCl_3$) 3500 (OH), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr (CCl_4) δ4.10 (m, 1, C<u>H</u>OH), 3.70 (s, 3, OC<u>H</u>$_3$) (s, 2, COC<u>H</u>$_2$CO$_2$Me), 3.00 (broad s, 1, exchangeable D_2O, O<u>H</u>), 2.62 (m, 2, HOCC<u>H</u>$_2$CO) and 1.12 ppm (m, 3; C<u>H</u>$_2$COH);

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mass spectrum m/e (rel intensity) 160(40), 142(54), 127(33), 116(60), 101(73), 85(42), 59(64) and 43(100);

analysis calcd for $C_7H_{12}O_4$: C 52.49 H 7.55

found: C 52.65 H 7.39

Methyl 5-hydroxy-6,6-dimethyl-3-oxoheptanoate (150d.

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole), and 2,2-dimethylpropanal (0.946 g, 11.0 mmole), which gave 1.654 g (82%) of 150d, bp 68-69° (0.2 mm).

ir ($CHCl_3$) 3500 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr (CCl_4) 3.70 (s, 3, OCH_3), 3.63 (m, 1, CHOH), 3.42 (s, 2, $COCH_2CO_2Me$), 3.00 (broad s, 1, exchangeable D_2O, OH), 2.58 (m, 2, $HOCCH_2CO$) and 0.87 ppm (s, 9, $CH_3)_3C$);

mass spectrum m/e (rel intensity) 202(1), 184(10), 170(22), 155(23), 145(90), 127(42), 116(48), 115(48), 113(92), 111(94), 101(60), 56(96), 83(87), 71(100), 69(94), 59(77), 55(100) and 43(100);

analysis calcd for $C_{10}H_{18}O_4$: C 59.39 H 8.97

found: C 59.15 H 8.95

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Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n)

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighted into an oven dried 50 ml flask, and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was fitted with a magnetic stirrer, stoppered (serum cap), cooled in ice to 0° and flushed with nitrogen. Methyl acetoaceate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry, and after the addition was complete, the reaction was allowed to stir for ten minutes. A solution of n-butyllithium (5 ml 2.1M in hexane, 10.5 mmole) was added dropwise to the solution and the reaction allowed to stir for a further ten minutes. o-Methoxyacetophenone (1.650 g, 11.0 mmoles) dissolved in THF (5 ml) was added in one portion and the reaction allowed to stir for ten minutes before being quenched with concentrated hydrochloric acid (ca. 2 ml). The reaction was worked up by the addition of water (10 ml) and diethyl ether (35 ml). The aqueous layer was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 15 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed under reduced pressure to give 2.550 g of pale yellow oil. Purification of this oil was achieved by tlc: crude 150n (544 mg) was chromatographed on a 20 x 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform

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and ethyl acetate (9:1, v/v) as eluent. After elution, the band lying in the region R_f 0.25 - 0.33 was removed and extracted with ether (15 ml). The solvent was removed by evaporation under reduced pressure to give 471 mg (73% extrapolated)* of 150n.

ir ($CHCl_3$) 3500 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

uv (CH_3OH) 276, 270 and 264 nm (shoulder);

nmr (CCl_4) δ7.70 - 6.70 (m, 4, aryl protons), 4.10 (broad s, 1, exchangeable D_2O, OH), 3.82 (s, 3, ester OCH_3), 3.63 (s, 3, aryl OCH_3), 3.33 - 1.65 (m, 4, CH_2COCH_2) and 1.50 ppm (s, 3, $HOCCH_3$);

mass spectrum: a) high resolution calcd for $C_{14}H_{18}O_5$, 266.1154 amu, found, 266.1135 m/e;

b) low resolution m/e (rel intensity) 266(10), 251(8), 234(16), 208(10), 159(34), 151(78), 135(94), 115(52), 91(25), 77(80), 59(47) and 43(100).

* Note: Extrapolated yield is calculated by purifying a small portion of the crude product, and assuming that the remainder of the crude product would yield the same proportion of pure compound.

Methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (151n)

Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n) (0.257 g, 0.99 mmole), chlorotrimethylsilane (0.108 g, 1.00 mmole) and hexamethyldisilazane (0.081 g, 0.50 mmole) were

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dissolved in dry pyridine (ca. 5 ml) and the solution stirred for ten minutes. A fine white precipitate was thrown down and this was filtered off and washed with ether (3 x 10 ml). The washings were added to the filtrate and the solvents removed by evaporation under reduced pressure. The resulting oil was distilled under high vacuum to give 0.176 g (65%) of 151n, bp 83-85° (0.3 mm).

ir ($CHCl_3$) 1740 (ester C=O), 1705 (C=O) and 1075 cm^{-1} (Si-OC);

nmr (CCl_4, ext TMS) 7.55 - 6.67 (m, 4, aryl protons), 3.80 (s, 3, ester OCH_3), 3.53 (s, 3, aryl OCH_3), 3.20 (s, 2, $COCH_2CO_2Me$), 2.80 (m, 2, $ArCCH_2CO$), 1.67 (2, 3, CCH_3) and 0.00 ppm (s, 9, $(CH_3)_3Si$);

mass spectrum m/e (rel intensity) 338(3), 323(2), 308(2), 265(2), 223(98), 173(35), 151(19), 135(80), 115(17), 105(46), 91(19), 75(100), 59(30), and 43(76);

analysis calcd for $C_{17}H_{26}O_5Si$: C 60.33 H 7.74

found: C 60.20 H 7.49

Hydrolysis of Methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (151n)

Methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (151n) (0.170 g, 0.50 mmole) was dissolved in methanol (10 ml) and the solution heated to reflux. After a period of thirty minutes at reflux the solution was cooled

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and filtered. The methanol was removed by evaporation under reduced pressure and the resulting oil purified by preparative tlc, using a 20 x 20 cm silica coated plate, adsorbant thickness 0.5 mm, and employing a mixture of chloroform and ethyl acetate (9:1, v/v) as eluent. The band lying in the region R_f 0.25 - 0.33 was removed and extracted with ether. The solvent was removed by evaporation under reduced pressure to give 95 mg (71%) of methyl 5-hydroxy-5-(2-methoxyphenyl) 3-oxohexanoate (150n), which showed identical ir and nmr spectra to 150n before derivitisation.

Methyl 5-(2-methoxyphenyl)-3-oxohex-4-enoate (153)

Chloroform (ca. 10 ml) was saturated with anhydrous hydrogen chloride, by direct passage of the gas through the solvent. Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n) (0.051 g, 0.19 mmole) was dissolved in this chloroform and the solution stirred for 30 minutes. The solution was washed with saturated sodium hydrogen carbonate solution (4 x 5 ml), and with saturated sodium chloride solution (2 x 5 ml), dried over anhydrous sodium sulphate and filtered. The chloroform was removed by distillation to give 0.040 g (85%) of a mixture of Z and E isomers of 153 (ratio of isomers, Z:E 1.0:2.3, by nmr).

ir ($CHCl_3$) 1740 (ester C=O), 1680 (C=CC=O) and 1600 cm^{-1} (C=C);

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uv (CH_3OH) 320 (shoulder) and 278 nm;

nmr (CCl_4) δ7.40 - 6.67 (m, 4, aryl protons), 6.20 (m, 0.7, E - C=C<u>H</u>), 6.10 (m, 0.3, Z - C=C<u>H</u>), 3.82 (s, 3, ester OC<u>H</u>$_3$), 3.70 (d, 2.1, J = 1 Hz, E- aryl OC<u>H</u>$_3$), 3.60 (d, 0.9, J = 1 Hz, Z- aryl OC<u>H</u>$_3$), 3.40 (s, 2, COC<u>H</u>$_2$CO$_2$Me), 2.43 (d, 2.1, J = 1 Hz, E- CC<u>H</u>) and 2.12 ppm (d, 0.9, J = 1 Hz, Z- CC<u>H</u>$_3$);

mass spectrum: a) high resolution calcd for $C_{14}H_{16}O_4$ 248.1048 amu, found 248.1064 m/e;

b) low resolution m/e (rel intensity) 248(2), 217(14), 189(3), 175(11), 160(13), 159(100), 150(5), 136(17), 119(4), 115(4), 105(6), 91(9), 77(4), 69(2), 59(2), and 43(22).

Thermolysis of Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (<u>150n</u>)

Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (0.570 g, 2.14 mmole) was heated in a bulb-to-bulb distillation apparatus to 190°C at a pressure of 0.2 mm. A colourless oil (0.511 g) condensed in the receiver, which was separated into three components by preparative glpc, (column A, 200°C). These components were, in order of elution (relative yield): <u>o</u>-methoxyacetophenone (64.5), mp 36-38, mixed mp 36-38°C. <u>Z</u>-4-(2-methoxyphenyl)-pent-3-en-2-one (<u>162</u>) (8.5);

ir ($CHCl_3$) 1675 (unsaturated C=O) and 1600 cm^{-1} (C=C);

uv (CH_3OH) 295 (shoulder) and 272 nm.

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E-4-(2-methoxyphenyl)-pent-3-en-2-one (162) (27);

ir ($CHCl_3$) 1675 (unsaturated C=O) and 1600 cm^{-1} (C=C);

uv (CH_3OH) 296 (shoulder) and 272 nm;

nmr (CCl_4) δ7.30 - 6.70 (m, 4, aryl protons), 6.10 (m, 1, C=C-H), 3.47 (d, J=0.9 Hz, 3, OCH_3), 2.33 (d, J=1 Hz, 3, C=C-CH_3) and 2.13 ppm (s, 3, CO-CH_3);

mass spectrum m/e (rel intensity) 190(5), 175(10), 161(12), 160(100), 147(4), 131(40), 115(7), 105(5), 91(14), 77(9), 63(5), 51(7), and 43(76);

analysis calcd for $C_{12}H_{14}O_2$: C 75.76 H 7.42

found: C 75.61 H 7.61

Methyl 5-hydroxy-3-oxo-5-phenylpentanoate (150e)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole), and benzaldehyde (1.168 g, 11.0 mmole), which gave 2.553 g of crude 150e, as a yellow oil. The crude product was purified by chromatography on a silica gel (200 g) column using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. The major component from the chromatography was 150e (1.973 g, 89%).

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ir ($CHCl_3$) 3500 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=C);

uv (CH_3OH) 280 (shoulder), 264, 258, 252 and 247 nm;

nmr (CCl_4) δ7.22 (s, 5, aryl protons), 5.05 (m, 1, HOC<u>H</u>), 3.65 (s, 3, OC<u>H_3</u>), 3.33 (s, 2, COC<u>H_2</u>CO_2Me), 3.30 (broad s, exchangeable D_2O, 1, O<u>H</u>) and 2.79 ppm (m, 2, HOCC<u>H_2</u>CO).

mass spectrum a) high resolution calcd for $C_{12}H_{14}O_4$ 222.089 amu, found 222.086 m/e;

b) low resolution m/e (rel intensity) 222(20), 204(74), 190(21), 188(18), 162(30), 149(58), 131(77), 116(86), 107(98), 106(88), 105(90), 91(32), 85(53), 84(72), 77(94), 58(90), 51(78), and 43(100).

Methyl 3-oxo-5-phenyl-5-trimethylsiloxypentanoate (<u>151e</u>)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-trimethysiloxyhexanoate (<u>151n</u>). The reagents used were: methyl 5-hydroxy-3-oxo-5-phenylpentanoate (<u>150e</u>) (0.208 g, 0.93 mmole), chlorotrimethylsilane (0.108 g, 1.00 mmole) and hexamethyldisilazane (0.080 g, 0.50 mmole), which gave 0.153 g (52%) of <u>151e</u>, bp 60-62° (0.2 mm).

ir ($CHCl_3$) 1740 (ester C=O), 1705 (C=O) and 1080 cm^{-1} (Si-OC);

nmr (CCl_4, ext TMS) 7.23 (s, 5, aryl protons), 5.20 - 4.87 (m, 1, SiOC<u>H</u>), 3.63 (s, 3, OC<u>H_3</u>), 3.27 (s, 2, COC<u>H_2</u>CO_2Me),

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2.93 - 2.27 (m, 2, $ArCCH_2CO$) and 0.00 ppm (s, 9, $(CH_3)_3Si$);

mass spectrum m/e (rel intensity) 294(1), 279(4), 264(3), 249(8), 221(16), 204(51), 189(12), 179(53), 162(34), 149(38), 144(52), 131(62), 117(45), 116(66), 105(76), 91(68), 85(54), 77(82), 69(62), 59(100), and 43(83);

analysis calcd for $C_{15}H_{22}O_4Si$: C 61.19 H 7.53

found: C 61.40 H 7.32

Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxopentanoate (150f)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmoles), methyl acetoacetate (1.160 g, 10.0 mmoles), n-butyllithium, as a 2.34M solution in hexane, (4.5 ml, 10.6 mmole) and o-methoxybenzaldehyde (1.498 g, 11.0 mmole) which gave 2.830 g of crude 150f as a yellow oil. Purification of this oil was achieved by tlc: crude 150f (374 mg) was chromatographed on a 20 x 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.2 - 0.3 was removed and extracted with ether (20 ml). The solvent was removed by evaporation under reduced pressure to give 243 mg (73% extrapolated) of 150f.

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ir ($CHCl_3$) 3600 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

nmr (CCl_4) δ7.50 - 6.67 (m, 4, aryl protons), 5.30 (m, 1, HOC<u>H</u>), 3.83 (s, 3, aryl OC<u>H</u>$_3$), 3.68 (s, 3, ester OC<u>H</u>$_3$), 3.50 (broad s, exchangeable D_2O, 1, O<u>H</u>), 3.36 (s, 2, COC<u>H</u>$_2$CO$_2$Me) and 2.77 ppm (m, 2, HOCC<u>H</u>$_2$CO);

uv(CH_3OH) 276, 271 and 257 nm;

mass spectrum a) high resolution: calcd for $C_{13}H_{16}O_5$, 252.099 amu, found 252.102 m/e;

b) low resolution m/e (rel intensity) 252(4), 234(36), 203(26), 179(16), 175(19), 161(43), 151(44), 137(60), 133(100), 127(36), 121(51), 116(39), 105(58), 91(47), 85(65), 77(54), 59(50) and 43(70).

<u>Methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxypentanoate (151f)</u>

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (<u>151n</u>). The reagents used in the preparation were: methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxopentanoate (<u>150f</u>) (149 mg, 0.59 mmole), chlorotrimethylsilane (69 mg, 0.64 mmole) and hexamethyldisilazane (52 mg, 0.32 mmoles), which gave 138 mg (71%) of <u>151f</u>, bp 64-65° (0.5 mm).

ir ($CHCl_3$) 1740 (ester C=O), 1705 (C=O) and 1070 cm^{-1} (Si-OC);

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nmr (CCl_4, ext TMS) 7.47 - 6.60 (m, 4, aryl protons), 5.43 (m, 1, ArC<u>H</u>), 3.80 (s, 3, aryl OC<u>H</u>$_3$), 3.63 (s, 3, $CO_2C\underline{H}_3$), 3.30 (s, 2, $COC\underline{H}_2CO_2Me$), 2.63 (m, 2, $ArCC\underline{H}_2CO$) and 0.00 ppm (s, 9, $OSi(C\underline{H}_3)_3$);

mass spectrum m/e (rel intensity) 324(7), 306(45), 293(10), 266(8), 251(15), 241(31), 209(97), 199(24), 195(17), 179(25), 173(95), 161(33), 145(25), 135(53), 127(24), 115(37), 105(53), 91(69), 85(20), 77(68), 75(92), 73(100), 60(22), 59(66) and 43(88);

analysis calcd for $C_{16}H_{24}O_5Si$: C 59.23 H 7.46

found: C 59.46 H 7.48

Methyl 5-(2-furyl)-5-hydroxy-3-oxopentanoate (<u>150h</u>)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxo-hexanoate (<u>150i</u>). The reagents used in the preparation were sodium hydride, as a 57% mineral oil dispersion, (0.463 g, 11.0 mmoles), methyl acetoacetate (1.160 g, 10.0 mmole), n-butyllithium, as a 2.34M solution in hexane, (4.5 ml, 10.6 mmole) and 2-furfuraldehyde (1.061 g, 11.0 mmole), which gave 1.445 g (68%) of <u>150h</u>, bp 82-84° (0.1 mm).

ir ($CHCl_3$) 3600 (O-H), 1740 (ester C=O) and 1710 cm^{-1} (C=O);

nmr (CCl_4) δ7.32 (m, 1, <u>H</u> on C_5 of furyl ring), 6.23

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(m, 2, H on C_3 and C_4 of furyl ring), 5.05 (m, 1, HOCH), 3.82 (broad s, exchangeable D_2O, 1, OH), 3.69 (s, 3, OCH_3), 3.42 (s, 2, $COCH_2CO_2Me$) and 2.93 ppm (m, 2, $HOCCH_2CO$);

mass spectrum m/e (rel intensity) 212(12), 194(11), 149(11), 121(50), 116(30), 101(13), 97(75), 96(71), 95(76), 69(26), 65(21), 59(35) and 43(100);

analysis calcd for $C_{10}H_{12}O_5$: C 56.60 H 5.70

found: C 56.66 H 5.35

Methyl 5-hydroxy-3-oxo-5-phenylhexanoate (150m)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.461 g, 11.0 mmole), methyl acetoacetate (1.163 g, 10 mmole), n-butyllithium, as a 2.34M solution in hexane, (4.5 ml, 10.6 mmole) and acetophenone (1.318 g, 11.0 mmole) which gave 2.801 g of crude 150m as a yellow oil. Purification of this oil was achieved by tlc: 563 mg of crude 150m was chromatographed on a 20 x 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.25 - 0.40 was removed and extracted with ether (20 ml). The solvent was removed under reduced pressure to give 367 mg of 150m (extrapolated yield 77%).

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ir ($CHCl_3$) 2550 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

uv (CH_3OH) 294 (shoulder), 278 and 273 nm;

nmr (CCl_4) δ7.30 (m 5, aryl protons), 3.85 (broad s, exchangeable D_2O, 1, OH), 3.63 (s, 3, OCH_3), 3.25 (m, 2, $COCH_2CO_2Me$), 2.67 (m, 2, $HOCCH_2CO$) and 1.65 ppm (s, 3, CCH_3);

mass spectrum a) high resolution calcd for $C_{13}H_{16}O_4$, 236.104 amu, found 236.105 m/e;

b) low resolution m/e (rel intensity) 236(2), 221(5), 218(5), 190(6), 170(2), 159(11), 145(12), 127(17), 121(64), 120(95), 116(88), 106(50), 105(88), 101(45), 85(95), 77(100), 74(95), 69(64), 59(97) and 43(100).

Methyl 3-oxo-5-phenyl-5-trimethylsiloxyhexanoate (151m)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (151n). The reagents used were: methyl 5-hydroxy-3-oxo-5-phenylhexanoate (150m) (305 mg, 1.30 mmole), chlorotrimethylsilane (155 mg, 1.43 mmole) and hexamethyldisilazane (115 mg, 0.72 mmole), which gave 242 mg (61%) of 151m, bp 82-83° (0.3 mm).

ir ($CHCl_3$) 1740 (ester C=O), 1705 (C=O) and 1075 cm^{-1} (Si-OC);

nmr (CCl_4, ext TMS) 7.20 (m, 5, aryl protons), 3.57 (s, 3, OCH_3), 3.03 (m, 2, $COCH_2CO_2Me$), 2.53 (m, 2, $ArCCH_2CO$), 1.66 (s, 3, CCH_3) and 0.00 ppm (s, 9, $OSi(CH_3)_3$);

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mass spectrum m/e (rel intensity) 308(1), 295(9), 279(7), 264(9), 250(4), 233(11), 221(5), 211(6), 185(100), 179(11), 169(46), 156(28), 146(12), 126(17), 113(48), 101(31), 91(9), 77(26) and 73(62);

analysis calcd for $C_{16}H_{24}O_4Si$: C 62.30 H 7.84

found: C 62.33 H 7.77

Methyl 5-(2,3-dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (150g)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.162 g, 10.0 mmole), n-butyllithium, as a 2.34M solution in hexane, (4.5 ml, 10.6 mmole) and 2,3-dimethoxybenzaldehyde (1.823 g, 11.0 mmole), which gave 3.044 g of crude 150g, as a pale brown oil. Purification of 150g was achieved by tlc: 306 mg of crude 150g was chromatographed on a 20 x 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.30 - 0.40 was removed and extracted with ether (20 ml). The solvent was removed by evaporation under reduced pressure to give 194 mg of 150g (extrapolated yield, 68%).

ir ($CHCl_3$) 3550 (O-H), 1740 (ester C=O) and 1705 cm^{-1} (C=O);

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uv (CH_3OH) 264 (shoulder), 256, 252 and 246 nm;

nmr (CCl_4) δ6.93 (m, 3, aryl protons), 5.20 (m, 1, HOC<u>H</u>), 4.03 (broad s, exchangeable D_2O, 1, O<u>H</u>), 3.80 (s, 6, aryl OC<u>H</u>$_3$), 3.67 (s, 3, ester OC<u>H</u>$_3$), 3.37 (s, 2, COC<u>H</u>$_2$CO$_2$Me) and 2.77 ppm (m, 2, HOCC<u>H</u>$_2$CO);

mass spectrum a) high resolution calcd for $C_{14}H_{18}O_6$, 282.110 amu, found 282.111 m/e;

b) low resolution m/e (rel intensity) 282(19), 264(7), 250(15), 233(11), 22(2), 217(2), 209(5), 205(4), 191(9), 182(3), 191(9), 182(3), 167(100), 166(46), 151(21), 139(22), 137(21), 116(11), 107(11), 91(7), 85(10), 77(21), 69(9), 59(15) and 43(73).

<u>Methyl 5-(2,3-dimethoxyphenyl)-3-oxo-5-trimethylsiloxypentanoate (151g)</u>

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (<u>151n</u>). The reagents used were: methyl 5-(2,3-dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (173 g, 0.61 mmole), chlorotrimethylsilane (74 mg, 0.68 mmole) and hexamethyldisolazane (55 mg, 0.34 mmole) which gave 114 mg (53%) of <u>151g</u>, bp 89-91° (0.4 mm).

ir ($CHCl_3$) 1740 (ester C=O), 1705 (C=O) and 1075 cm^{-1} (Si-OC):

nmr (CCl_4, ext TMS) δ6.87 (m, 3, aryl protons), 5.42 (m, 1, ArC<u>H</u>), 3.80 (s, 6, aryl OC<u>H</u>$_3$), 3.63 (s, 3, CO_2CH_3), 3.29 (s, 2, COC<u>H</u>$_2$CO$_2$Me), 2.70 (m, 2, HOCC<u>H</u>$_2$CO) and 0.00 ppm

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(s, 9, $OSi(CH_3)_3$);

mass spectrum m/e (rel intensity) 354(16), 323(8), 304(4), 241(14), 236(100), 223(4), 209(8), 193(22), 183(47), 165(24), 151(13), 149(11), 135(13), 121(25), 115(21), 105(11), 91(11), 89(19), 75(44), 73(52), 59(17) and 43(11);

analysis calcd for $C_{17}H_{26}O_6Si$: C 57.60 H 7.40

found: C 57.80 H 7.29

Methyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate (150p)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (150n). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.160 g, 10.0 mmole), n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole) and benzophenone (2.003 g, 11.0 mmole) which gave 3.124 g of a semi-solid. Recrystallisation from a hexane-ether mixture gave a first crop of 150p (1.831 g). Subsequent concentration of the mother liquors gave a second crop of 150p (0.321 g) and finally chromatography of the residual solution on silica gel (50 g) using chloroform as eluent gave 0.622 g of 150p, to total 2.774 g (93%) of product as colourless needles, mp 77-79°C.

ir ($CHCl_3$) 3550 (O-H), 1740 (ester C=O) and 1710 cm^{-1} (C=O);

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uv (CH_3OH) 253 (785), 259 (820), 265 (685) and 269 nm (52);

nmr (CCl_4) δ7.27 (m, 10, aryl protons), 4.43 (broad s, exchangeable D_2O, 1, O<u>H</u>), 3.67 (s, 3, OC<u>H</u>$_3$), 3.40 (s, 2, HOCC<u>H</u>$_2$CO) and 3.27 ppm (s, 2, COC<u>H</u>$_2$CO$_2$Me);

mass spectrum m/e (rel intensity) 298(6), 207(22), 189(14), 184(66), 183(98), 165(11), 154(18), 116(10), 105(100), 91(19), 77(85), 69(22), 59(45), 51(59) and 43(60);

analysis calcd for $C_{18}H_{18}O_4$: C 72.47 H 6.08

found: C 72.47 H 6.05

Ethyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate (<u>152</u>)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (<u>150i</u>). The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), ethyl acetoacetate (1.303 g, 10.0 mmole) and benzophenone (2.001 g, 11.0 mmole), which gave 3.642 g of a yellow oil. This oil was dissolved in cyclohexane and addition of a small quantity of methanol to the solution precipitated <u>152</u> (2.510 g, 81%) as colourless needles, mp 68-69°C (lit[23] mp 68.5-69.5°C).

Methyl 4-(1-hydroxycyclohex-2-enyl)-3-oxobutanoate (<u>164</u>)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-

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methyl-3-oxohexanoate (150i). The reagents used were: sodium hydride, as a 57% mineral oil dispersion (0.467 g, 11.0 mmole), methyl acetoacetate (1.162 g, 10.0 mmole), n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole) and cyclohex-2-enone (0.962 g, 10.0 ,,ole), which gave 2.210 g of pale yellow oil. Careful distillation of this oil in base-washed apparatus gave 1.229 g (58%) of 164, bp 83-85°C (0.1 mm) as a colourless oil which rapidly darkened on standing.

ir (CCl_4) 3600 (broad, O-H), 1740 (ester C=O), 1705 (C=O) and 1630 cm^{-1} (C=C-COH);

nmr (CCl_4) δ5.67 (m, 2, vinyl protons), 3.70 (s, 3, OCH_3), 3.40 (s, 2, $COCH_2CO_2Me$), 2.83 (broad s, exchangeable D_2O, 1, OH), 2.67 (s, 2, $HOCCH_2CO$) and 2.10 - 1.46 ppm (m, 6, cyclohexyl protons on C_{4-6});

mass spectrum a) high resolution calcd for $C_{11}H_{16}O_4$, 212.1048 amu, found 212.1063 m/e;

b) low resolution m/e (rel intensity) 212(8), 197(12), 194(13), 180(15), 169(23), 136(27), 135(100), 134(15), 121(65), 108(58), 97(85), 96(54), 91(46), 84(38), 79(69), 77(58), 68(69), 55(43) and 43(77).

Methyl 4-(3-hydroxycyclohex-1-enyl)-3-oxobutanoate (165)

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven-dried 50 ml

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flask, and tetrahydrofuran (ca. 25 ml) was distilled, from lithium aluminium hydride, directly into this flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0°C and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. A solution of n-butyllithium (4.5 ml, 2.35M in hexane, 10.6 mmole) was added dropwise to the solution and the mixture allowed to stir for an additional ten minutes, to allow complete formation of the dianion. Cyclohex-2-enone (0.961 g, 10.0 mmole) was added in one portion to the reaction which was allowed to stir for ten minutes before being quenched, which was achieved by dropwise addition of the reaction, via a stainless steel cannula, to a vigorously stirred mixture of ether (ca. 50 ml) and hydrochloric acid (12 ml 2M solution). The aqueous and organic phases were separated. The aqueous phase was further extracted with ether (2 x 25 ml) and the ethereal phases combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting oil chromatographed on silica gel using a mixture of hexane, ether and acetic acid (50:100:1) as eluent. The two major fractions were identified as: methyl 4-(1-hydroxycyclohex-2-enyl)-3-oxobutanoate (164) (0.703 g, 33%) by comparison of ir and nmr spectra with those

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of 164 prepared previously, and methyl 4-(3-hydroxycyclohex-1-enyl)-3-oxobutanoate (165) (0.594 g, 28%), bp 100-101°C (0.1 mm).

ir (CCl_4) 3650 (sharp, O-H), 3500 (broad, O-H), 1740 (ester C=O), 1720 (C=O) and 1630 cm^{-1} (C=C-COH);

nmr ($CDCl_3$) δ6.67 (m, 1, C=CH), 4.20 (m, 1, HOCH), 3.73 (s, 3, OCH_3), 3.48 (s, 2, $COCH_2CO_2Me$), 3.20 (broad s, 2, $C=C-CH_2-CO$), 2.30 (broad s, exchangeable D_2O, 1, OH) and 2.00 - 1.34 ppm (m, 6, cyclohexyl protons on C_{4-6});

mass spectrum a) high resolution calcd for $C_{11}H_{16}O_4$, 212.1048 amu, found 212.1088 m/e;

b) low resolution m/e (rel intensity) 212(1), 194(22), 162(11), 161(9), 136(91), 121(100), 116(37), 108(85), 93(57), 91(52), 79(39), 77(33), 65(32), 59(15), 55(26) and 43(59).

Attempted conjugate addition of dianion 132 to cyclohex-2-enone

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven-dried 50 ml flask, and tetrahydrofuran (ca. 25 ml) was distilled, from lithium aluminium hydride, directly into this flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0°C and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for

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ten minutes after the addition was complete. A solution of n-butyllithium (4.5 ml 2.35M in hexane, 10.6 mmole) was added dropwise to the solution and the mixture allowed to stir for an additional ten minutes, to allow complete formation of the dianion. Cuprous iodide (4.208 g, 22.0 mmole), dried at 110° *in vacuo* (0.1mm) for twenty hours prior to use, was weighed under dry conditions into a 100 ml flask and tetrahydrofuran distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap) and flushed with nitrogen. Both the solution of dianion and the cuprous iodide suspension were cooled in a dry ice/acetone slurry to -78°C. The dianion solution was transferred, via a stainless steel cannula, in a dropwise manner to the flask containing the cuprous iodide. The resulting dark brown mixture was stirred for an hour at the end of which time most of the solid had dissolved. Cyclohex-2-enone (0.963 g, 10.0 mmole) dissolved in tetrahydrofuran (*ca.* 5 ml) was added to the reaction which was maintained at -78°C for an additional hour before being allowed to warm to 0°C. The reaction was quenched by dropwise addition of it to a vigorously stirred mixture of ether (50 ml) and hydrochloric acid (12 ml 2M solution). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 25 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the

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resulting oil chromatographed on silica gel using a mixture of hexane, ether and acetic acid as eluent. The major fractions were identified, by comparison of ir and nmr spectra with authentic or previously prepared materials, as: methyl acetoacetate (0.708 g, 61%), cyclohex-2-enone (0.564 g, 59%), methyl 4-(1-hydroxyclohex-2-enyl)-3-oxobutanoate (164) (0.360 g, 17%), and methyl 4-(3-hydroxycyclohex-1-enyl)-3-oxobutanoate (165) (0.276 g, 13%).

Methyl 5-hydroxy-5-methyl-3-oxohept-6-enoate (163)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (150i). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.163 g, 10.00 mmole), n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole), and methyl vinyl ketone (0.661 g, 11.0 mmole), which gave 1.450 g (78%) of 163 bp 101-103°C (0.3 mm).

ir ($CHCl_3$) 3550 (O-H), 1740 (ester C=O), 1705 (C=O) and 1630 cm^{-1} (C=C-COH);

nmr (CCl_4) δ5.87 (m, 1, C=C<u>H</u>), 5.10 (m, 2, C=C<u>H_2</u>), 3.72 (s, 3, OC<u>H_3</u>), 3.36 (s, 2, COC<u>H_2</u>CO_2Me), 3.20 (broad s, exchangeable D_2O, 1, O<u>H</u>), 2.20 (m, 2, HOCC<u>H_2</u>CO) and 1.27 ppm (s, 3, CC<u>H_3</u>);

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mass spectrum a) high resolution, calcd for $C_9H_{14}O_4$, 186.0891 amu, found 186.0921 m/e

b) low resolution m/e (rel intensity) 186(1), 171(1), 168(3), 139(4), 127(6), 116(15), 101(10), 97(9), 95(8), 85(20), 84(14), 74(12), 71(31), 69(16), 59(26), 55(60) and 43(100).

Base Dependency Study

a) Generation of Dianion 132 by means of Lithium Diisopropylamide.

Diispropylamine, which had been dried by distillation and stored over potassium hydroxide pellets prior to use (1.129 g, 11.3 mmole) was weighed into a 50 ml oven dried flask and tetrahydrofuran (ca. 25 ml) distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. n-butyllithium, as a 2.35M solution in hexane, (5 ml), 11.75 mmole) was added dropwise to the solution and the reaction allowed to stir for ten minutes after the addition was complete, to ensure complete formation of the amide. Methyl acetoacetate (0.638 g, 5.5 mmole) was added dropwise to solution and after a further ten minutes, benzophenone (1.003 g, 5.5 mmole) dissolved in tetrahydrofuran (5 ml) was added. The reaction was quenched after ten minutes by addition of concentrated hydrochloric acid (2 ml) and worked up by the addition of

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ether (50 ml) and water (15 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 35 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure to give a semi-solid which was recrystallised from a mixture of hexane and ether to give 0.827 g of methyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate (150p). Chromatography of the mother liquors on silica gel using chloroform as eluent gave an additional 0.184 g of 150p, to total 1.011 g (62%) as colourless needles, mp 77-79°C.

b) Attempted Generation of Dianion 132 by means of Lithium bis-(trimethylsilyl)amide

Lithium bis-(trimethylsilyl)amide was prepared by the method of Shaw,[92] from hexamethyldisilazane and n-butyllithium, and dissolved in tetrahydrofuran. This solution was standardised by titration against hydrochloric acid to determine its total base equivalence. An aliquot of this solution, which had been found to be 1.52M (5 ml, 7.60 mmole) was diluted to 25 ml with tetrahydrofuran and transferred to a 50 ml oven dried flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (0.420 g, 3.62 mmole) was added dropwise to the solution of base and the

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reaction allowed to stir for one hour after the addition was complete. Benzophenone (0.655 g, 3.65 mmoles) dissolved in tetrahydrofuran (3 ml) was added to the reaction which was quenched after a further fifteen minutes by addition of concentrated hydrochloric acid (0.75 ml). The reaction was worked up by the addition of ether (25 ml) and water (5 ml). The aqueous layer was separated and further extracted with ether (2 x 25 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 25 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure to a pale yellow oil. Glpc analysis (col B, 110°C) indicated that this oil was mainly methyl acetoacetate contaminated with hexamethyldisolazane and benzophenone, and distillation at reduced pressure gave essentially pure methyl acetoacetate (0.352 g, 84%). No product could be detected by glpc or tlc either in the crude oil or the residue from the distillation, that was not starting materials or hexamethyldisilazane.

Temperature Dependency Study

The dianion of methyl acetoacetate was generated as outlined below and then treated with propanal at low and room temperature.

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Generation of Dianion 132

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven-dried 50 ml flask, and tetrahydrofuran (ca. 25 ml) was distilled from lithium aluminium hydride directly into this flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0°C and flushed with nitrogen. Methyl acetoacetate (1.160g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. A solution of n-butyllithium (4.5 ml 2.35M in hexane, 10.6 mmole) was added dropwise to the solution and the mixture allowed to stir for an additional ten minutes, to allow complete formation of the dianion.

Reaction of Dianion 132 with Propanal at -78°C

The solution of dianion 132 was cooled to -78°C in a dry ice/acetone slurry, and propanal (0.640 g, 11.0 mmole) added. The reaction was stirred at -78°C for one hour and then allowed to warm to 0°C before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up by the addition of ether (25 ml) and water (5 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 25 ml), dried over sodium sulphate and filtered. The solvents were

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removed by evaporation at reduced pressure and the resulting oil distilled under high vacuum to give methyl acetoacetate (0.915 g, 79% recovery), identified by glpc analysis, (col B, 110°C) and comparison of its ir spectrum with that of authentic material, and methyl 5-hydroxy-3-oxoheptanoate (150b) (0.191 g, 11%), identified by comparison of its ir and nmr spectra with those of previously prepared 150b.

Reaction of Dianion 132 with Propanal at 25°C

The solution of dianion 132 was allowed to warm to room temperature before propanal (0.641 g, 11.0 mmole) was added. The reaction was stirred at room temperature for one half hour before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up in an identical manner to the previous low temperature reaction to give 0.993 g (57%) of 150b, bp 48-49°C (0.2 mm), which showed identical ir and nmr spectra to that prepared previously.

Claisen Condensations of the Dianion of Beta-ketoesters

Methyl 3,5-dioxohexanoate (176a)

Sodium hydride, as a 57% mineral oil dispersion, (0.467 g, 11.0 mmole) was weighed into a 50 ml oven dried flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap),

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cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. n-Butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) was added dropwise to the reaction and after ten minutes the first portion of methyl acetate, (0.372 g, 5.0 mmole) was added. After a further fifteen minutes, additional n-butyllithium (5 ml, 10.5 mmole) was added very slowly. A further period of fifteen minutes was allowed to elapse before the second portion of methyl acetate (0.371 g, 5.0 mmole) was added and the reaction stirred for a final fifteen minutes before being quenched with concentrated hydrochloric acid (3 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium hydrogen carbonate solution (2 x 10 ml) and with saturated sodium chloride solution (4 x 15 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting yellow oil distilled under high vacuum to give 1.120 g (71%) of 176a, bp 44-46°C (0.3 mm).

ir ($CHCl_3$) 3450 (C=C-O-H), 1740 (ester C=O) and 1600 cm^{-1} (broad, O=C-C=C-OH);

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nmr ($CDCl_3$) δ14.2 (broad s, exchangeable D_2O, 1, C=COH), 5.62 (s, 0.67, C=CH), 3.79 (s, 3, OCH_3), 3.57 (s, 0.64, $COCH_2CO$), 3.35 (s, 2, $COCH_2CO_2Me$), 2.27 (s, 0.95, CH_3CO) and 2.10 ppm (s, 2.13, $CH_3C=C$), 68% enol;

mass spectrum m/e (rel intensity) 158(6), 127(6), 126(8), 116(8), 107(8), 101(6), 98(9), 91(9), 85(43), 77(6), 69(21), 59(10) and 43(100);

analysis calcd for $C_7H_{10}O_4$: C 53.16 H 6.37

found: C 53.14 H 6.26

Methyl 3,5-dioxooctanoate (170c)

This compound was prepared by the same procedure as that employed in the preparation of methyl 3,5-dioxohexanoate (170a). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), two portions of n-butyllithium, as a 2.35M solution in hexane, (4.6 ml, 10.6 mmole) which gave 1.250 g (67%) of 170c, bp 83-85°C (0.1 mm).

ir (CCl_4) 3500 (C=C-O-H), 1740 (ester C=O) and 1595 cm^{-1} (HO-C=C-C=O);

nmr (CCl_4) δ14.3 (broad s, 0.97, C=C-OH), 5.52 (s, 0.98, C=CH), 3.66 (s, 3, OCH_3), 3.20 (s, 1.96, $COCH_2CO_2Me$), 2.26 (t, J=7Hz, $CH_2CH_2C=C$), 1.66 (m, 2.0, $CH_3CH_2CH_2$) and 0.96 ppm (t, J=7Hz, 3.0, CH_3CH_2), 97% enol;

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mass spectrum m/e (rel intensity) 186(41), 172(22), 158(68), 157(57), 143(81), 126(73), 115(62), 113(92), 101(100), 97(28), 85(73), 84(72), 71(90), 69(51), 59(81) and 43(17);

analysis calcd for $C_9H_{14}O_4$: C 58.05 H 7.58

found: C 58.35 H 7.47

Condensation of ethyl butanoate with dianion 132

This reaction was performed in a similar manner to that in which methyl 3,5-dioxohexanoate was prepared. The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), two portions of n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole) and two portions of ethyl butanoate (0.582 g, 5.0 mmole), which gave 1.441 g of a pale yellow oil. Glpc analysis (col C, 140°C) of this oil showed it to contain two components. Distillation through a short Vigreux column gave partial separation of these components and repeated distillation (three more times), although accompanied by considerable resinification of the oil, gave the pure components identified as: methyl 3,5-dioxooctanoate (176c) (0.619 g, 33%) by comparison of ir and nmr spectra with those of previously prepared 176c, and, ethyl 3,5-dioxooctanoate (177), (0.223 g, 11%) bp 94-96°C (0.1 mm).

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ir (CCl_4) 3500 (C=C-OH), 1740 (ester C=O) and 1600 cm^{-1} (HO-C=C-C=O);

nmr (CCl_4) δ14.6 (broad s, exchangeable D_2O, 1, OH), 5.57 (s, 1, C=CH), 4.13 (q, H=7Hz, 2, OCH_2CH_3), 3.08 (s, 2, $COCH_2CO_2Me$), 2.27 (t, J=7Hz, 2, CH_2CH_2CO), 1.65 (m, 2, $CH_3CH_2CH_2$), 1.27 (t, J=7Hz, 2, OCH_2CH_3) and 0.95 ppm (t, J=7Hz, 3, $CH_2CH_2CH_3$);

mass spectrum m/e (rel intensity) 200(20), 156(47), 143(78), 126(70), 115(64), 113(80), 101(100), 97(30), 85(74), 84(70), 71(85), 69(15), 59(60) and 43(28);

analysis calcd for $C_{10}H_{16}O_4$: C 59.98 H 8.05

found: C 59.98 H 8.08

Methyl 3,5-dioxopentanoate (176b)

This compound was prepared by the same procedure as that employed in the preparation of methyl 3,5-dioxohexanoate (176a). The reagents used in the preparation were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.160 g, 10.0 mmole), two portions of n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole) and two portions of methyl formate (0.300 g, 5.0 mmole), which gave 0.993 g (69%) of 176b, bp 55-56°C (0.1 mm).

ir (CCl_4) 3500 (C=C-O-H), 1740 (ester C=O), 1640 (chelated C=O) and 1590 cm^{-1} (C=C);

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nmr (CCl_4) δ13.5 (broad s, exchangeable D_2O, 1, O<u>H</u>), 7.72 (d, J=5Hz, 1, CH=C<u>H</u>-OH), 5.63 (d, J=5Hz, 1, C=C<u>H</u>), 3.72 (s, 3, OCH_3), and 3.32 ppm (s, 2, $COCH_2CO_2Me$);

mass spectrum m/e a) high resolution calcd for C H O : 144.0422 amu, found 144.0421 m/e;

b) m/e (rel intensity) 144(5), 131(3), 127(2), 126(11), 113(15), 112(17), 101(100), 97(30), 85(67), 71(63), 59(43) and 43(28).

Condensation of methyl benzoate with dianion 132

Sodium hydride, as a 57% mineral oil dispersion, (0.468 g, 11.0 mmole) was weighed into a 50 ml oven dried flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.164 g, 10.0 mmole) was added dropwise to the cooled slurry, and after the addition was complete the reaction was allowed to stir for ten minutes. n-Butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) was added dropwise to the reaction and after ten minutes the first portion of methyl benzoate (0.680 g, 5.0 mmole) was added. After a further fifteen minutes additional n-butyllithium (5 ml, 10.5 mmole) was added very slowly. A further period of fifteen minutes was allowed to elapse before the second portion of methyl benzoate (0.680 g, 5.0 mmole) was added and the reaction was

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stirred for a final fifteen minutes before being quenched with concentrated hydrochloric acid (3 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium hydrogen carbonate solution (4 x 15 ml) and with saturated sodium chloride solution (2 x 15 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting red oil distilled under high vacuum to give 0.817 g (37%) of methyl 3,5-dioxo-5-phenylpentanoate (176d), bp 127-129°C (0.1 mm), characterised as outlined below. The basic aqueous extract (saturated sodium hydrogen carbonate washings) were acidified to pH 2 by addition of 1M hydrochloric acid and the resulting solution extracted with ether (3 x 35 ml) and these ethereal extracts combined, washed with saturated sodium chloride solution (3 x 15 ml), dried over sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting solid recrystallised from a mixture of hexane and ether to give 0.684 g (30%) of 3,5-dioxo-5-phenylpentanoic acid (178d) mp 93-97°C, (literature[23] mp 94-96°C). Methyl 3,5-dioxo-5-phenypentanoate was characterised by:

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ir (CCl_4) 3450 (C=C-O-H), 1740 (ester C=O) and 1600 cm^{-1} (HO-C=C-C=O);

uv (CH_3OH) 322 nm (1.3×10^3);

nmr (CCl_4) δ14.3 (broad s, exchangeable D_2O, 1, O<u>H</u>), 7.87 (m, 2, protons on C_2 and C_6 of benzene ring), 7.37 (m, 3, protons on C_3, C_4 and C_5 of benzene ring), 6.26 (s, 1, C=C<u>H</u>), 3.70 (s, 3, OCH_3) and 3.38 ppm (s, 2, $COCH_2CO_2Me$);

mass spectrum m/e (rel intensity) 220(21), 205(11), 203(34), 189(26), 188(65), 174(16), 173(11), 163(57), 161(58), 147(74), 105(100), 85(15), 77(48), 69(51), 51(37) and 43(28);

analysis calcd for $C_{12}H_{12}O_4$: C 65.45 H 5.49

found: C 65.42 H 5.65

Condensation of methyl 4-methoxybenzoate with dianion 132

This reaction was performed in a similar manner to the condensation of methyl benzoate with dianion 132. The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.467 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), two portions of n-butyllithium, as a 2.35M solution in hexane, (4.5 ml, 10.6 mmole) and two portions of methyl 4-methoxybenzoate (0.831 g, 5.0 mmole) which gave 0.741 g (29%) of 5-(4-methoxyphenyl)-3,5-dioxopentanoic acid (178e), as colourless needles (from hexane/ether) mp 103-105°C, and 1.051 g (42%) of methyl 5-(4-methoxyphenyl)-3,5-dioxopentanoate (176e), bp 142-143°C

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(0.1 mm). These compounds were characterised as follows:

a) 5-(4-methoxyphenyl)-3,5-dioxopentanoic acid

ir ($CHCl_3$) 3700 (sharp, non-hydrogen bonded CO_2H), 3500 (hydrogen bonded CO_2H and C=C-OH), 1720 (carboxylic acid C=O) and 1600 cm^{-1} (O=C-C=C-OH);

uv (CH_3OH) 326 (7.1 x 10) and 287 nm (shoulder, 4.4 x 10^3);

nmr (CD_3COCD_3) δ14.6 (broad s, exchangeable D_2O, 1, enol O<u>H</u>), 11.2 (broad s, exchangeable D_2O, 1, CO_2<u>H</u>), 7.87 (m, 2, protons on C_3 and C_4 of benzene ring), 6.93 (m, 2, protons on C_2 and C_6 of benzene ring), 3.90 (s, 3, OCH_3) and 3.37 ppm (s, 2, $COCH_2CO_2H$);

mass spectrum m/e (rel intensity) 237(5), 236(43), 219(5), 218(42), 193(43), 192(96), 191(67), 178(50), 177(84), 161(68), 149(20), 136(57), 135(100), 121(21), 109(75), 108(57), 105(15), 92(32), 85(30), 77(37), 69(45), 51(35), 44(40) and 43(35);

analysis calcd for $C_{12}H_{12}O_5$: C 61.02 H 5.12

found: C 61.08 H 5.26

b) methyl 5-(4-methoxyphenyl)-3,5-dioxopentanoate:

ir (CCl_4) 3500 (enol OH), 1740 (ester C=O) and 1600 cm^{-1} (O=C-C=C-OH);

uv (CH_3OH) 325 (5.4 x 10) and 285 nm (shoulder, 2.0 x 10^3);

nmr (CCl_4) δ14.3 (broad s, exchangeable D_2O, 1, O<u>H</u>), 7.85 (m, 2, protons on C_3 and C_5 of benzene ring), 6.90

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(m, 2, protons on C_2 and C_6 of benzene ring), 6.20 (s, 1, C=C<u>H</u>), 3.90 (s, 3, aryl OC<u>H</u>$_3$), 3.77 (s, 3, ester OC<u>H</u>$_3$) and 3.47 ppm (s, 2, CO<u>CH</u>$_2$CO$_2$Me);

mass spectrum m/e (rel intensity) 250(21), 217(57), 190(44), 177(65), 135(100), 109(23), 108(13), 107(15), 105(16), 104(32), 91(29), 77(29), 69(65), 59(23) and 43(55);

analysis calcd for $C_{13}H_{14}O_5$: C 62.39 H 5.64

found : C 62.43 H 5.72

<u>Base Dependency Study</u>

a) <u>Lithium diisopropylamide</u>.

(i) <u>Attempted acylation with methyl acetate</u>.

Diisopropylamine (1.536 g, 15.0 mmole) was weighed into an oven-dried flask, and tetrahydrofuran (<u>ca</u>. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The fask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. n-Butyllithium, as a 2.1M solution in hexane, (7.5 ml, 15.8 mmole) was added dropwise to the cooled solution and the reaction allowed to stand for ten minutes after the addition was complete. Methyl acetoacetate (0.580 g, 5.0 mmole) was added to the reaction over a period of about ten minutes and a further period of ten minutes allowed to elapse before methyl acetate, (0.370 g, 5.0 mmole) was added. After ten minutes the reaction was quenched with concentrated hydrochloric acid (<u>ca</u>. 4 ml) and the reaction worked up by the

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addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with water (3 x 20 ml) and with saturated sodium chloride solution (2 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation at reduced pressure to give 0.601 g of pale yellow oil. Glpc analysis of this oil (col C, 120°C) showed it to be methyl acetoacetate contaminated with minor amounts of diisopropylamine and methyl acetate. Both glpc and tlc analysis of this oil and the acidified crude reaction mixture failed to indicate any of the desired product, methyl 3,5-dioxohexanoate (176a). Distillation of the oil at reduced pressure gave 0.521 g (90%) of methyl acetoacetate, bp 51-52°C (17 mm) identified by glpc analysis and comparison of its ir and nmr spectra with those of authentic material.

ii) Attempted acylation with methyl benzoate.

Diisopropylamine (1.536 g, 15.0 mmole) was weighed into an oven-dried flask, and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. n-Butyllithium, as a 2.1M solution in hexane, (7.5 ml, 15.8 mmole) was added dropwise to the cooled solution and the reaction allowed to stand for ten minutes after the addition was complete. Methyl acetoacetate (0.580 g, 5.0

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mmole) was added to the reaction over a period of about ten minutes and a further period of ten minutes allowed to elapse before methyl benzoate (0.680 g, 5.0 mmole) was added. After ten minutes the reaction was quenched with concentrated hydrochloric acid (ca. 4 ml) and the reaction worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with water (3 x 20 ml) and with saturated sodium chloride solution (2 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting yellow oil crystallised on standing overnight. Recrystallisation from ether gave 0.924 g (91%) of N,N-diisopropylbenzamide mp 68-69°C (lit[118] mp 69-71°C).

ir ($CHCl_3$) 1620 cm^{-1} (C=O);

nmr ($CDCl_3$) δ7.30 (s, 5, aryl protons), 3.67 (septuplet, J=6Hz, 2, $N(C\underline{H}Me_2)_2$), and 1.32 ppm (d, H=6Hz, 12, $N(CH(C\underline{H}_3)_2)_2$). Glpc and tlc analysis of the crude oil failed to show any of the desired products methyl 3,5-dioxo-5-phenylpentanoate (176d) or 3,5-dioxo-5-phenylpentanoic acid (178d).

b) Lithium N-cyclohexyl-N-isopropylamide.

(i) Acylation with methyl acetate.

N-Cyclohexyl-N-isopropylamine, which had been distilled from calcium hydride and stored over potassium hydroxide until used, (2.130 g, 15.0 mmole) was weighed into

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an oven dried flask and to this was added 2,2'-bipyridyl (ca. 10 mg). Tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Sufficient n-butyllithium solution was added to the reaction to produce a permanent red colouration, and then the measured volume of n-butyllithium (6 ml of a 2.5M solution in hexane, 15.0 mmole) was added dropwise to the reaction mixture. After a period of ten minutes had elapsed, methyl acetoacetate (0.581 g, 5.0 mmole) was added dropwise and the reaction allowed to stand for twenty minutes before the methyl acetate (0.371 g, 5.0 mmole) was added. After a further twenty minutes the reaction was quenched with concentrated hydrochloric acid (ca. 4 ml) and worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with water (2 x 20 ml) and with saturated sodium chloride solution (2 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressureto give 0.537 g of yellow oil. Glpc analysis of this oil (col C, 120°C) showed it to contain methyl acetoacetate and methyl 3,5-dioxohexanoate (176a) in the ratio 93:7. Distillation of the oil at reduced pressure gave 0.486 g (88%) of methyl acetoacetate bp 49-52°C (17 mm), identified by comparison of ir and nmr spectra

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with those of authentic material, and 40 mg of residue. The residue was distilled in a bulb-to-bulb distillation apparatus (bath temperature 50°C) under high vacuum (0.2 mm) to give 37 mg (4%) of methyl 3,5-dioxohexanoate (176a) which was identified by comparison with previously prepared material by glpc (col C, 120°C) and tlc:

(ii) Acylation with methyl benzoate.

N-Cyclohexyl-N-isopropylamine, which had been distilled from calcium hydride and stored over potassium hydroxide until used, (2.130 g; 15.0 mmole) was weighed into an oven dried flask and to this was added 2,2'-bipyridyl (ca. 10 mg). Tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Sufficient n-butyllithium solution was added to the reaction to produce a permanent red colouration, and then the measured volume of n-butyllithium (6 ml of a 2.5M solution in hexane, 15.0 mmole) was added dropwise to the reaction mixture. After a period of ten minutes had elapsed, methyl acetoacetate (0.581 g, 5.0 mmole) was added dropwise and the reaction allowed to stand for twenty minutes before the methyl benzoate (0.680 g, 5.0 mmole) was added. After a further twenty minutes the reaction was quenched with concentrated hydrochloric acid (ca. 4 ml) and worked up by the addition of ether (35 ml) and

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water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with water (3 x 20 ml) and with saturated sodium chloride solution (2 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure to give a yellow semi-crystalline material. Recrystallisation from ether gave 1.080 g (88%) of N-cyclohexyl-N-isopropylbenzamide (196), mp 76-78 C, which was characterised as outlined below. The mother liquors from the recrystallisation were found, by glpc analysis, (col C, 200 C) to contain methyl 3,5-dioxo-5-phenylpentanoate (176d) and were subjected to chromatography on silica gel, using chloroform as eluent. The major component isolated from this chromatography was methyl 3,5-dioxo-5-phenylpentanoate (176d), (0.085 g, 8%), identified by comparison of its ir spectrum with that of previously prepared material.

N-cyclohexyl-N-isopropylbenzamide was characterised by:

ir ($CHCl_3$) 1620 cm^{-1} (C=O);

nmr (CCl_4) δ7.30 (s, 5, aryl protons), 3.87 - 3.00 (m, 2, $N(CH_3)_2$), 2.20 - 1.00 (m, 10, protons on C_2 - C_6 of cyclohexyl ring) and 1.30 ppm (d, H=6Hz, 6, $NC(CH_3)_2$);

mass spectrum m/e (rel intensity) 246(22), 245(37), 244(14), 230(22), 203(27), 202(46), 189(15), 188(39), 165(11), 164(37), 163(54), 162(62), 149(11), 148(41), 146(23), 145(32), 129(19), 128(19), 118(36), 117(41), 115(33), 105(72), 103(35), 85(33), 79(35), 78(44), 76(93), 56(83) and 54(100).

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Condensation of the sodium salt of methyl acetoacetate with dianion 132.

a) At room-temperature, acid quenching.

Sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole) was weighed into an oven dried flask, and freed from mineral oil by washing with hexane (ca. 15 ml) and decantation. The washing procedure was repeated twice with hexane and the residual hexane was removed by washing with tetrahydrofuran. After decantation of the tetrahydrofuran, fresh tetrahydrofuran was distilled directly into the flask, from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.162 g, 10.0 mmole) was added dropwise to the cooled slurry, and after the addition was complete the reaction was allowed to stand for a period of about ten minutes. n-Butyllithium, as a 2.3M solution in hexane, (2.2 ml, 5.1 mmole) was added dropwise to the reaction, which was then allowed to warm to room temperature. After a period of twenty four hours the reaction was quenched by addition of concentrated hydrochloric acid (ca. 1.5 ml) and worked up by addition of ether (35 ml) and water (5 ml). The aqueous phase, the pH of which was ca. 2, was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 20 ml), dried over anhydrous

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sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure to give 0.983 g of brown oil. Distillation of this oil at reduced pressure gave 0.716 g (62%) of methyl acetoacetate, bp 45-47°C (14 nm), identified by comparison of its ir and nmr spectra with those of authentic material, and a brown solid residue which was crystallised from methanol to give 0.220 g (24%) of methyl orsellinate (183), mp 138-140°C (lit[119], mp 138-139°C), mixed mp 138-140°C.

ir ($CHCl_3$) 3650 (Free OH), 3300 (hydrogen bonded OH), 1655 (free C=O) and 1620 cm^{-1} (hydrogen bonded C=O);

nmr ($CDCl_3$) δ6.30 (s, 2, aryl protons), 6.10 (broad s, exchangeable D_2O, 2, O<u>H</u>), 3.95 (s, 3, $OC\underline{H}_3$) and 2.50 ppm (s, 3, $C\underline{H}_3$).

b) <u>At room temperature, buffered quenching</u>.

This reaction was performed in the same manner as the preceding reaction. The reagents employed were: sodium hydride, as a 57% mineral oil dispersion, (0.463 g, 11.0 mmole), methyl acetoacetate (1.160 g, 10.0 mmole) and n-butyllithium, as a 2.1M solution in hexane, (2.5 ml, 5.2 mmole). After the twenty four hour reaction period, the reaction was quenched by adding it, via a stainless steel cannula, to a vigorously stirred mixture of ether (50 ml) and buffer solution (prepared by dissolving sodium dihydrogen orthophosphate (4 g) and disodium hydrogen orthophosphate

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(4 g) in water (20 ml). The aqueous phase was separated, saturated with sodium chloride and further extracted with ether (3 x 20 ml). The ethereal layers were combined, washed with saturated sodium chloride solution (20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting oil chromatographed on silica gel, using a mixture of benzene and ethyl acetate (1:1 v/v) as eluent. Three components were obtained from the chromatography, and these, in order of their elution, were:

methyl 3,5,7-trioxooctanoate (182), (83 mg, 8%) as a pale yellow, unstable oil, which on standing overnight at 0°C was converted to methyl orsellinate in quantitative yield, and was characterised as outlined below,

methyl orsellinate (183) (155 mg, 17%) as cream coloured needles, mp 138-140°C, identified by comparison of its ir spectrum with that of authentic material, and

methyl acetoacetate (0.679 g, 59%) identified by comparison of its ir spectrum with that of authentic material.

Methyl 3,5,7-trioxooctanoate was characterised by:

ir ($CHCl_3$) 3400 (enol OH), 1740 (ester C=O), 1720 (C=O), 1640 (C=C-C=O), 1620 (HO-C=C-C=O) and 1600 cm^{-1} (C=C);

nmr (CCl_4) δ14.60 (broad s, exchangeable D_2O, 1.1, enol O-H), 6.20 (m, 1.1, C=CH), 3.96 (s, 3, OCH_3), 3.70 (s, 4, $COCH_2CO_2Me$), 3.67 (s, 1.8, $COCH_2CO$) and 2.43 ppm (s, 3, $COCH_3$);

mass spectrum m/e (rel intensity) 184(9), 182(4), 151(4),

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150(13), 143(7), 142(26), 127(40), 117(9), 113(27), 101(9), 100(24), 85(100), 73(21), 69(20), 61(34) and 43(100).

c) At reflux temperature.

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven dried flask, and freed from mineral oil by washing with hexane and tetrahydrofuran as previously outlined. After removal of the solvents used in the washing, fresh tetrahydrofuran was distilled into the flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161g, 10.0 mmole) was added dropwise to the cooled slurry, and after the addition was complete, the reaction was allowed to stand for a period of ten minutes. n-Butyllithium, as a 2.3M solution in hexane, (2.2 ml, 5.1 mmole) was added dropwise to the reaction, which was then allowed to warm to room temperature. The flask was then transferred to a glove bag, where, under an atmosphere of nitrogen, the septum cap was removed and replaced with a reflux condenser, the top of which was stoppered with a fresh septum cap. The flask and condenser assembly was withdrawn from the glove bag and heated till a moderate rate of reflux was obtained. After two hours at reflux temperature, the heating was discontinued and the flask cooled in ice to 0°C. The reaction was quenched with concentrated hydrochloric acid

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(ca. 1.5 ml) and worked up by the addition of ether (35 ml) and water (5 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 20 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure, and distillation of the resulting oil at reduced pressure gave 0.821 g (71%) of methyl acetoacetate, bp 46-48°C (14 mm), identified by comparison of its ir spectrum with that of authentic material, and a brown residue, which on titration with methanol gave 0.213 g (23%) of methyl orsellinate (183), as pale yellow needles, identified by comparison of its ir spectrum with that of authentic material.

Alkylation of the Dianion of Beta-ketoesters with dihaloalkanes.

Reaction of 1,3-dibromopropane with dianion 132.

a) With 1 equivalent of 1,3-dibromopropane.

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmoles) was weighed into an oven dried flask, and tetrahydrofuran (ca. 25 ml) distilled directly into this flask, from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry and the

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reaction allowed to stand for ten minutes after the addition was complete. n-Butyllithium, as a 2.3M solution in hexane, (4.5 ml, 10.6 mmole) was added dropwise to the reaction which was allowed to stand for a further ten minutes before the addition of 1,3-dibromopropane (2.022 g, 10.0 mmole) in one portion. After a final period of ten minutes, the reaction was quenched with concentrated hydrochloric acid (2 ml) and worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 25 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting yellow oil chromatographed on silica gel using chloroform as eluent. Two components were isolated from this chromatography, and these were, in order of elution, methyl 2-oxocyclohexanecarboxylate (145) (0.515 g, 33%), identified by comparison of its ir and nmr spectra with those of previously prepared material and by tlc comparison, and dimethyl 3,9-dioxoundecanedicate (187a) (0.503 g, 37%), bp 117-119°C (0.2 mm), which was characterised by:

ir ($CHCl_3$) 1745 (ester C=O) and 1720 cm^{-1} (C=O);

nmr ($CDCl_3$) δ3.76 (s, 6, OCH_3), 3.43 (s, 4, $COCH_2CO_2Me$), 2.37 (t, J=6Hz, 4, $COCH_2CH_2$) and 1.93 - 1.10 ppm (m, 6, $COCH_2CH_2CH_2CH_2CH_2CO$);

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mass spectrum m/e (rel intnesity) 254(65), 241(3), 222(5), 209(3), 167(85), 157(55), 139(17), 129(16), 121(50), 116(39), 101(25), 82(68), 59(40), 55(58) and 43(100);

analysis calcd for $C_{13}H_{20}O_6$: C 57.34 H 7.40

found: C 57.03 H 7.29

b) With 0.5 equivalents of 1,3-dibromopropane.

This reaction was performed in the same manner as the previous experiment in which dibromopropane and the dianion of methyl acetoacetate were reacted. The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.160 g, 11.0 mmole), n-butyllithium, as a 2.3M solution in hexane, (4.5 ml, 10.6 mmole) and 1,3-dibromopropane (1.012 g, 5.0 mmole), which gave 1.049 g (77%) of dimethyl 3,9-diouxoundecanedioate (187a), isolated by distillation. This product had identical ir and nmr spectra as that prepared previously.

c) Dilution study.

A solution of dianion 132 was prepared as outlined below:

Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole) was weighed into an oven dried flask, and tetrahydrofuran (ca. 25 ml) distilled directly into this flask, from lithium aluminium hydride. The flask was equipped with

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a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stand for ten minutes after the addition was complete. n-Butyllithium, as a 2.3M solution in hexane, (4.5 ml, 10.6 mmole) was added dropwise to the reaction which was allowed to warm to room temperature. 1,3-Dibromopropane (2.023 g, 10.0 mmole) was weighed into an oven dried flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride and the flask stoppered with a septum cap. A 250 ml flask was equipped with a Soxlet extraction apparatus which carried a three necked adaptor and a reflux condenser. The assembly was flame-dried, after which the condenser was fitted with a calcium chloride drying tube and the two remaining openings stoppered with septum caps. Tetrahydrofuran (ca. 50 ml) was placed in the apparatus by means of a syringe, and the flask heated to produce a moderate rate of reflux. The solutions of dianion and bromopropane were then added to the Soxlet extractor, via stainless steel cannulae, at such a rate that one drop of each solution was added to each cycle of the extractor. The rate of addition was controlled by applying nitrogen pressure to the flasks containing the solutions. After the addition was complete, reflux was maintained for several more cycles to ensure all of the reagents were transferred to the flask. The apparatus was

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allowed to cool before the reaction was quenched with concentrated hydrochloric acid (2 ml). Water (10 ml) was added and the aqueous phase separated and extracted with ether (2 x 35 ml). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting oil distilled, also under reduced pressure, to give 1.059 g (68%) of methyl 2-oxocyclohexanecarboxylate (145) which was identified by comparison of its ir and nmr spectra with those of previously prepared material. The residue from the distillation was chromatographed on silica gel using chloroform as eluent to give 0.149 g (11%) of dimethyl 3,9-dioxoundecanedioate (147a), which was identified by comparison of its ir and nmr spectra with those of previously prepared material.

Methyl 2-(2-carbomethoxy-3-oxocyclohex-1-enyl)-acetate (188).

This compound was prepared by the same procedure as that employed in the reaction of 1 equivalent of 1,3-dibromopropane with dianion 132. The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.466 g, 11.0 mmole), methyl acetoacetate (1.161 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5.0 ml, 10.5 mmole) and dibromomethane (0.872 g, 5.0 mmole), which gave 0.701 g (62%) of 188, bp 75-78°C (0.2 mm) characterised by:

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ir ($CHCl_3$) 3600 (broad, enol OH), 1740 (ester C=O), 1735 (C=C-CO Me) and 1680 cm^{-1} (C=C-C=O);

uv (CH_3OH) 228 nm (1.2 x 10);

nmr ($CDCl_3$) δ3.83 (s, 3, $C=C-CO_2\underline{CH_3}$), 3.75 (s, 3, $CO_2\underline{CH_3}$), 3.35 (s, 2, $\underline{CH_2}CO_2Me$) and 2.40 - 1.70 ppm (m, 6, cyclohexenyl protons);

mass spectrum m/e (rel intensity) 226(19), 195(43), 194(100), 166(45), 162(100), 138(40), 129(23), 112(24), 107(28), 101(21), 82(38), 79(48), 70(46), 59(51) and 43(57);

analysis calcd for $C_{11}H_{14}O_5$: C 58.40 H 6.24

found : C 58.53 H 6.24

Dimethyl 3,16-dioxooctadecanedioate (187b).

This compound was prepared by the same procedure as that employed in the reaction of 1 equivalent of 1,3-dibromopropane with dianion 132. The reagents used were: sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmole), methyl acetoacetate (1.162 g, 10.0 mmole), n-butyllithium, as a 2.1M solution in hexane, (5.0 ml, 10.5 mmole) and 1,10-dibromodecane (1.501 g, 5.0 mmole). The crude product from this reaction solidified on standing overnight and was subsequently recrystallised from ether to give 1.516 g, (98%) of 187b, mp 80-82°C.

ir ($CHCl_3$) 1745 (ester C=O) and 1720 cm^{-1} (C=O);

nmr (CCl_4) δ3.50 (s, 6, $OC\underline{H_3}$), 3.27 (s, 4, $COC\underline{H_2}CO_2Me$), 2.43 (t, H=6Hz, 4, $COC\underline{H_2}CH_2$) and 1.27 ppm (m, 20, $COCH_2(C\underline{H_2})_{10}CH_2CO$);

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mass spectrum m/e (rel intensity) 370(10), 339(13), 338(12), 320(16), 296(20), 265(18), 256(17), 255(100), 237(21), 223(14), 205(12), 195(11), 181(23), 178(14), 163(27), 158(12), 143(9), 129(71), 116(90), 101(51), 69(58), 59(95) and 43(65);

analysis calcd for $C_{20}H_{34}O_6$: C 64.84 H 9.25

found: C 64.72 H 9.28

Condensation of Nitriles with the Dianion of β-Ketoesters.

Condensation of Benzonitrile with dianion 132.

Sodium hydride, as a 57% mineral oil dispersion, (0.467 g, 11.0 mmole) was weighed into a 50 ml oven dried flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. n-Butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) was added dropwise to the reaction and after ten minutes benzonitrile (1.031 g, 10.0 mmole) was added. The reaction mixture was allowed to warm to room temperature and stirred for twelve hours before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked-up by the addition of ether (35 ml) and water (10 ml) and the resulting precipitate filtered off.

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The precipitate was washed with acetone (2 x 10 ml), air dried and sublimed at 150°C (0.2 mm) to give 0.547 g (29%) of 6-phenylpyridine-2,4-dione (191a) as colourless spars, characterised as outlined below.

The aqueous phase of the filtrate was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 x 15 ml), dried over anhydrous sodium sulphate and filtered. The solvents were removed by evaporation under reduced pressure and the resulting oil chromatographed on silica gel using ethyl acetate as eluent. The major fraction from this chromatography was collected, and freed from eluent by distillation at room temperature under reduced pressure to give 1.466 g (66%) of methyl 5-amino-3-oxo-5-phenylpent-4-enoate (194a) as a pale yellow oil.

ir ($CHCl_3$) 3550 (N-H), 1740 (ester C=O), 1615 (O=C-C=C-NH_2) and 1600 cm^{-1} (C=C);

uv (C_2H_5OH) 325 nm;

nmr (CCl_4) δ8.00 (broad s, exchangeable D_2O, 1, hydrogen bonded NH), 7.41 (m, 5, aromatic protons), 6.20 (broad s, exchangeable D_2O, 1, NH), 5.37 (s, 1, C=CH), 3.60 (s, 3, OCH_3) and 3.27 ppm (s, 2, $COCH_2CO_2Me$);

mass spectrum a) high resolution calcd for $C_{12}H_{13}NO_3$: 219.0895 amu, found 219.0896 m/e;

b) low resolution m/e (rel intensity) 219(26), 159(15), 146(47), 127(35), 121(32), 119(95), 118(95),

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103(30), 84(52), 82(22), 59(46) and 43(100).

6-Phenylpyridine-2,4-dione (191) was characterised by:

mp 314-316°C (lit[116] mp 315-318°C);

ir (KBr disc) 1640, 1620, 1595 and 1560 cm^{-1};

uv (C_2H_5OH) 310 and 255 nm, (C_2H_5OH + NaOH) 240 nm;

mass spectrum m/e (rel intensity) 188(16), 187(100), 186(17), 160(6), 159(15), 158(10), 147(11), 146(61), 130(19), 104(33), 103(33), 91(14), 77(21), 69(9) and 51(15).

Thermolysis of Methyl 5-amino-3-oxo-5-phenylpent-4-enoate (194a).

Enamine 194a (156 mg, 0.71 mmole) was placed in a bulb-to-bulb distillation apparatus and heated to 150°C under reduced pressure (0.2 mm). After one half hour the starting material had completely disappeared and white spars had been deposited on the cooler parts of the apparatus. These crystals were collected and found to amount to 134 mg (100%) of 6-phenylpyridine-2,4-dione (191), which exhibited identical mp and ir and uv spectra to that obtained previously.

Methyl 5-amino-3-oxohex-4-enoate (194b).

Sodium hydride, as a 57% mineral oil dispersion, (0.467 g, 11.0 mmole) was weighed into a 50 ml oven dried flask and tetrahydrofuran (ca. 25 ml) was distilled directly into this flask from lithium aluminium hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap),

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cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmole) was added dropwise to the cooled slurry and the reaction allowed to stir for ten minutes after the addition was complete. n-Butyllithium, as a 2.1M solution in hexane, (5 ml, 10.5 mmole) was added dropwise to the reaction and after ten minutes acetonitrile (0.409 g, 10.0 mmole) was added. The reaction mixture was allowed to warm to room temperature and stirred for sixteen hours before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 x 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 x 15 ml), dried over anhydrous magnesium sulphate and filtered. The solvents were removed by evaporation under reduced pressure. The resulting semi-solid was crystallised from chloroform to give 1.490 g (86%) of 194b as long yellow needles, mp 103-104°C. Sublimation at 175°C (0.2 mm) gave colourless spars, but did not raise the melting point.

ir ($CHCl_3$) 3550 (N-H), 1740 (ester C=O), 1625 (O=C-C=C-NH_2) and 1610 cm^{-1} (C=C);

uv (CH_3OH) 303 nm (16.8×10^3) and (CH_3OH + NaOH) 274 nm;

nmr ($CDCl_3$) δ10.0 (broad s, exchangeable D_2O, 1, hydrogen bonded N-H), 5.5 (broad s, exchangeable D_2O, 1, NH), 5.10 (s, 1, C=CH), 3.70 (s, 3, OCH_3), 3.33 (s, 2, $COCH_2CO_2Me$) and 1.97 ppm (s, 3, CCH_3);

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mass spectrum m/e (rel intensity) 158(3), 157(26), 126(2), 125(3), 85(7), 84(100), 83(2), 70(2), 68(2), 54(2), 43(3), 42(5) and 41(4);

analysis calcd for $C_7H_{11}O_3N$: C 53.49 H 7.05 N 8.91

found: C 53.18 H 6.99 N 8.84

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SPECTRAL APPENDIX

The ir, nmr and mass spectra of all compounds, which have not been previously reported in the literature, are shown in this appendix.

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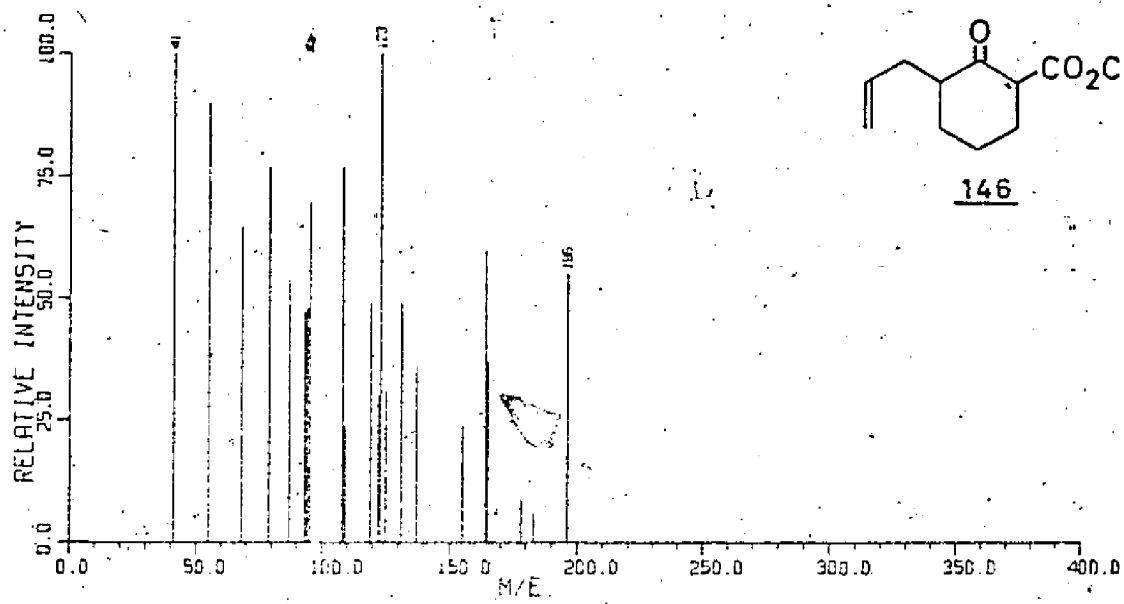

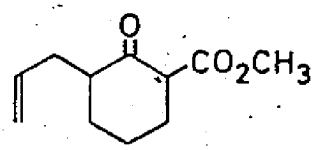

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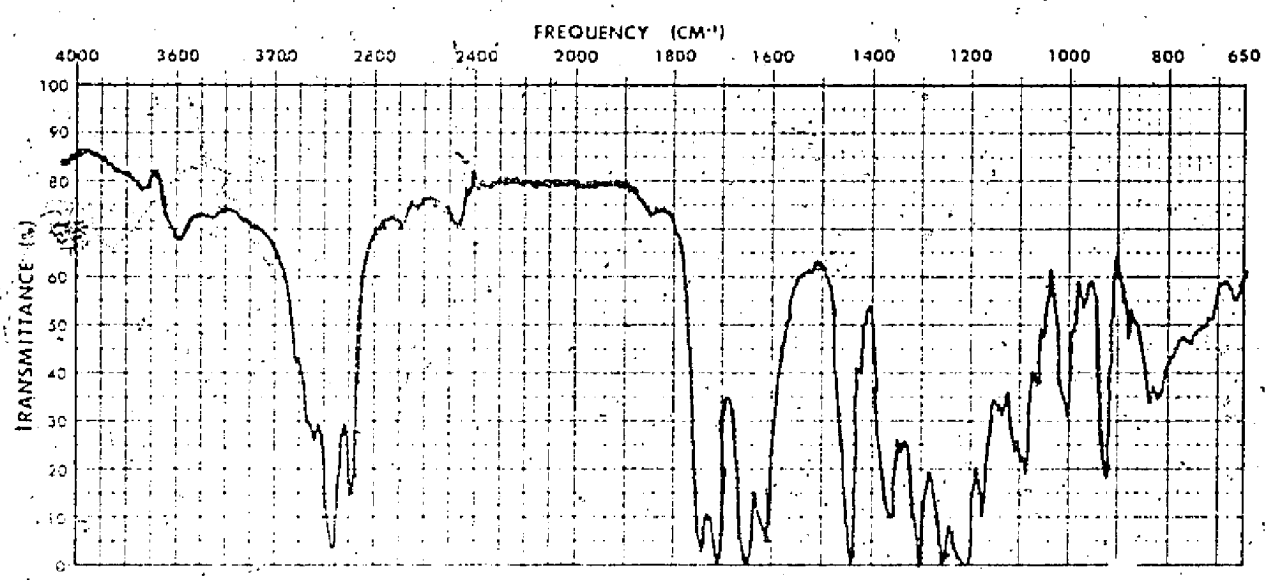

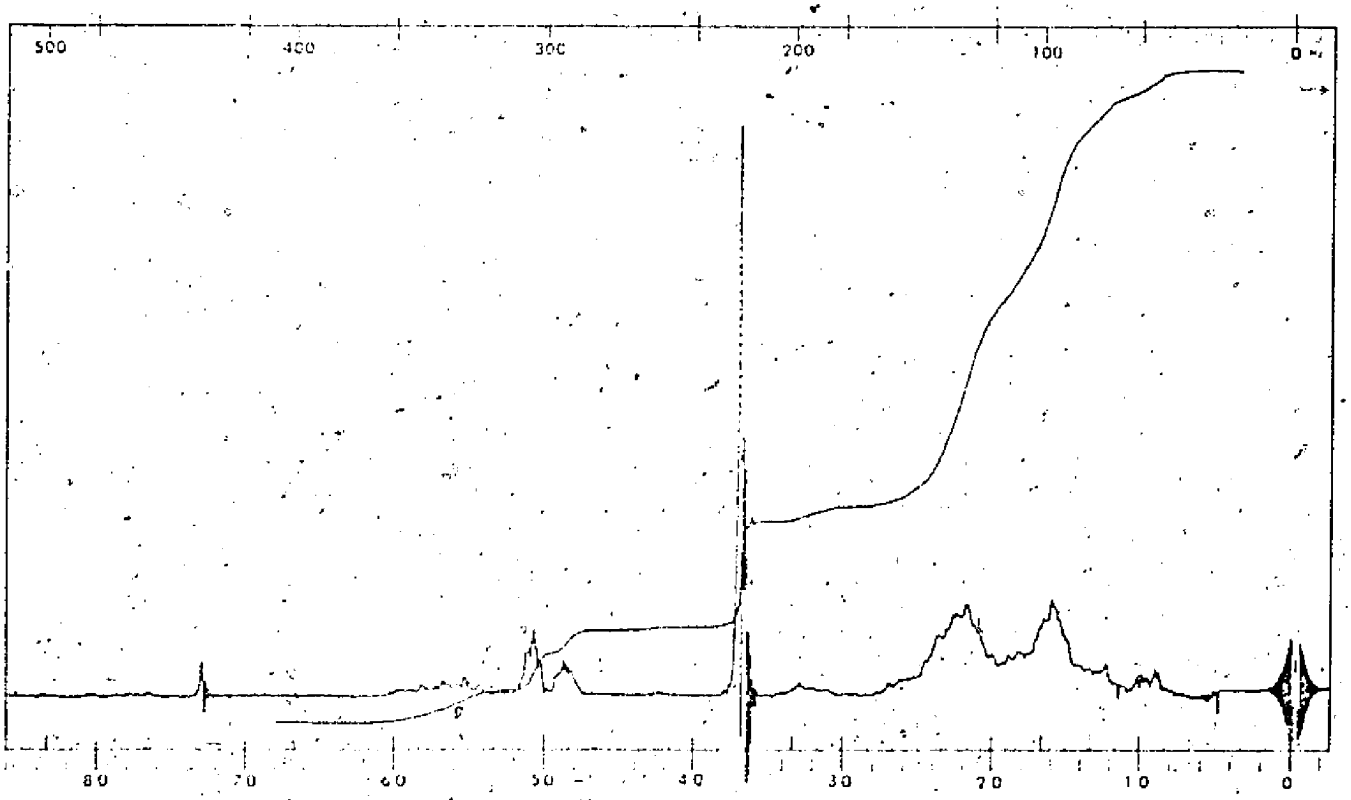

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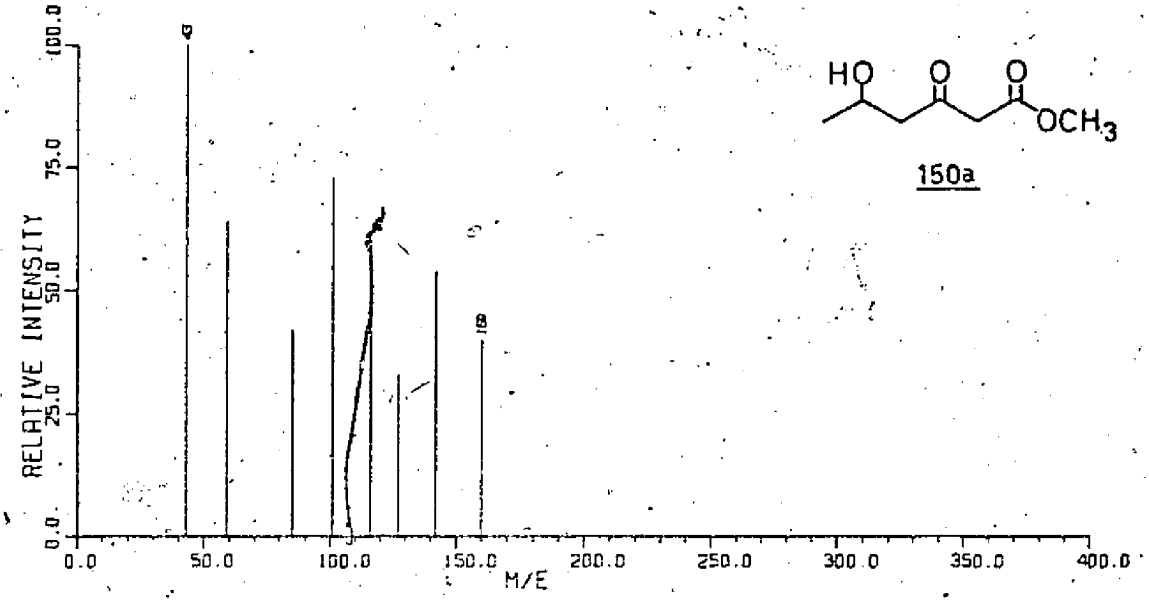

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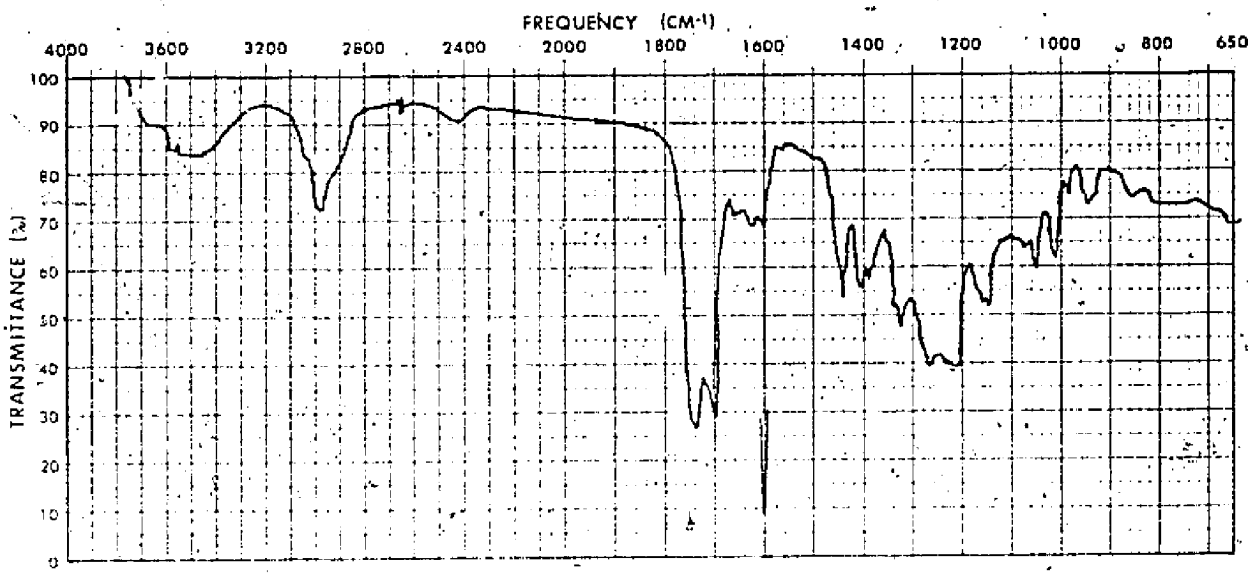

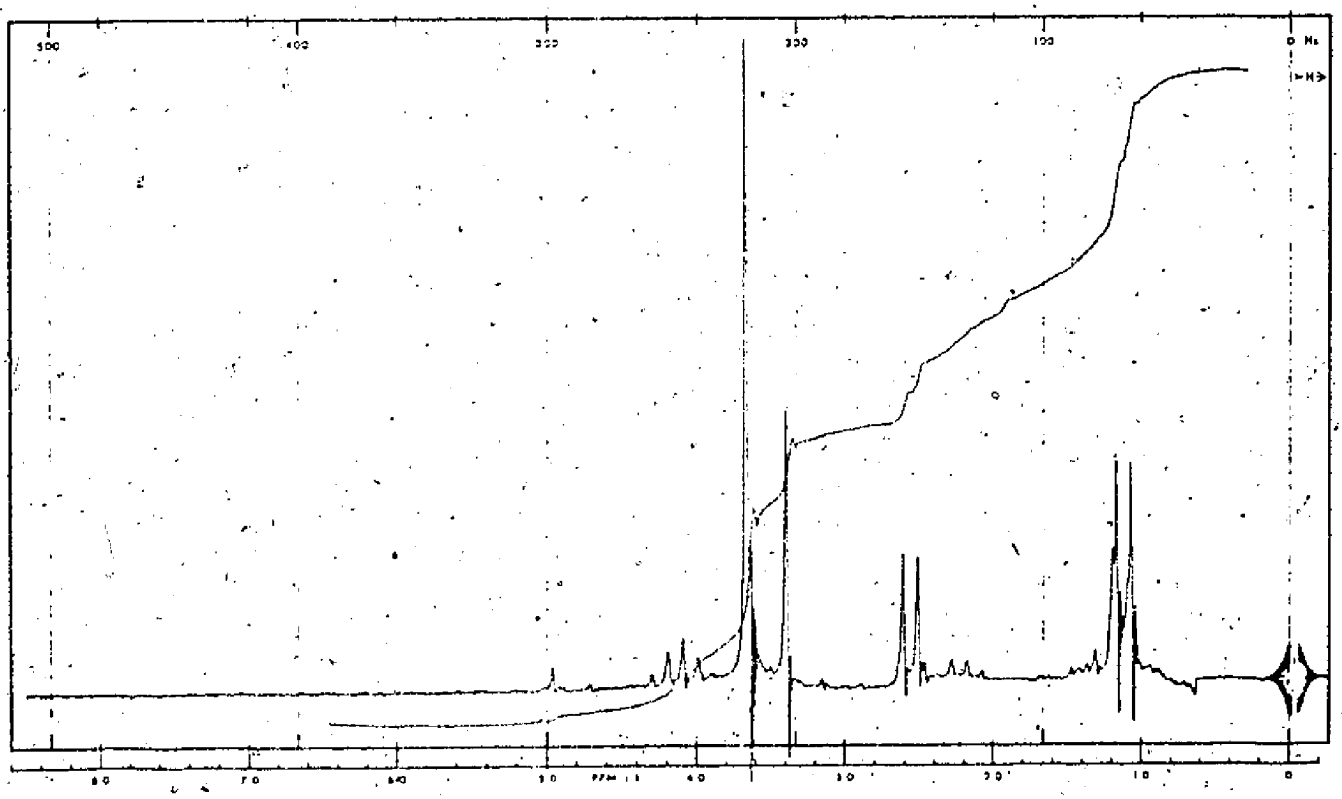

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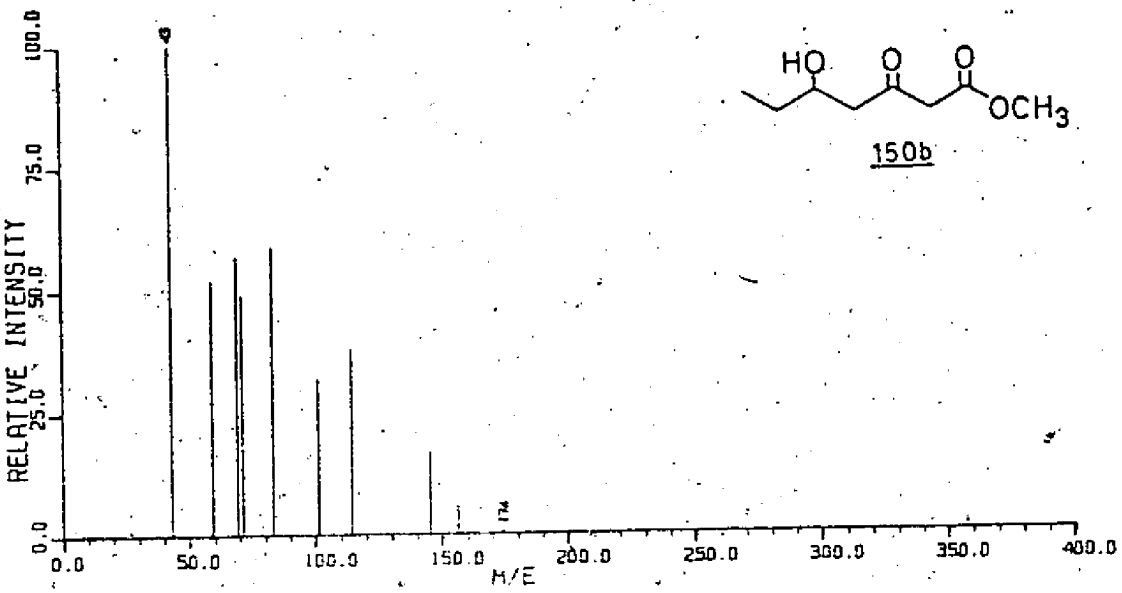

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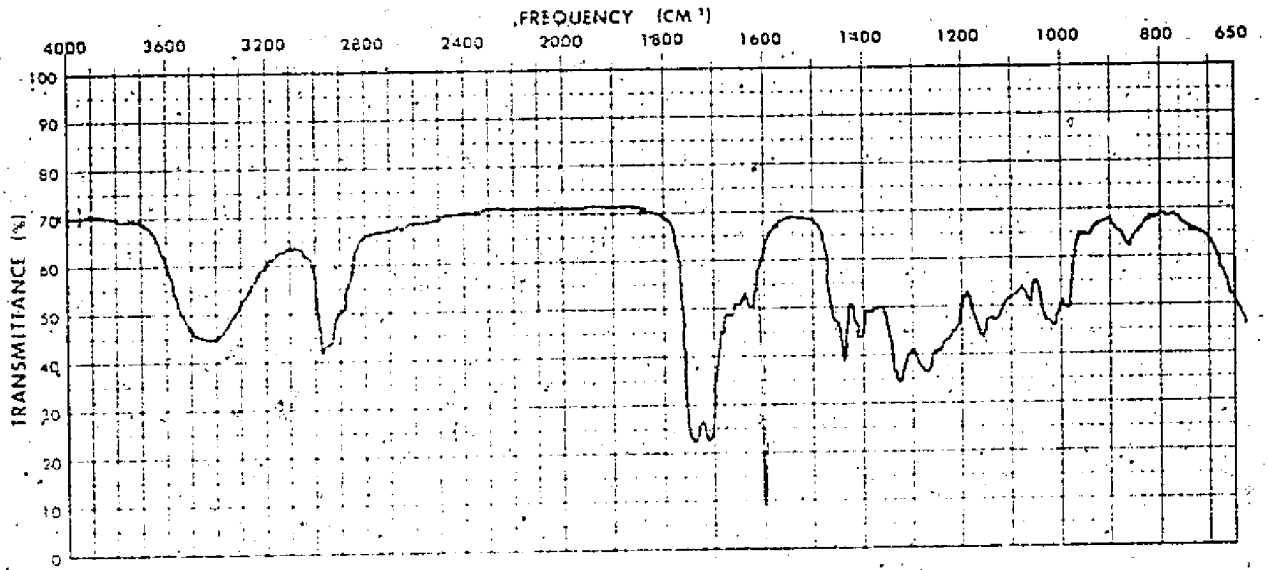

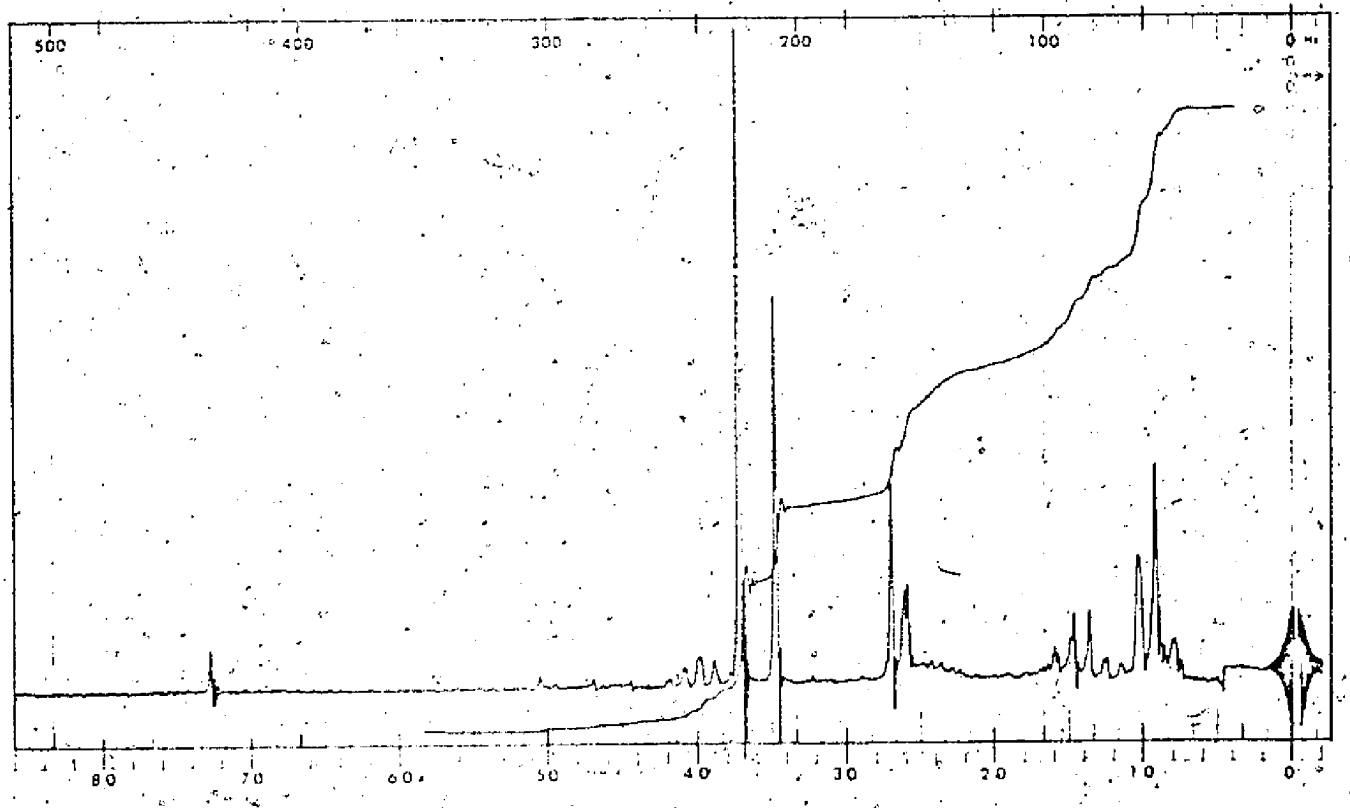

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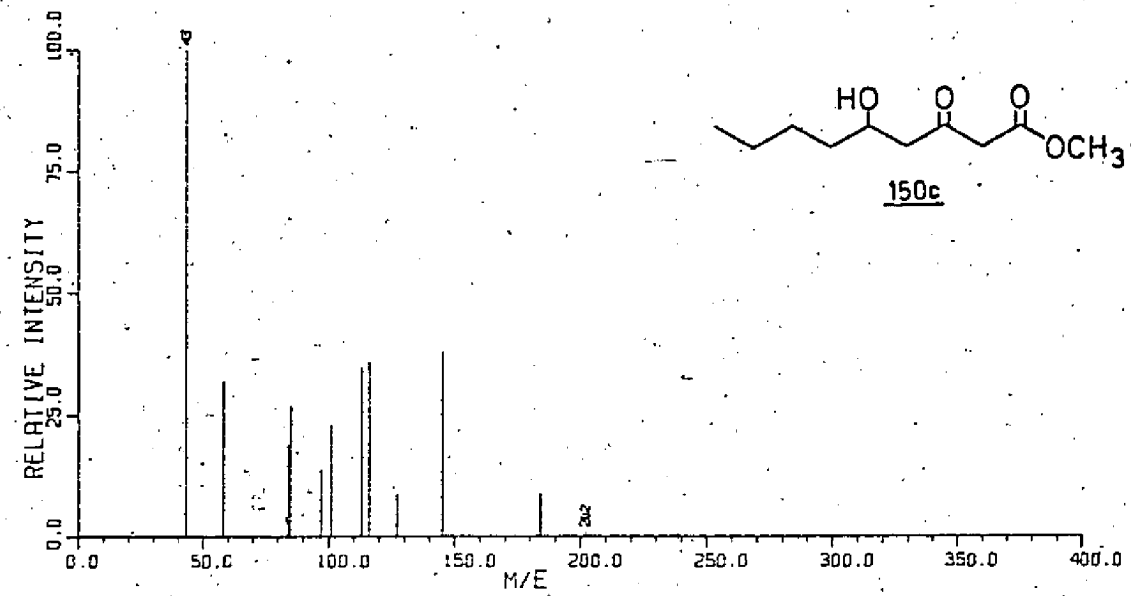

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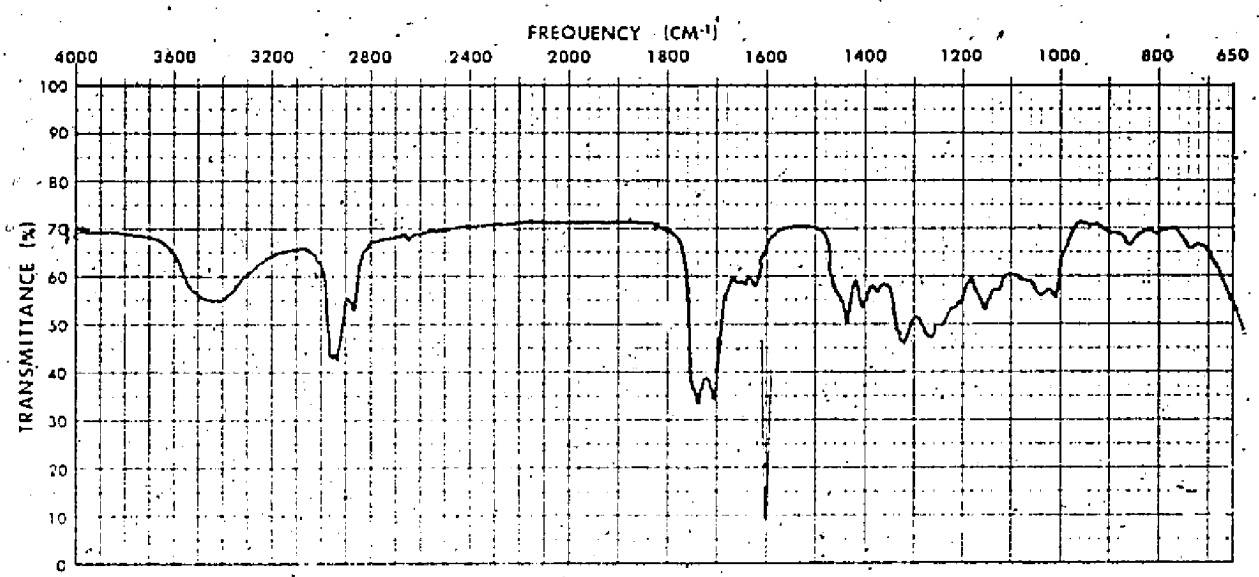

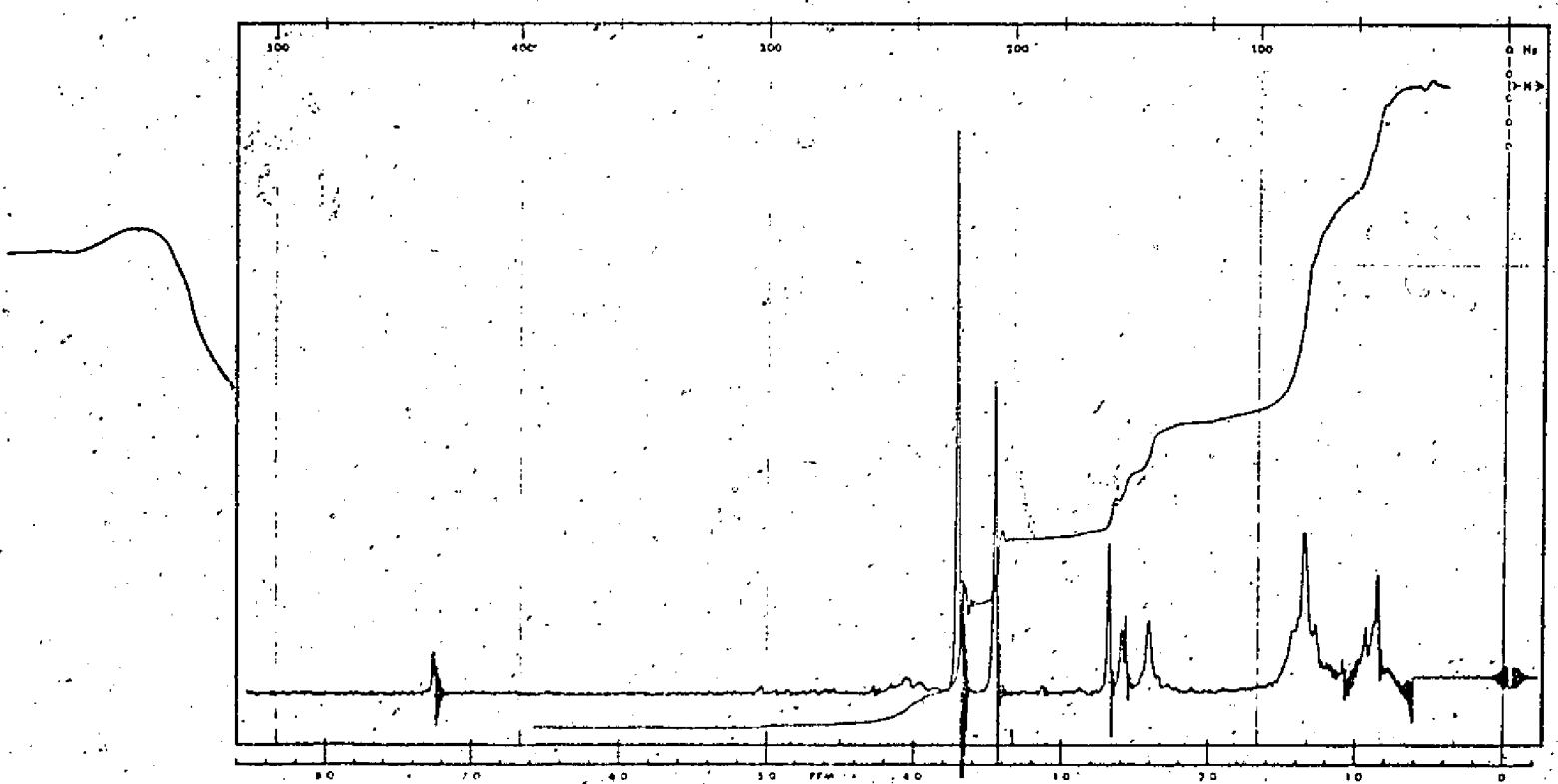

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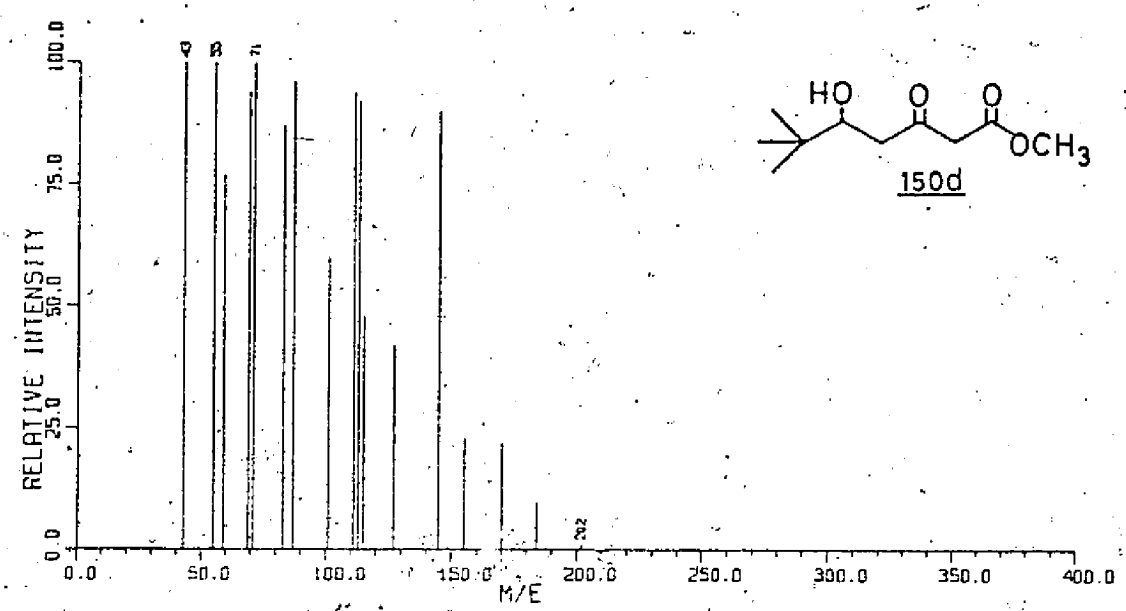

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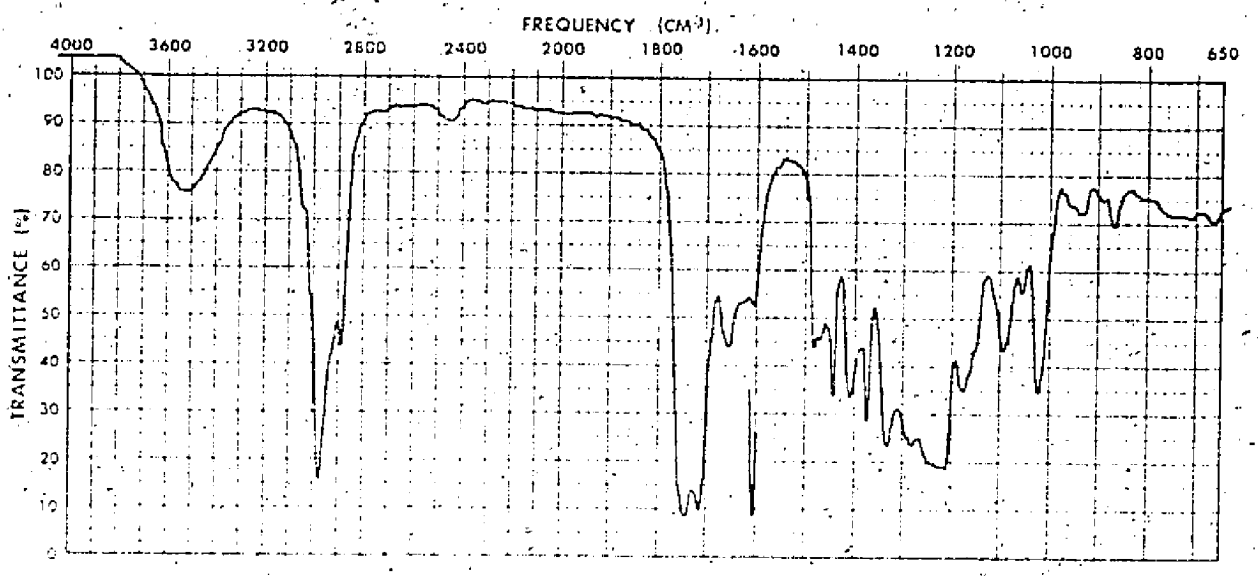

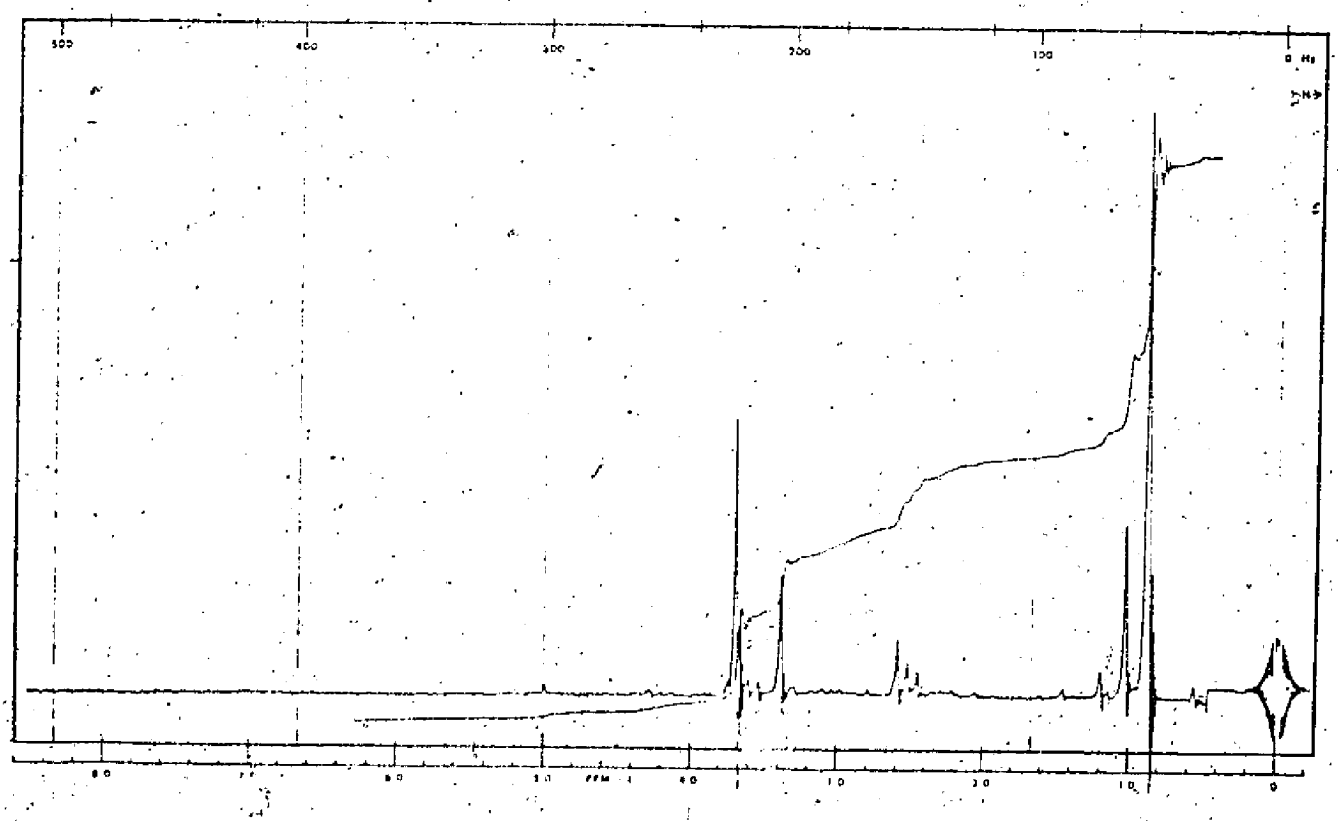

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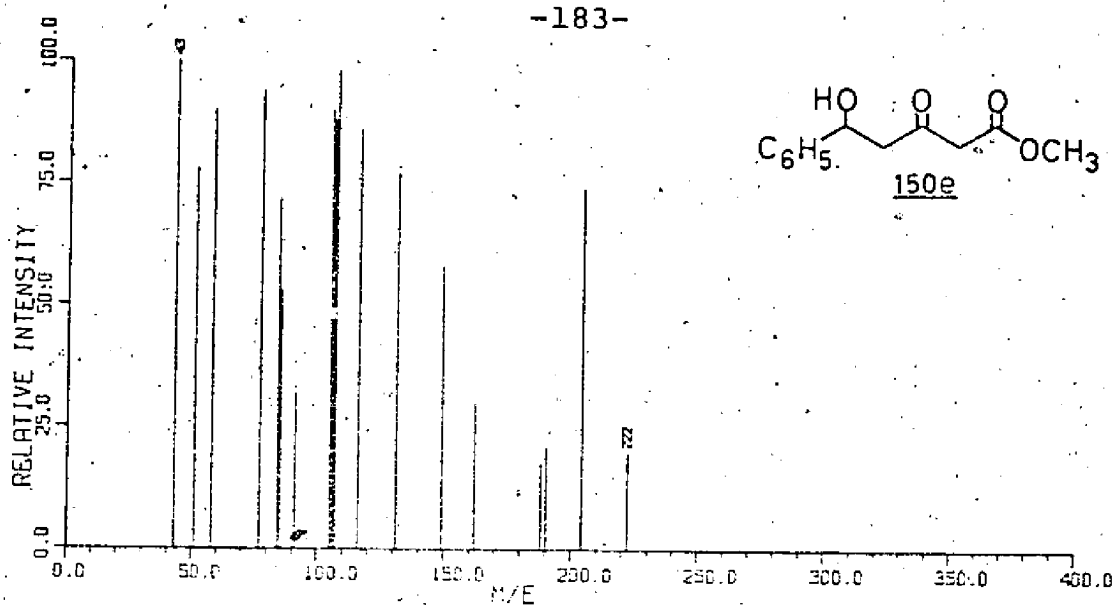

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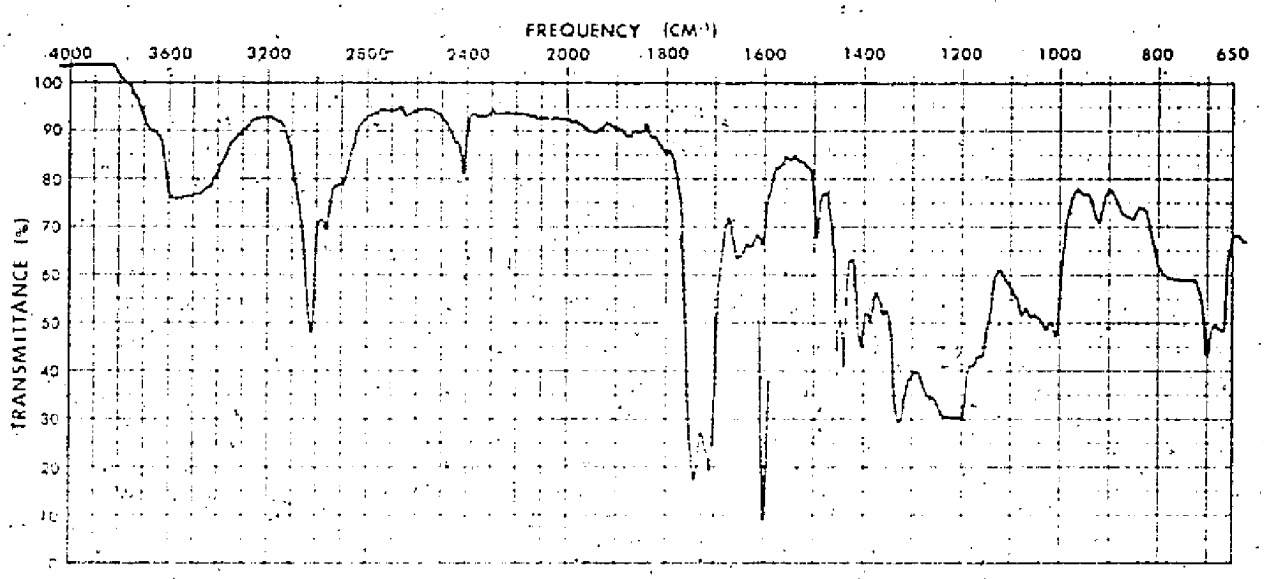

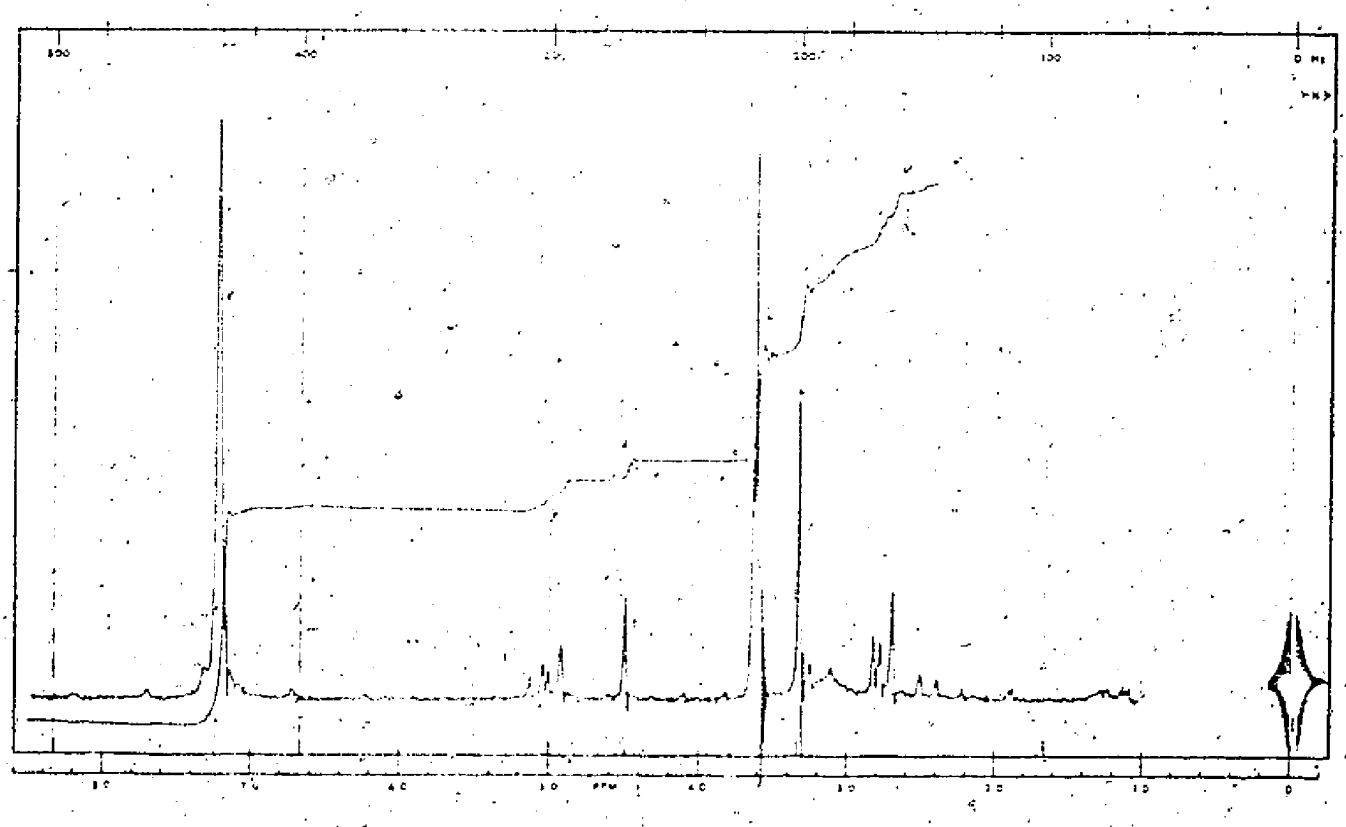

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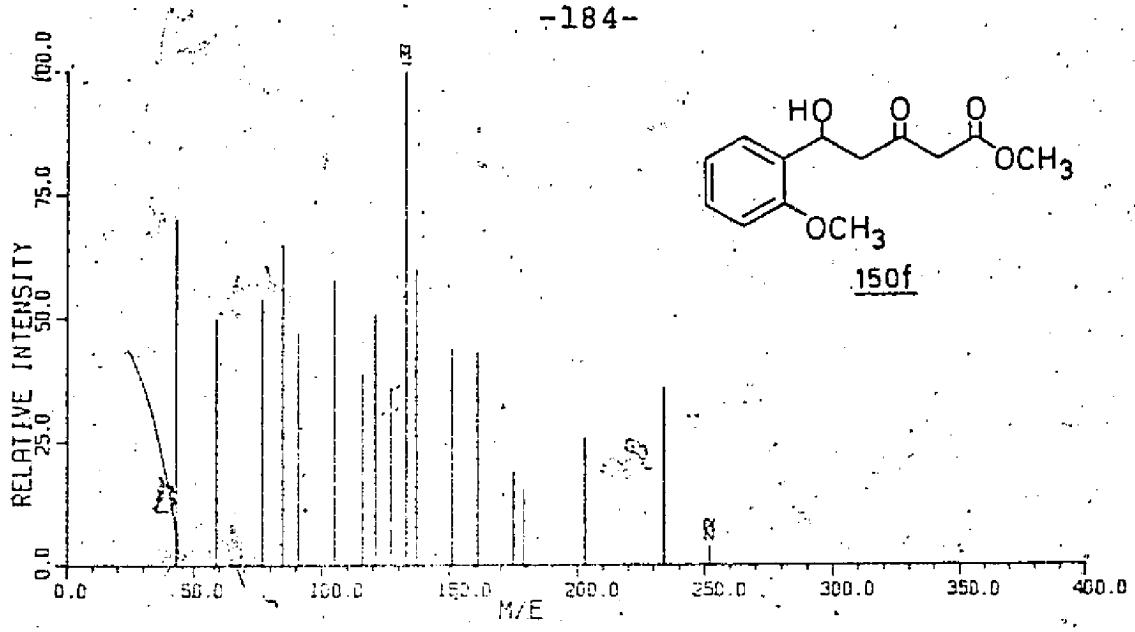

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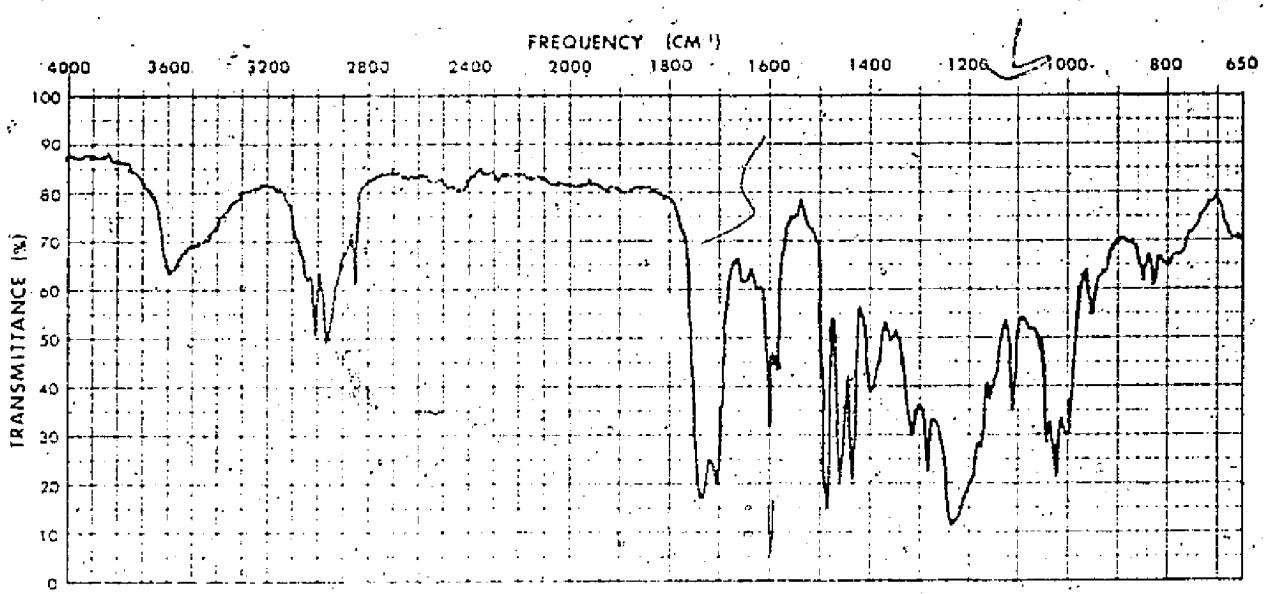

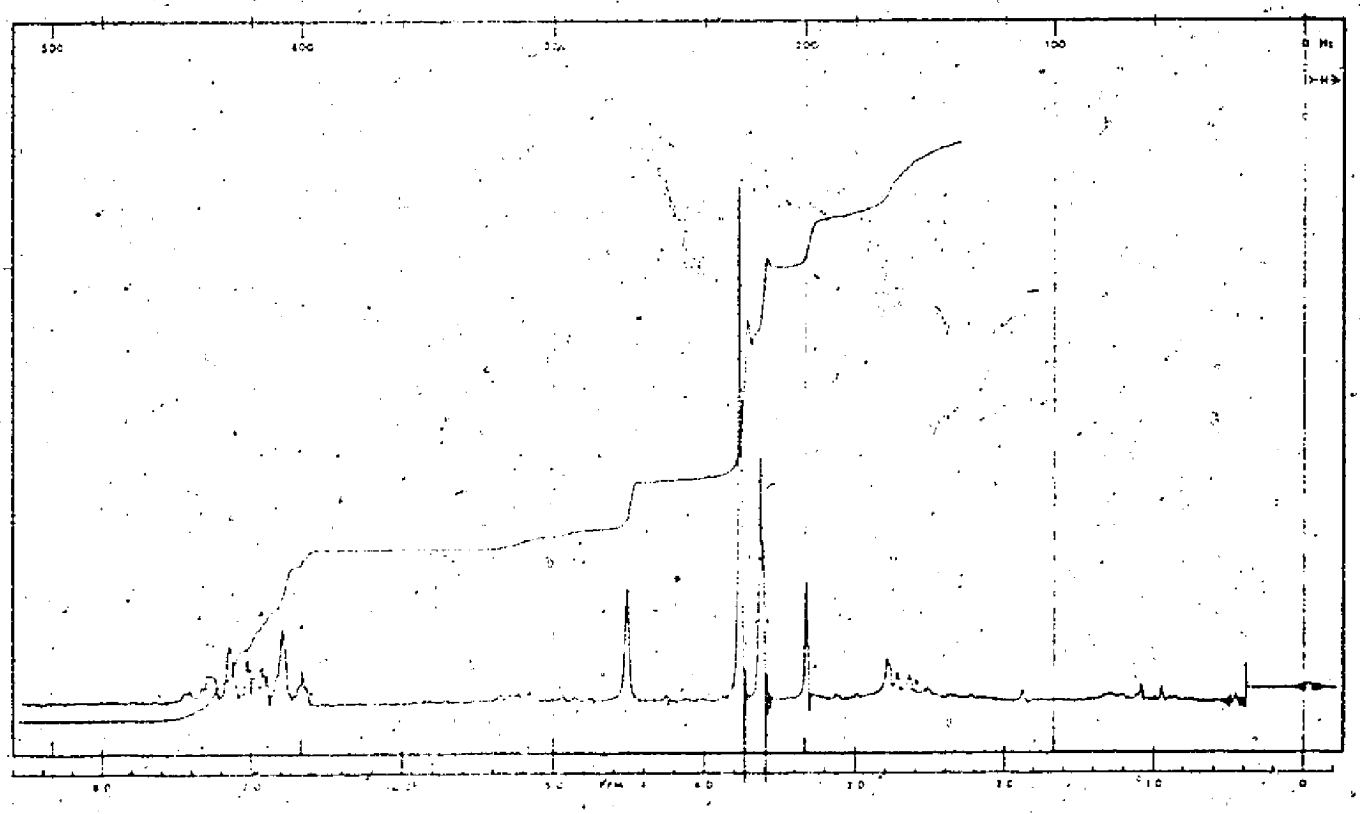

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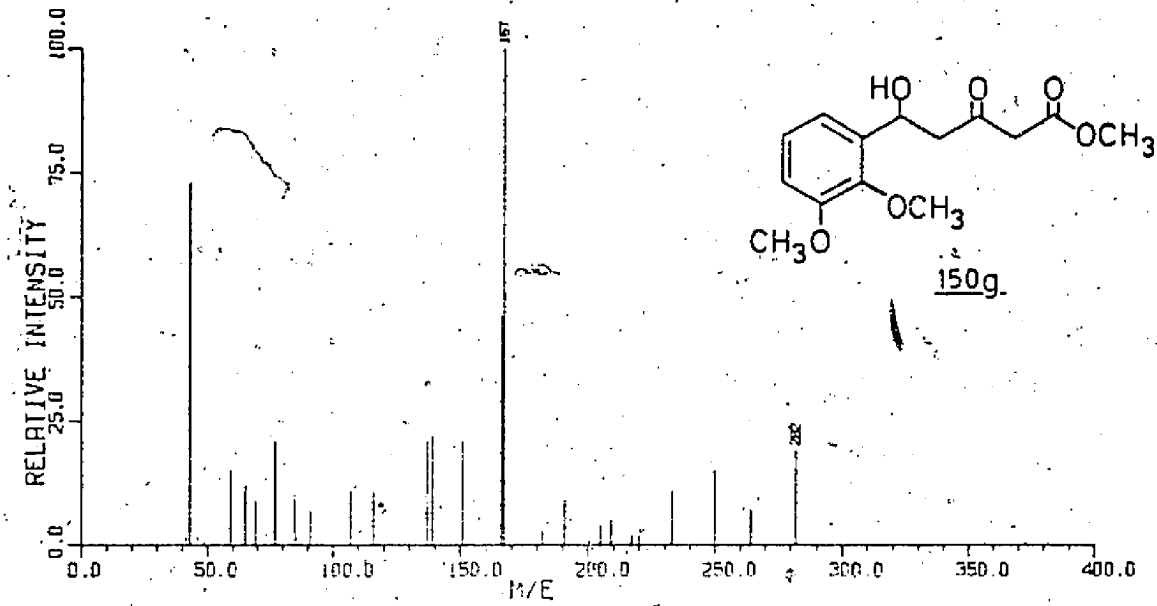

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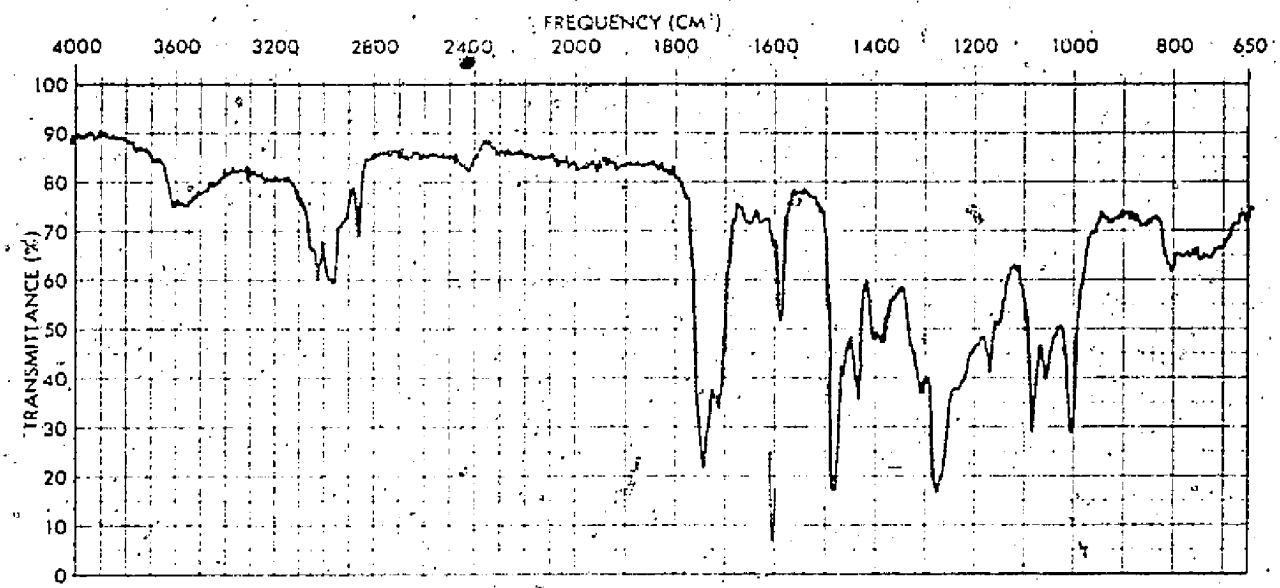

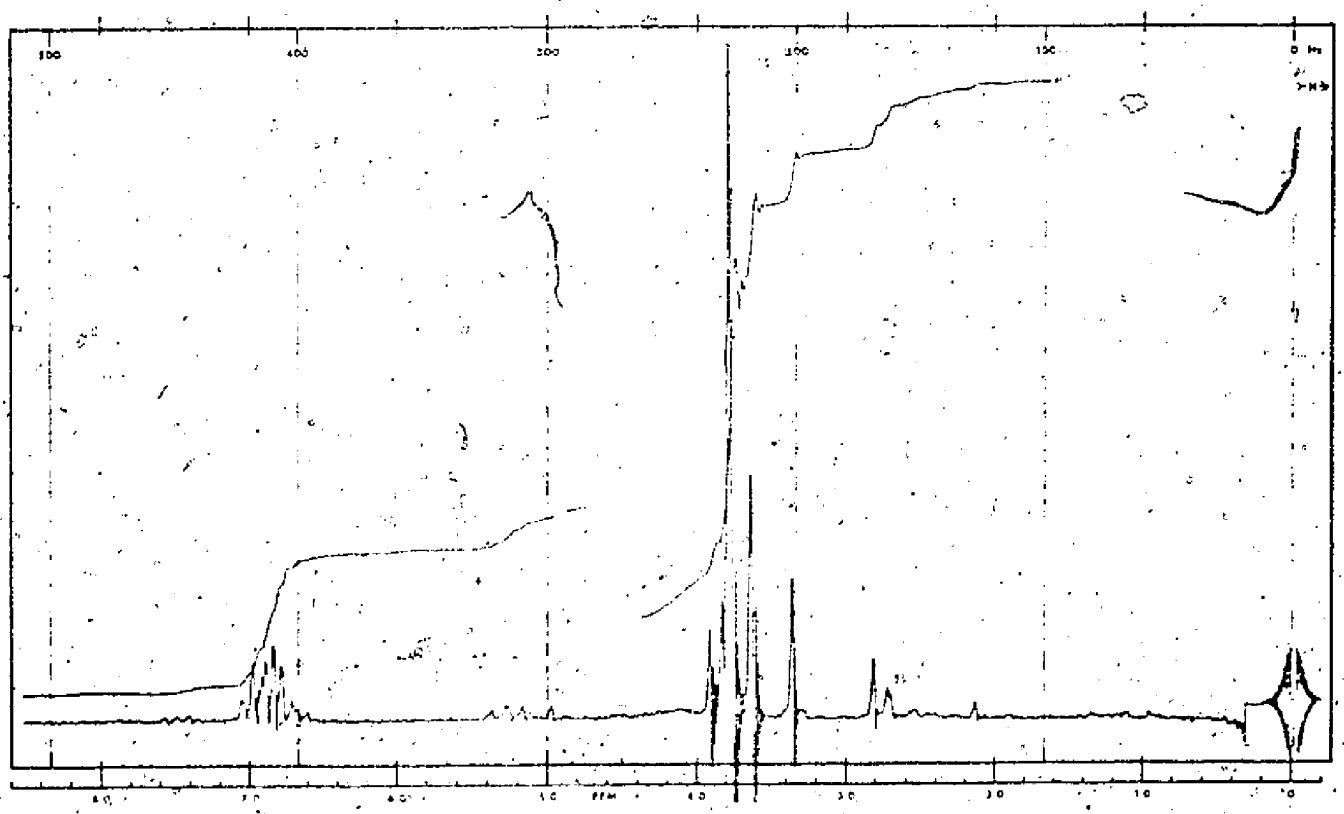

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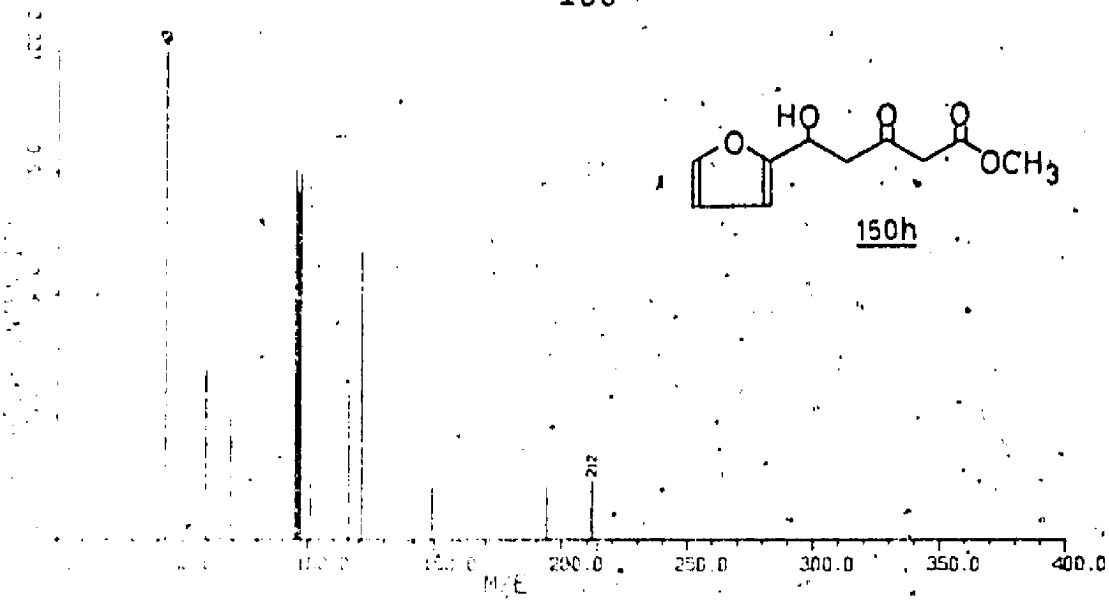

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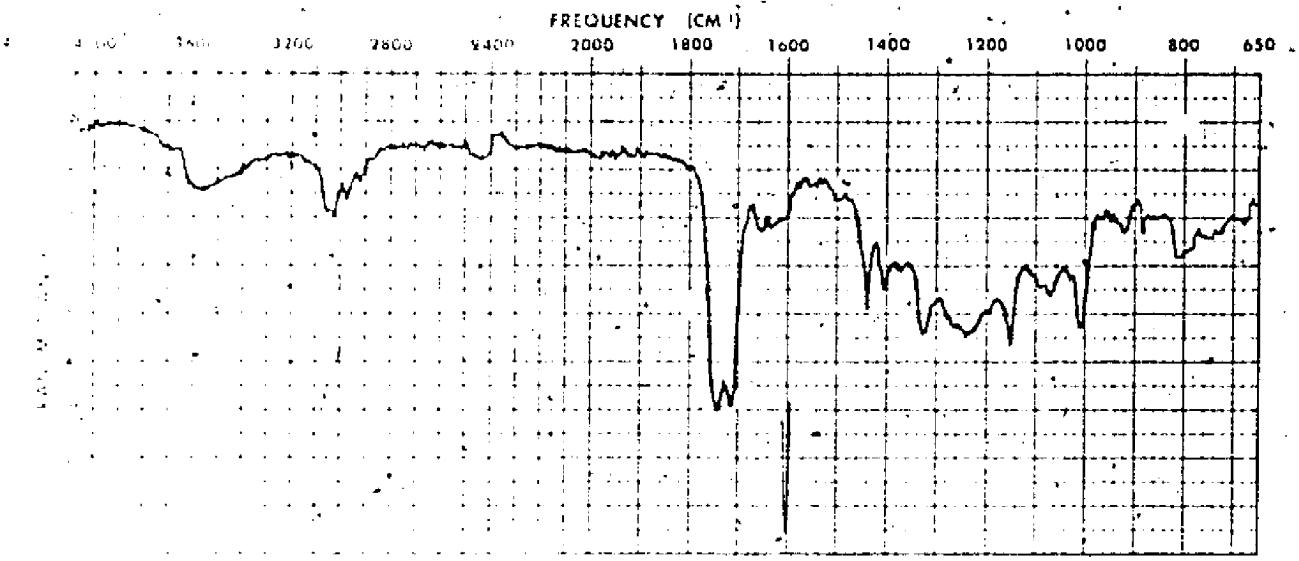

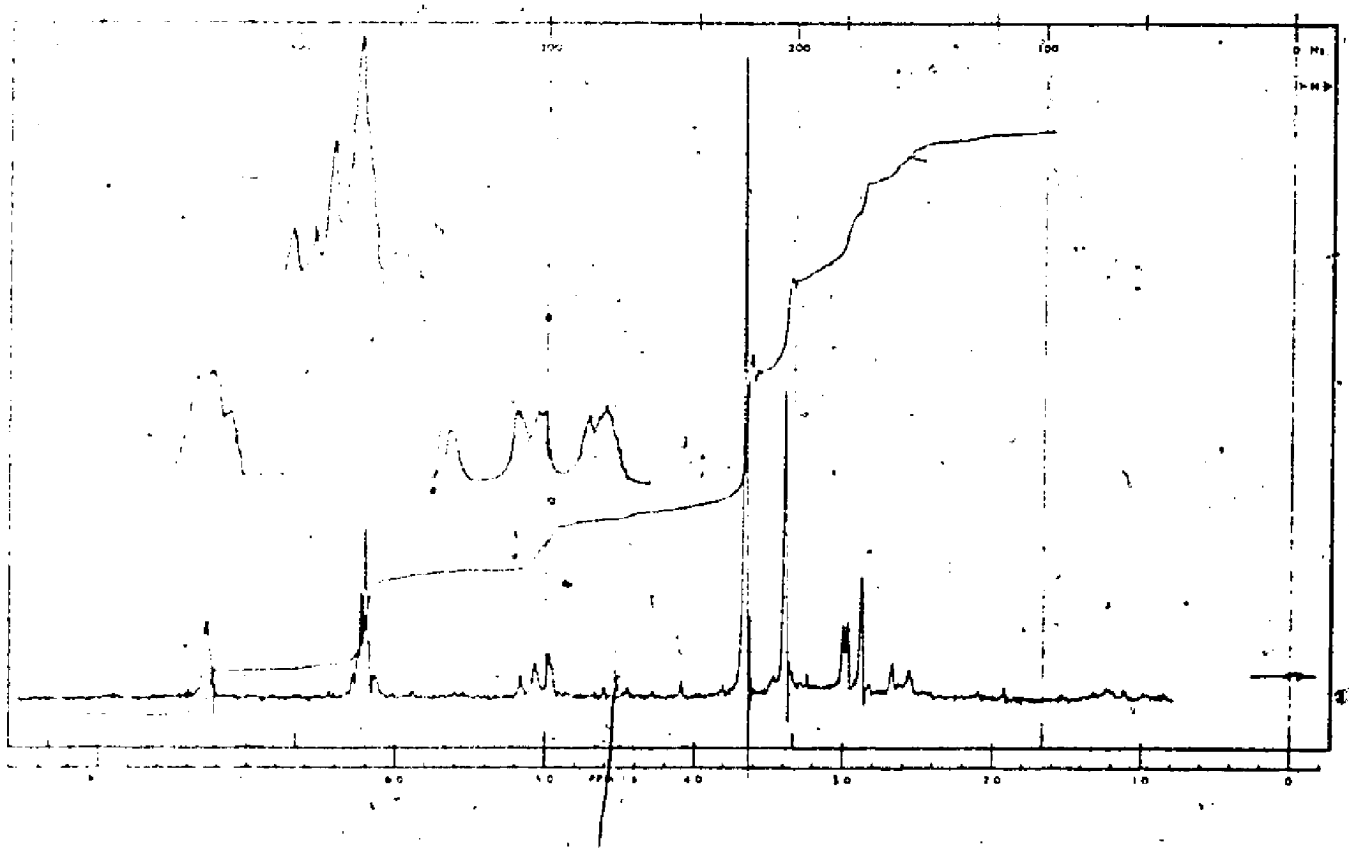

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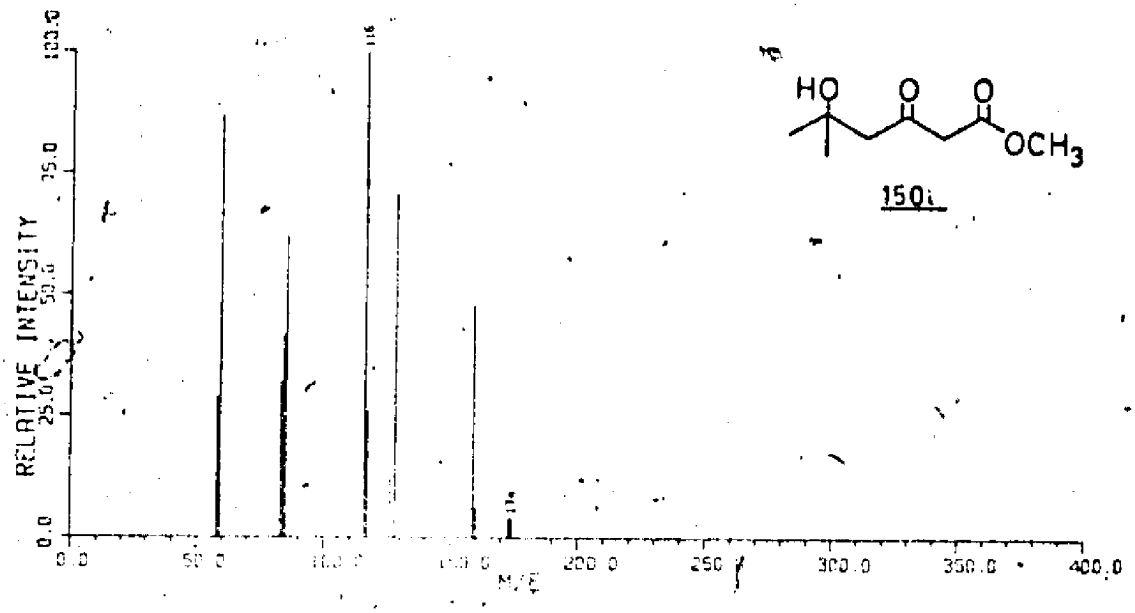

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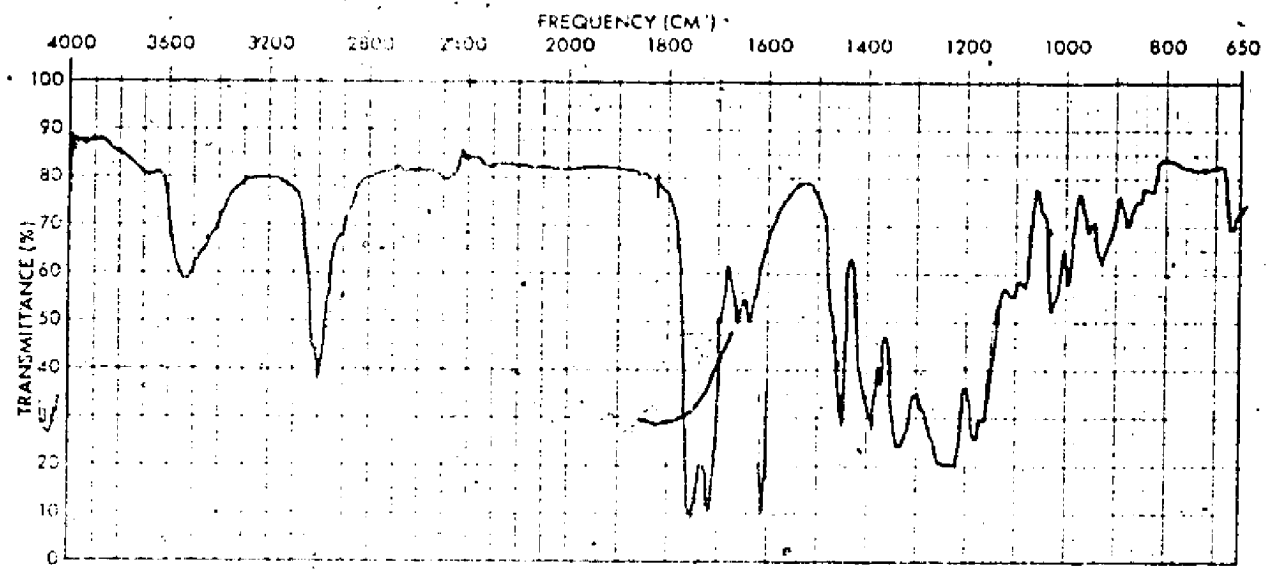

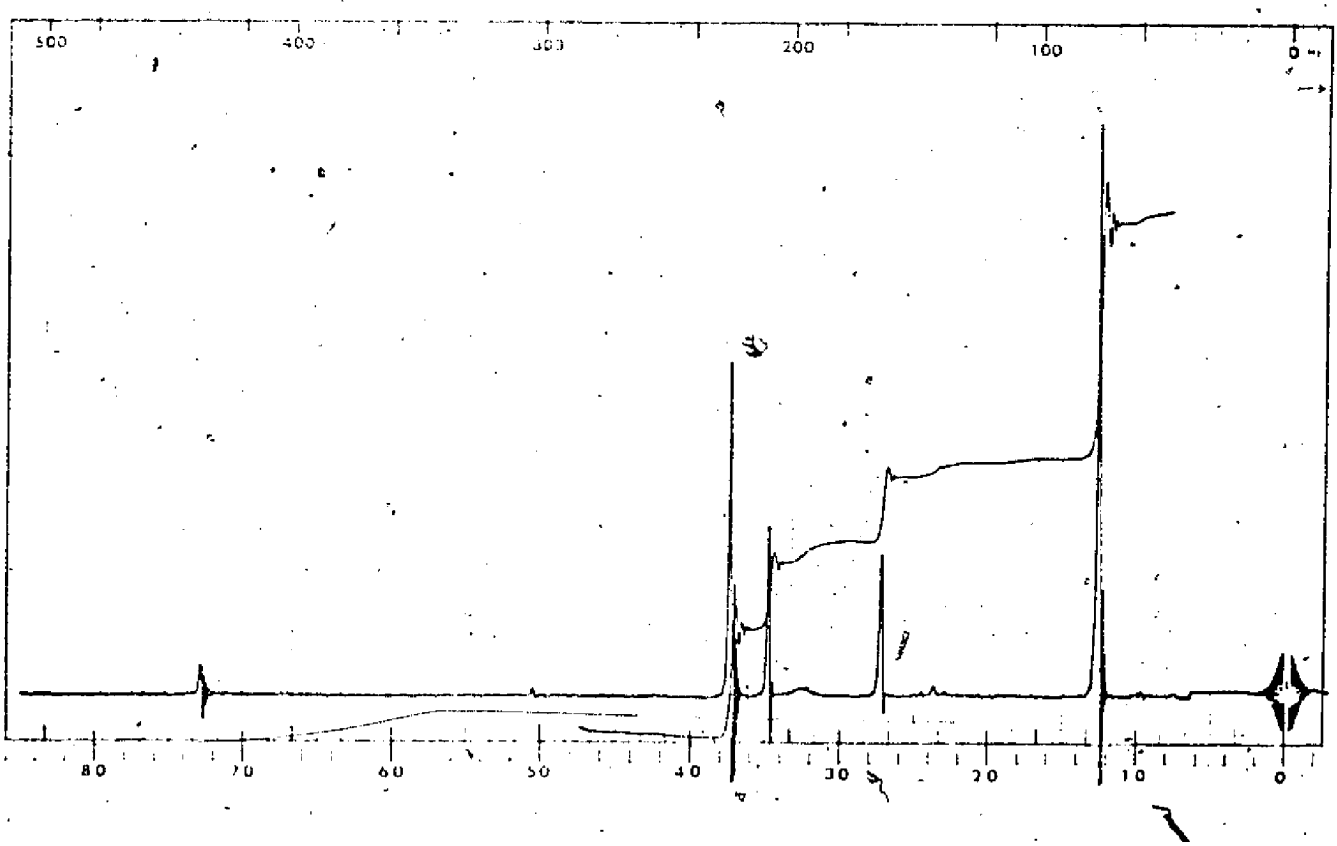

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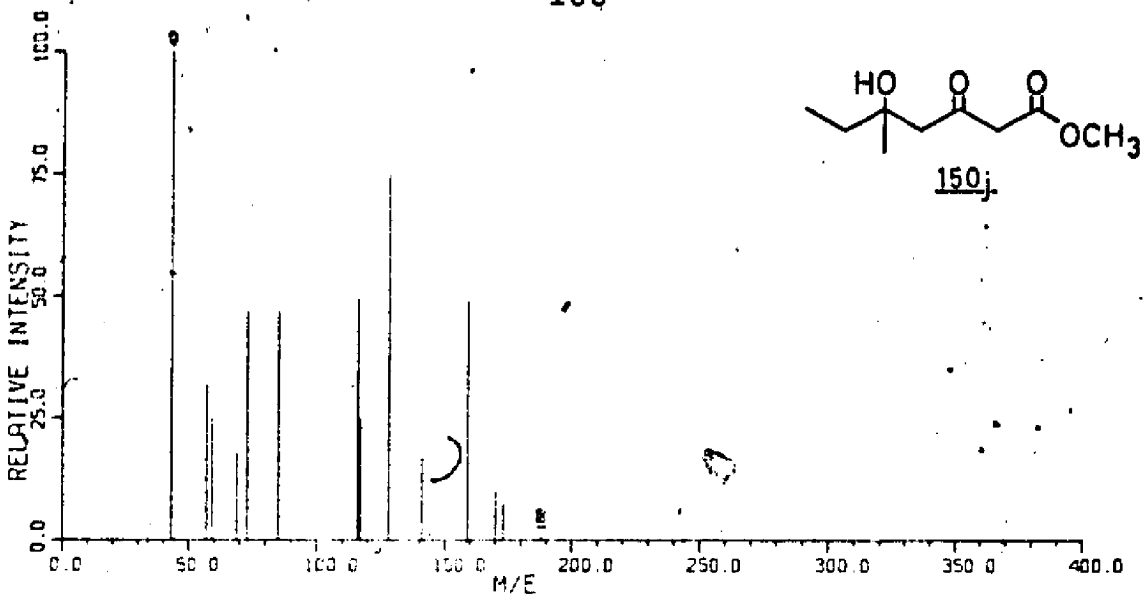

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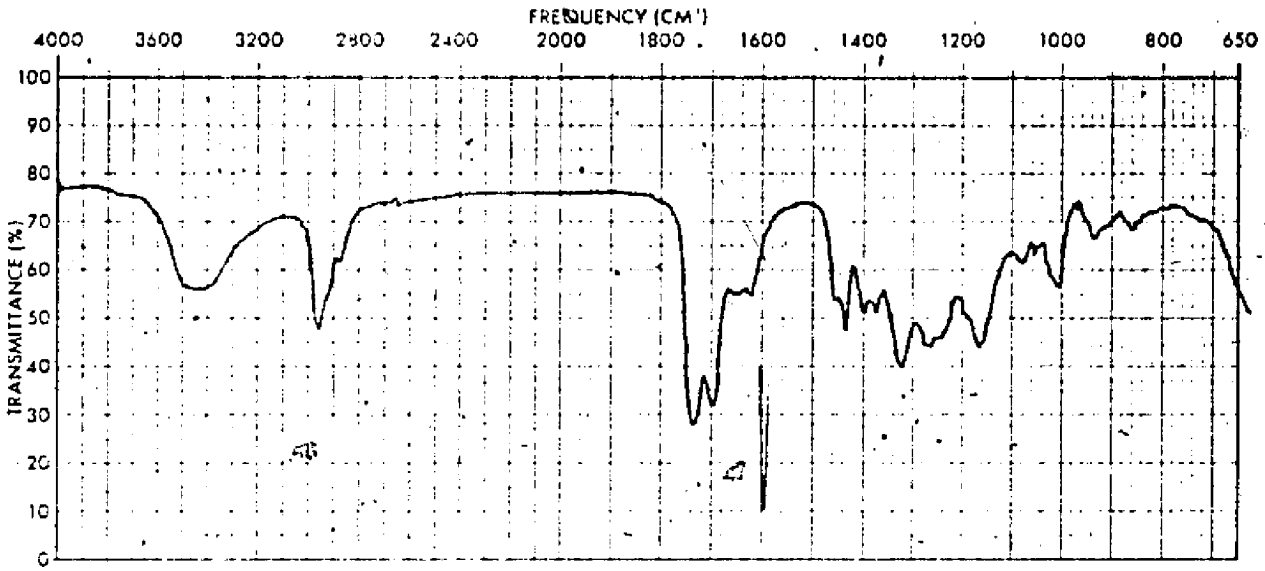

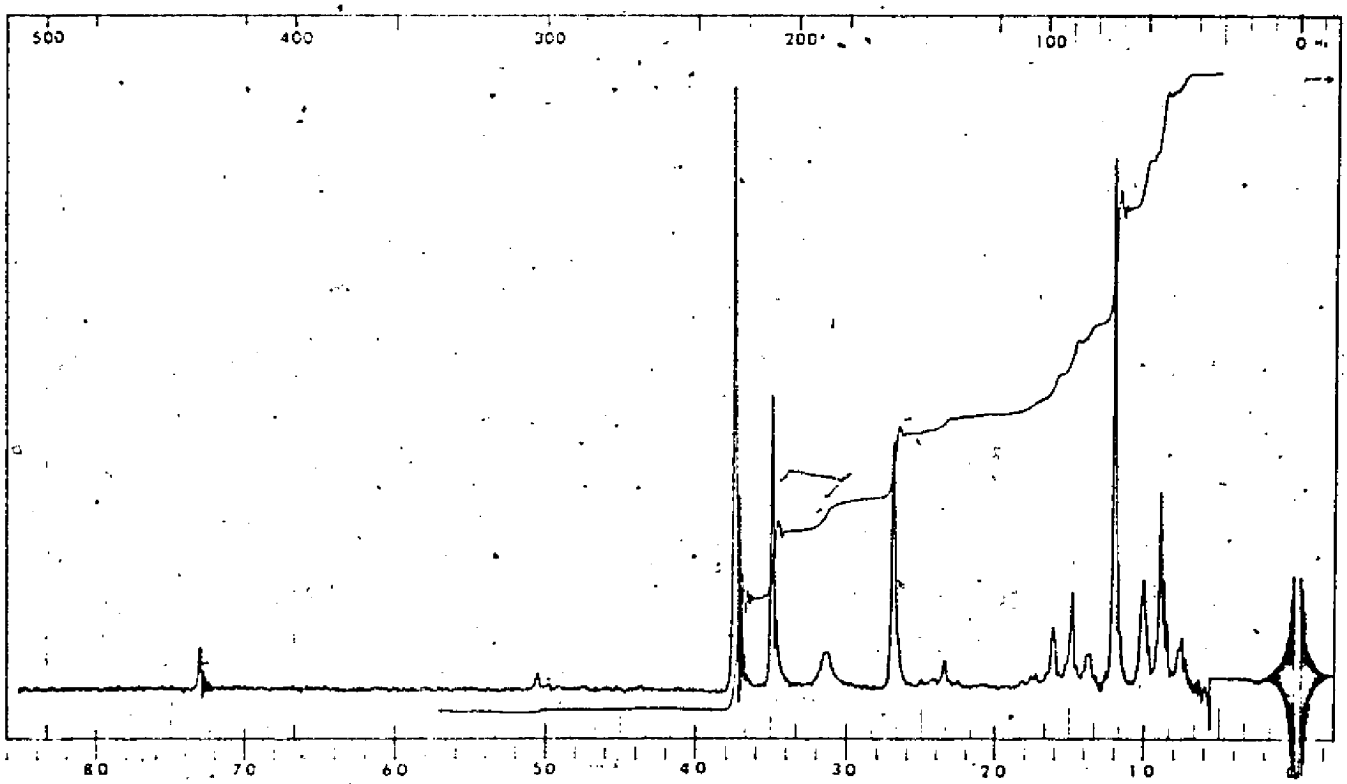

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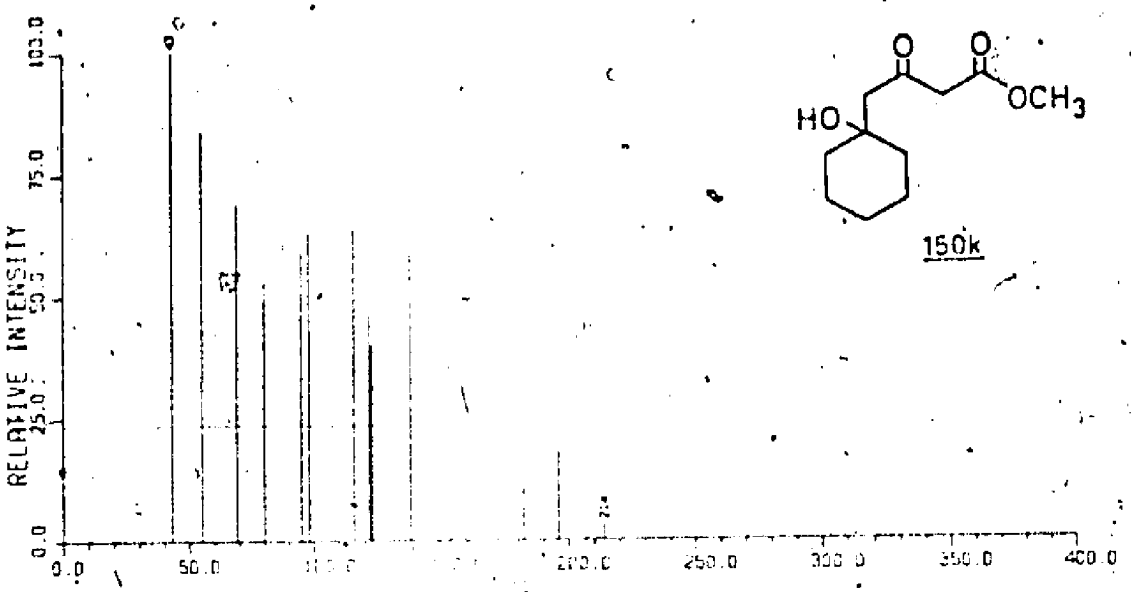

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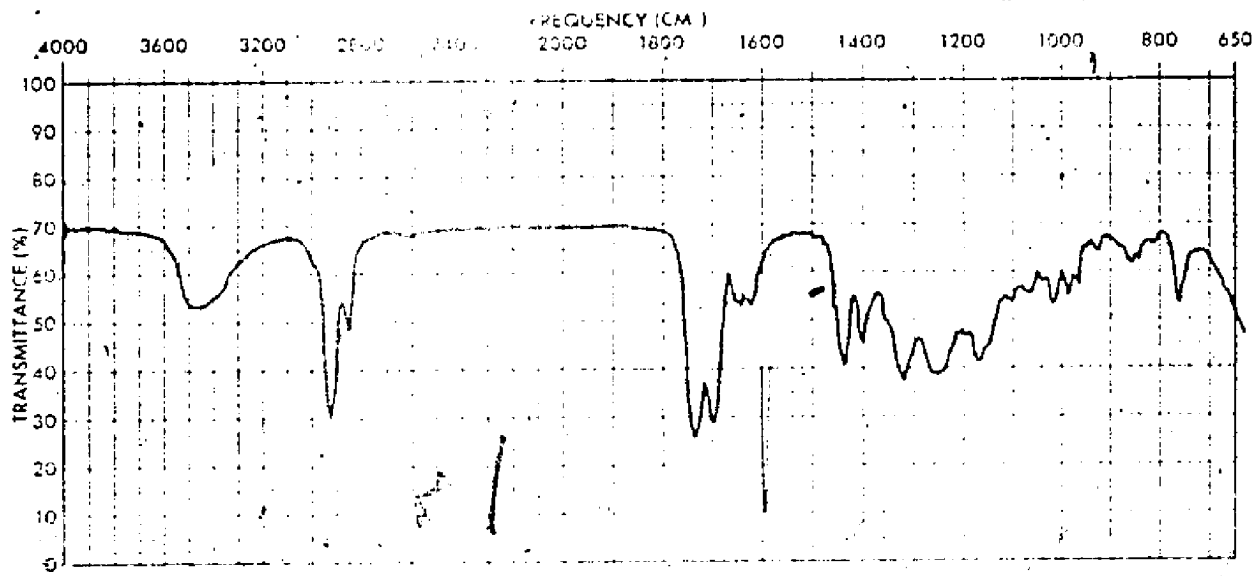

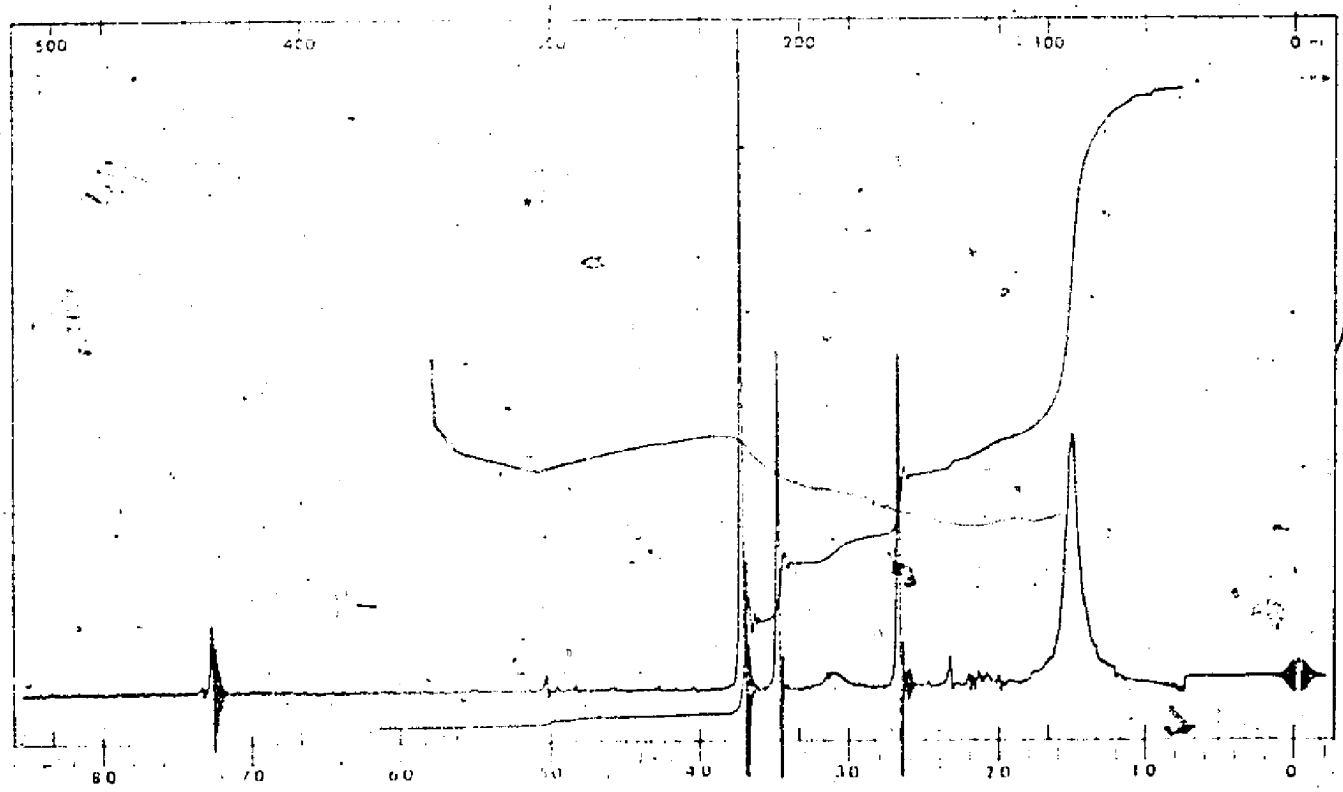

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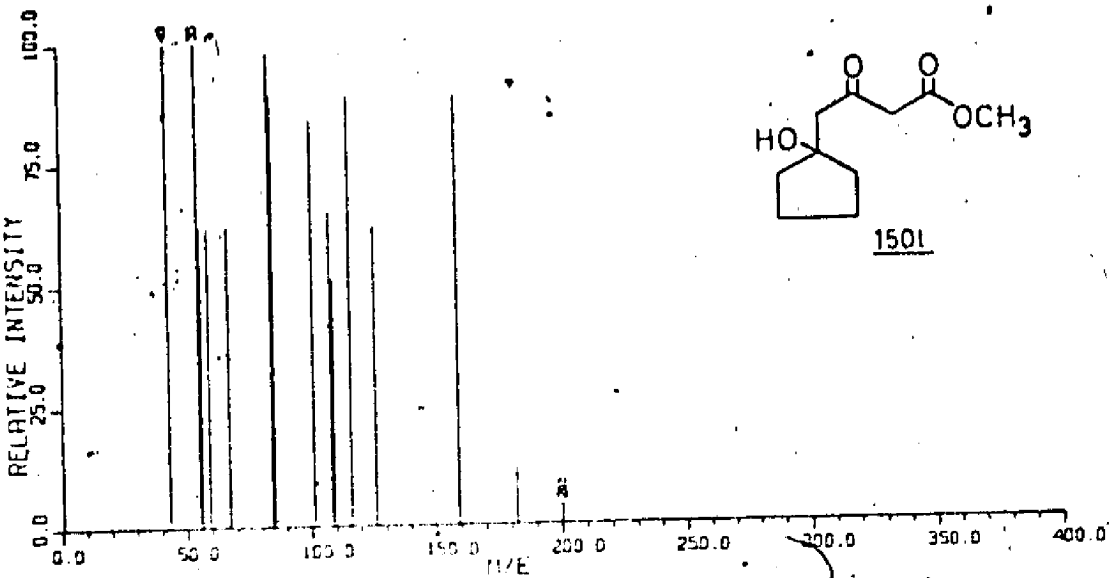

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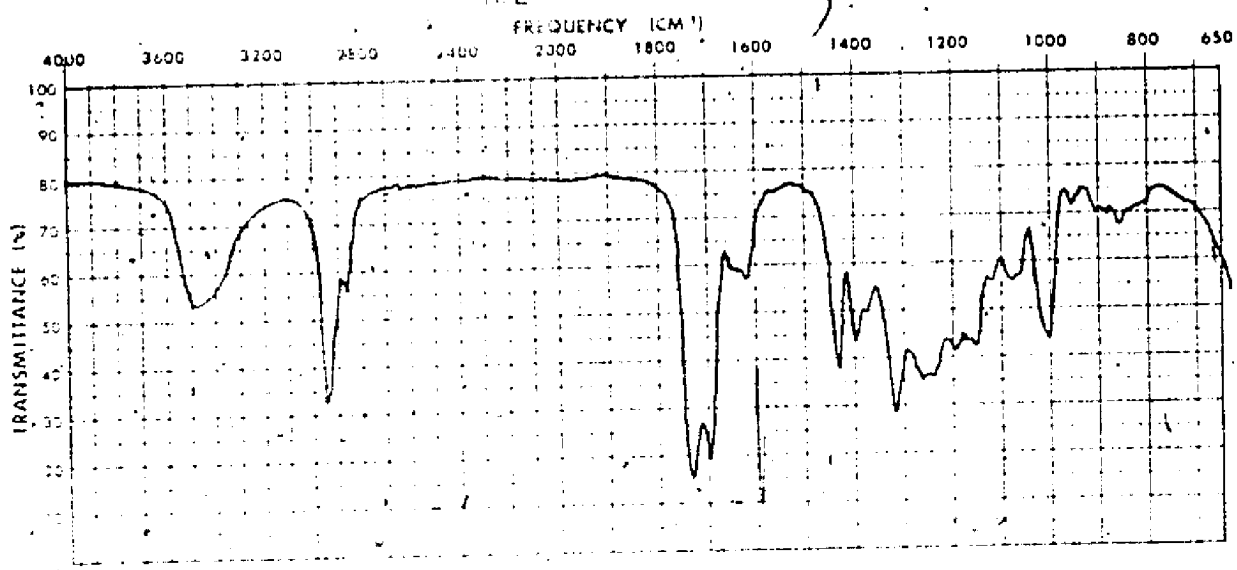

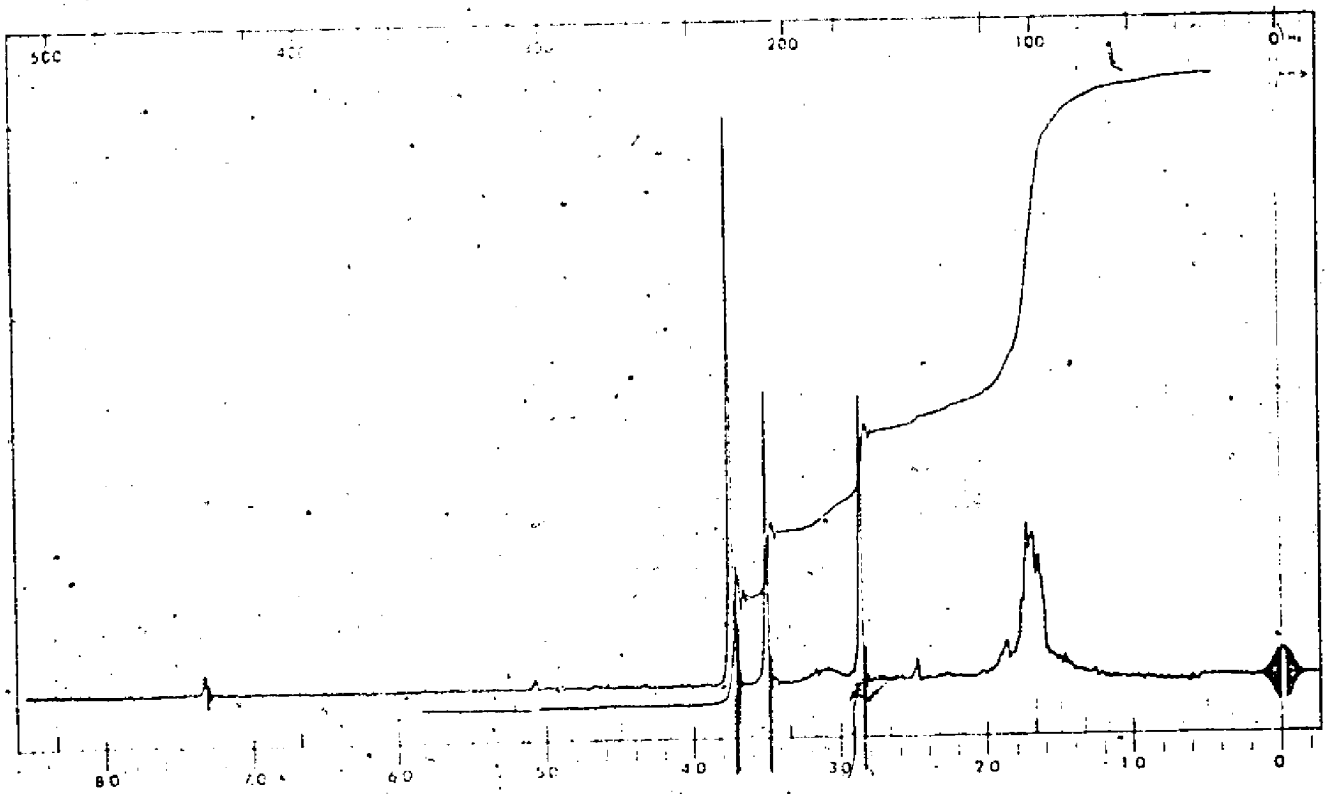

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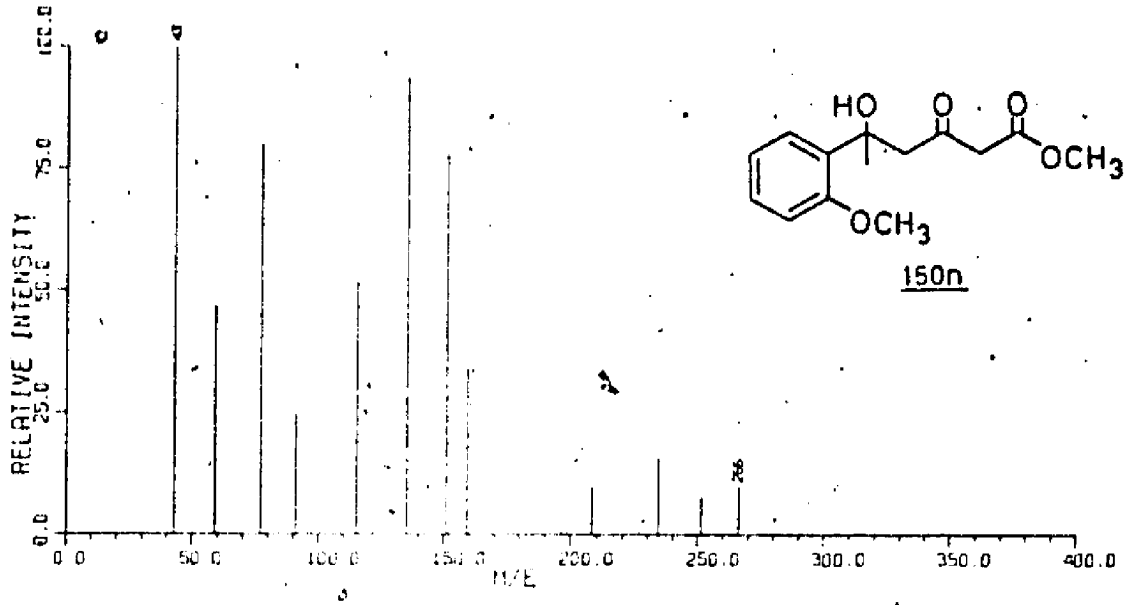

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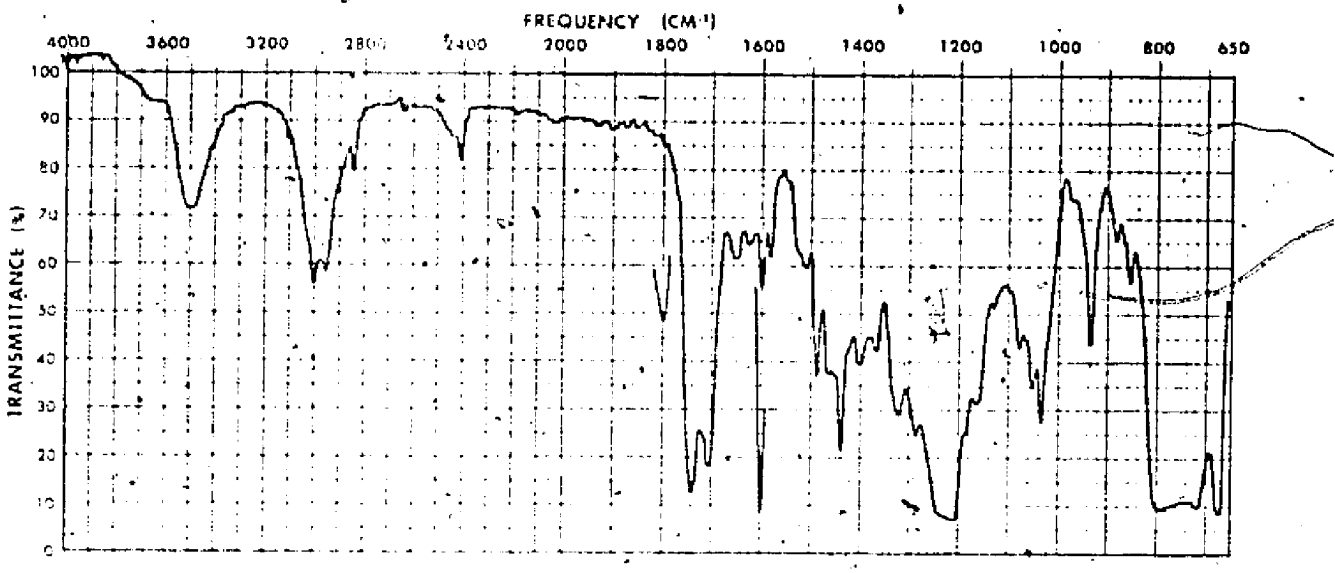

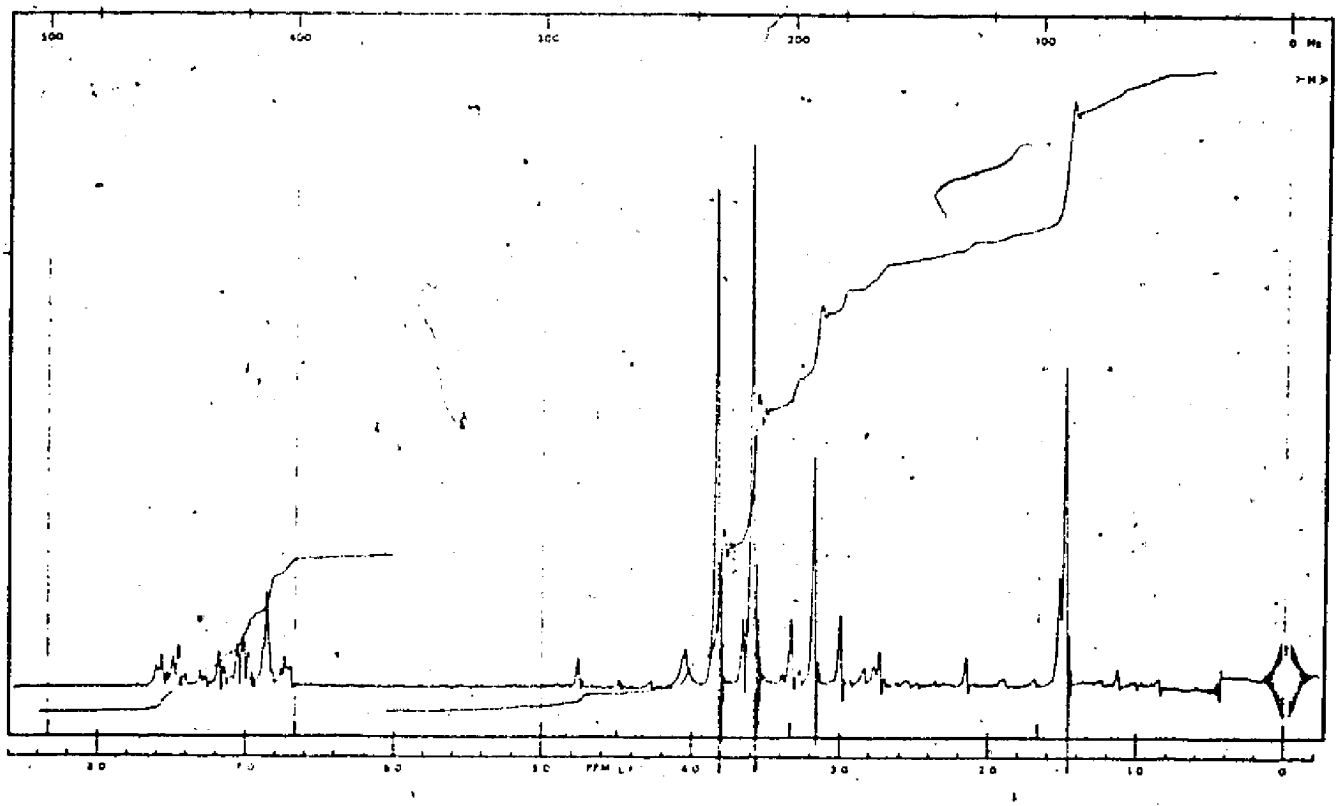

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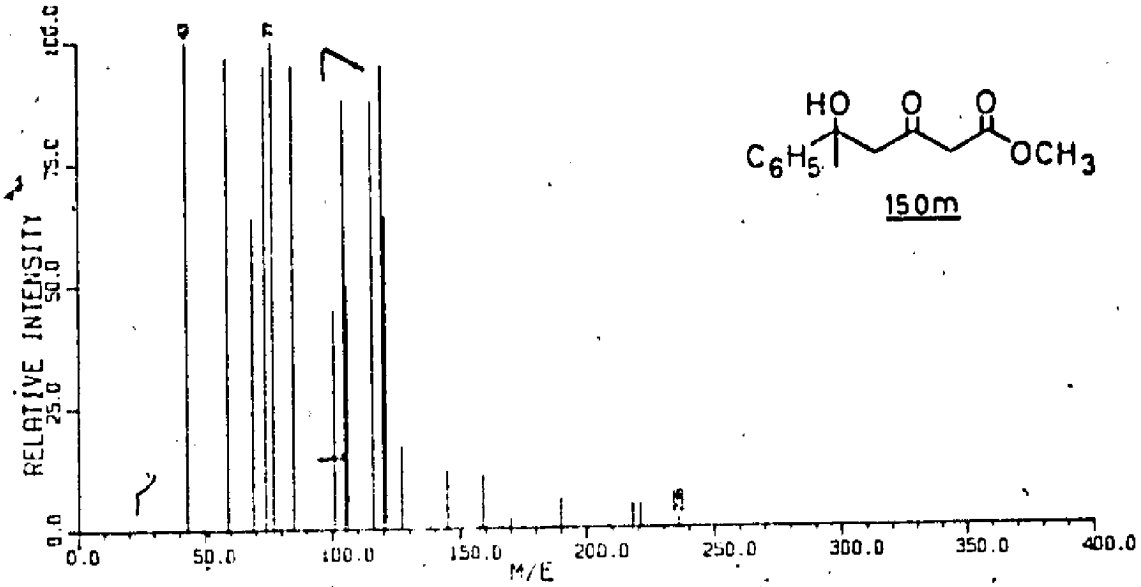

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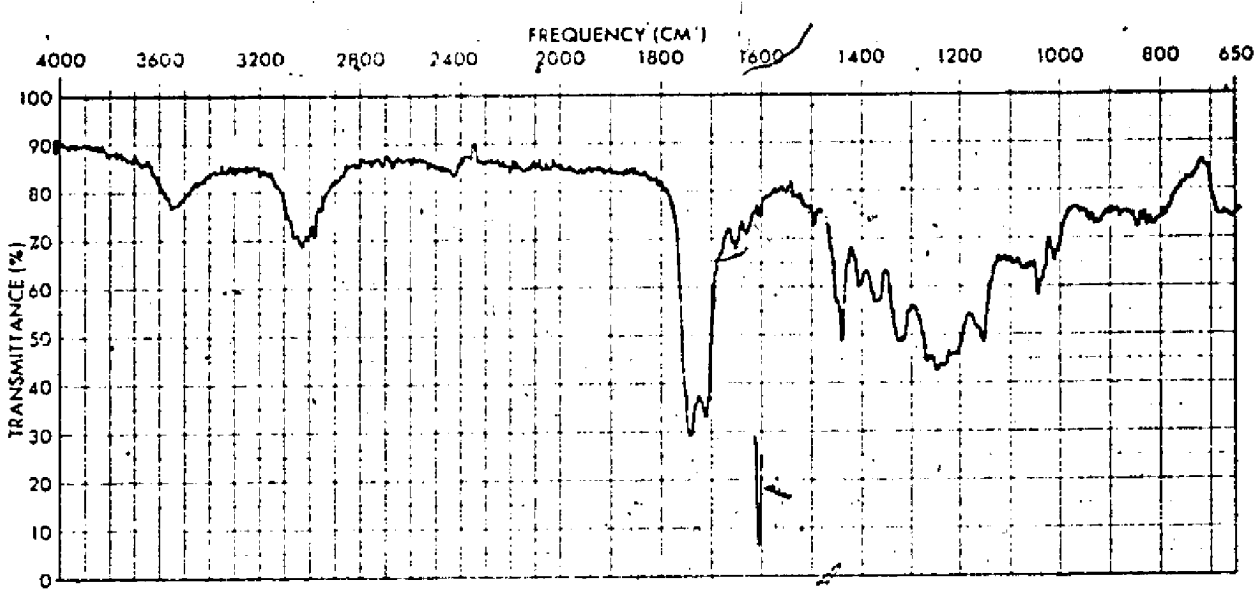

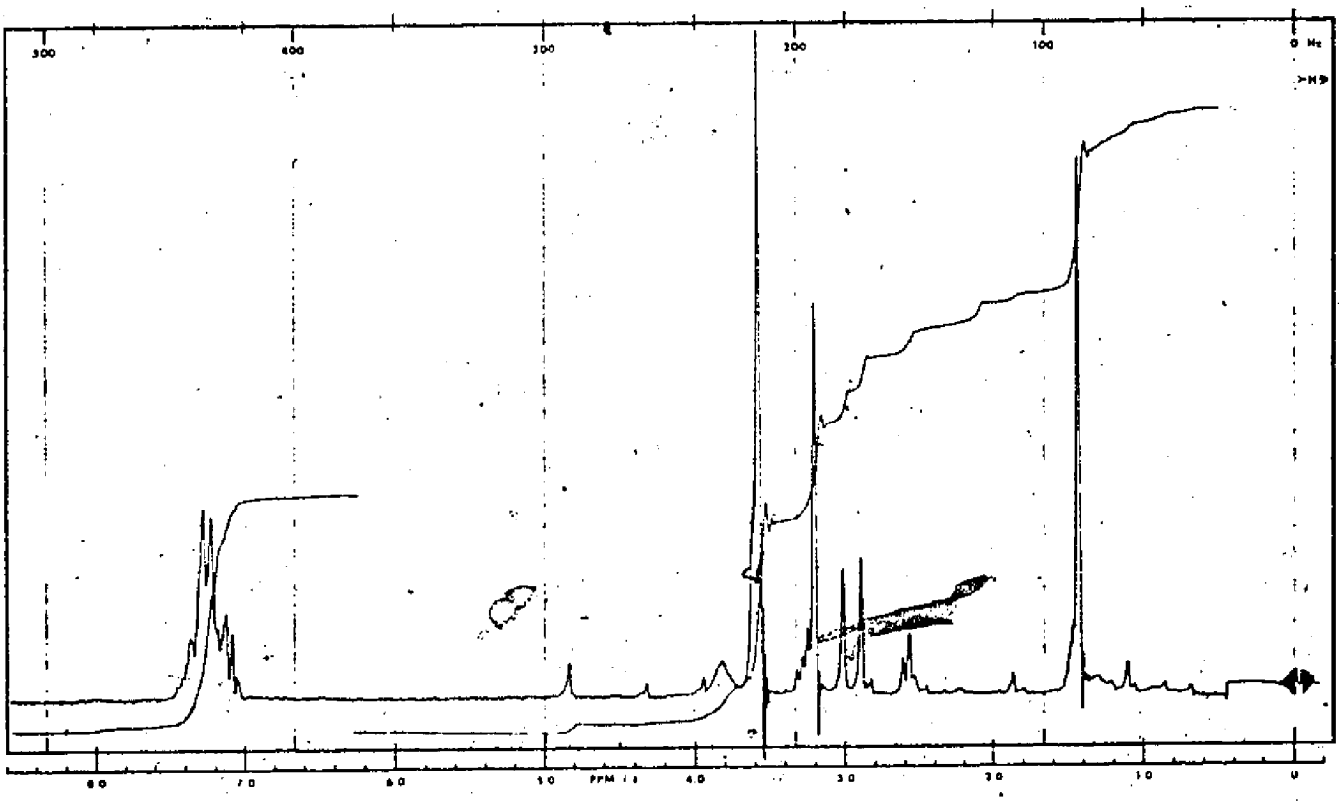

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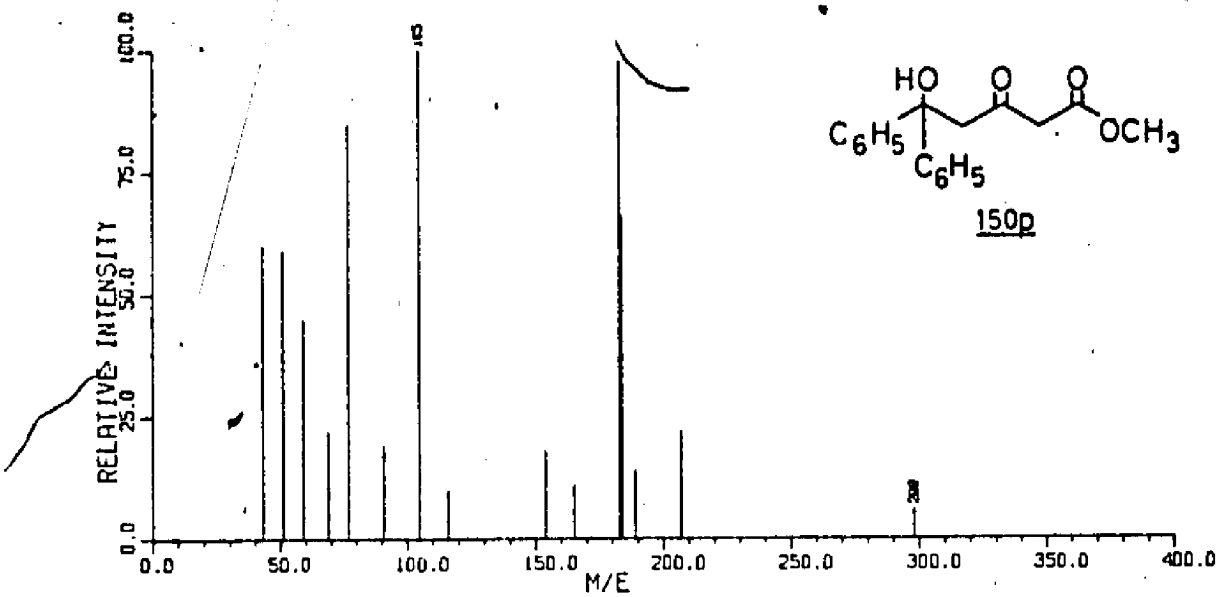

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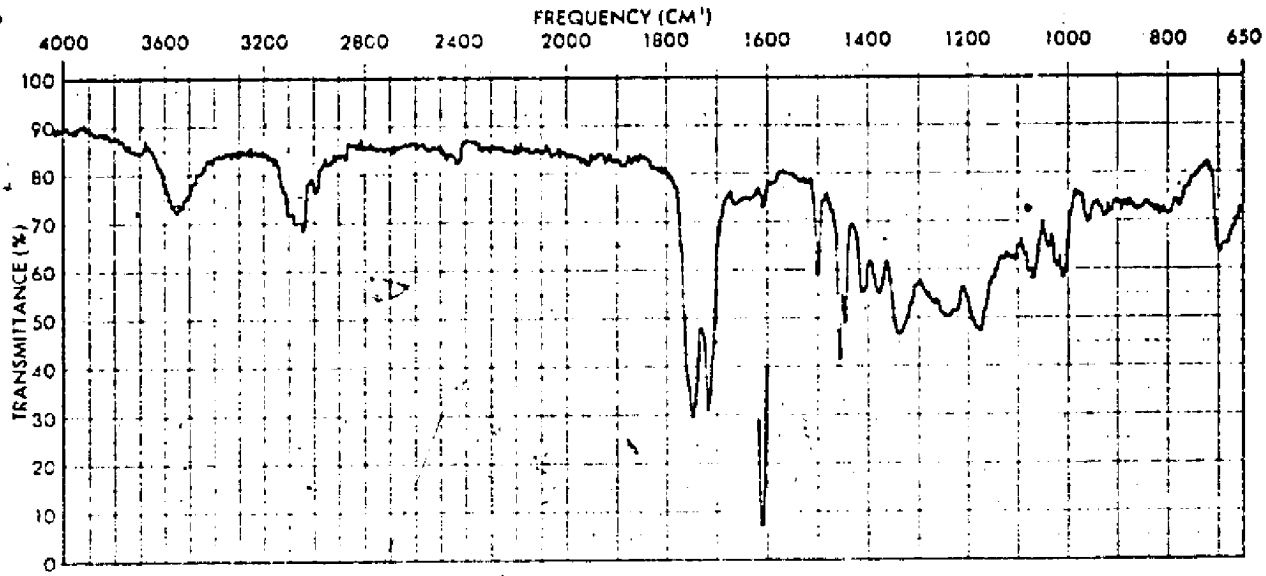

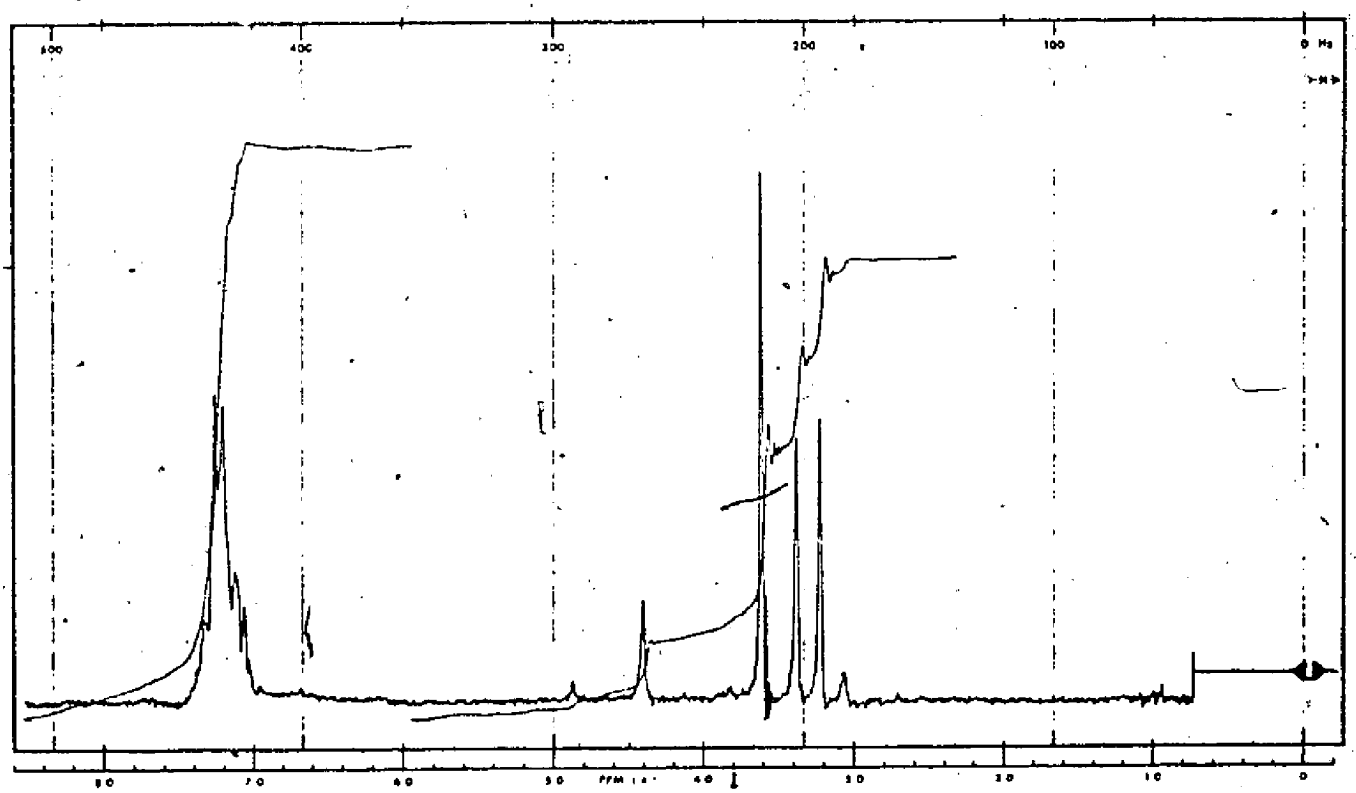

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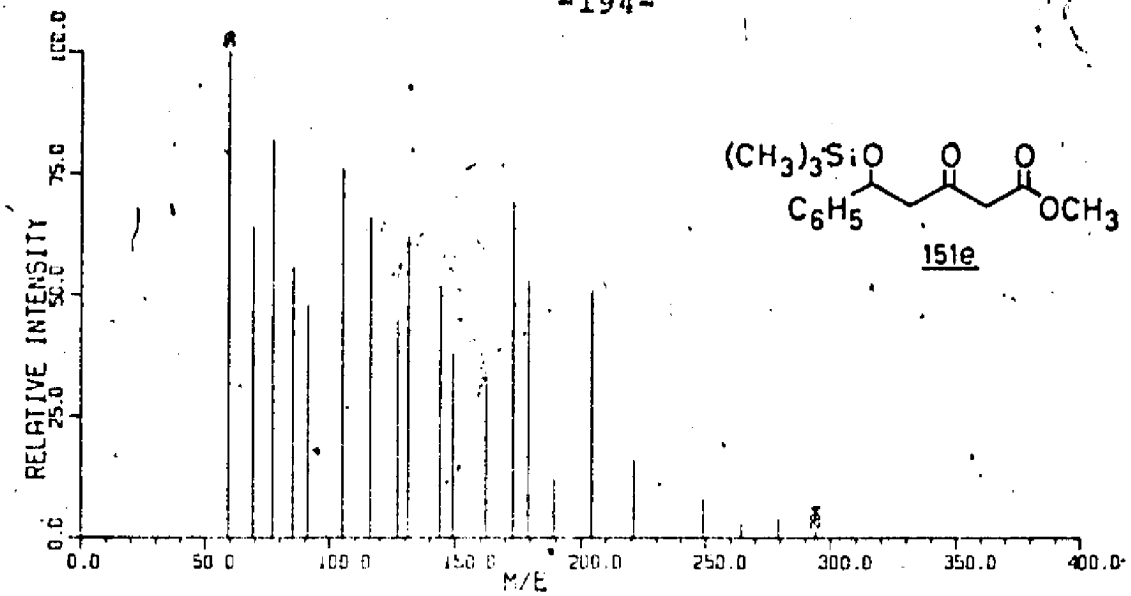

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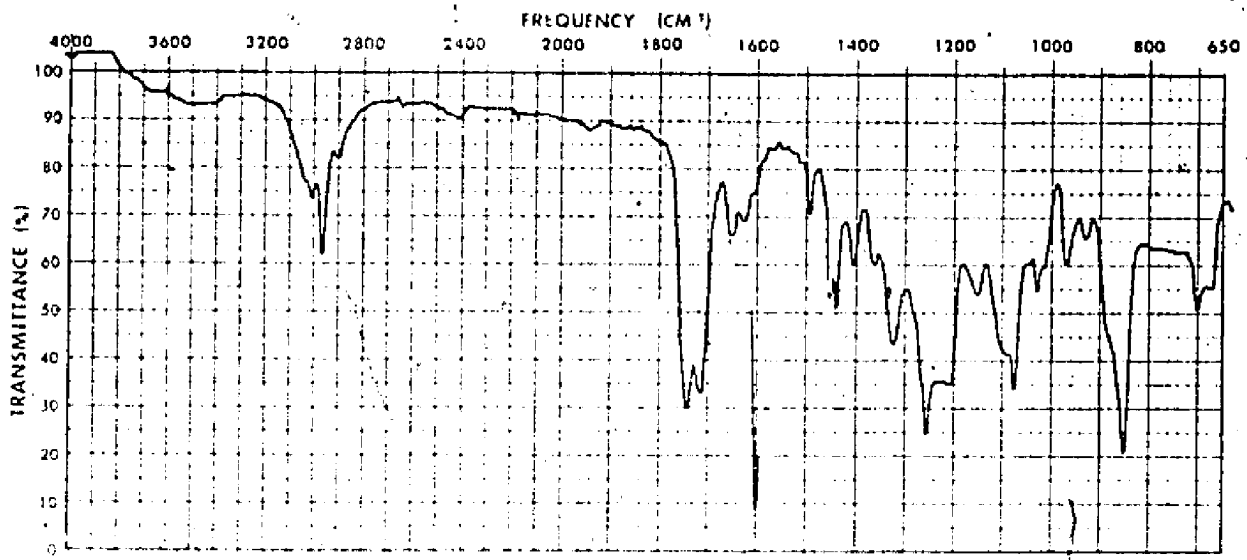

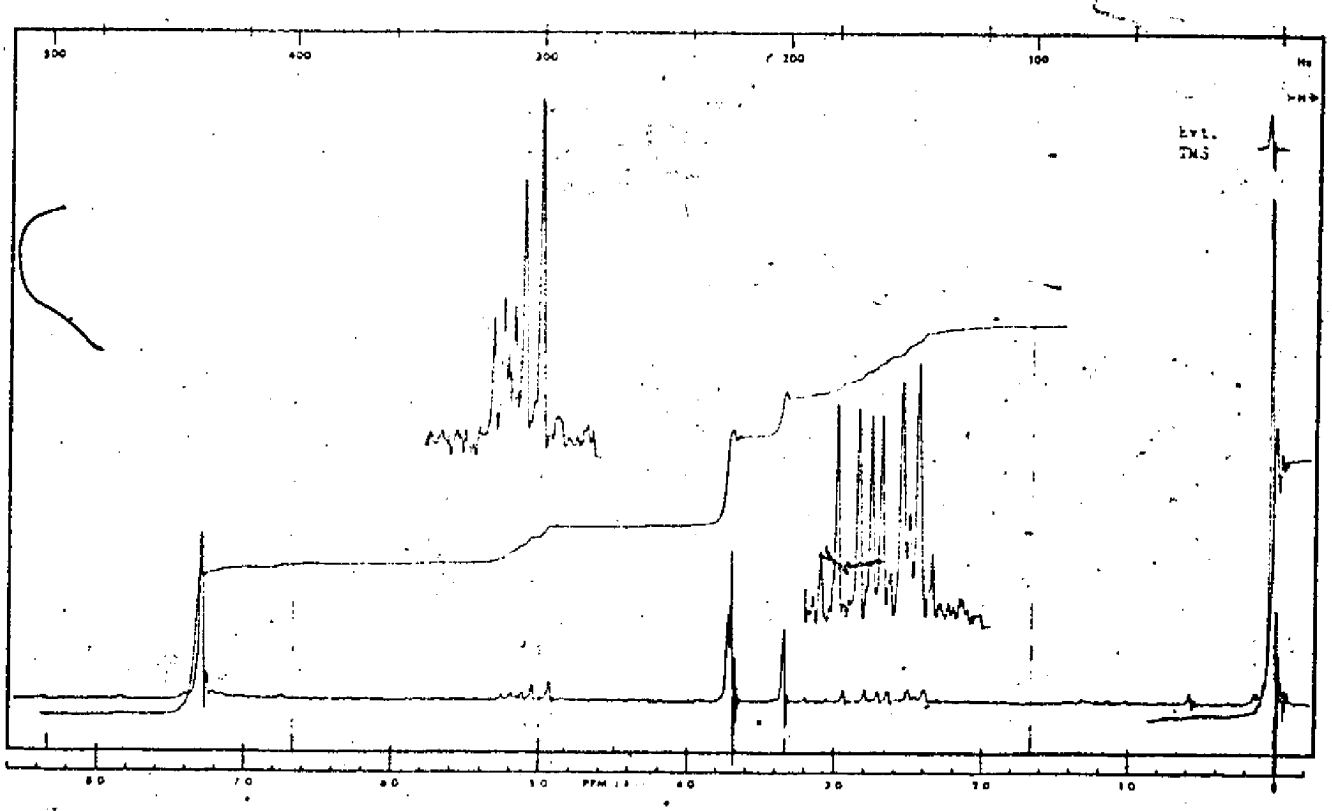

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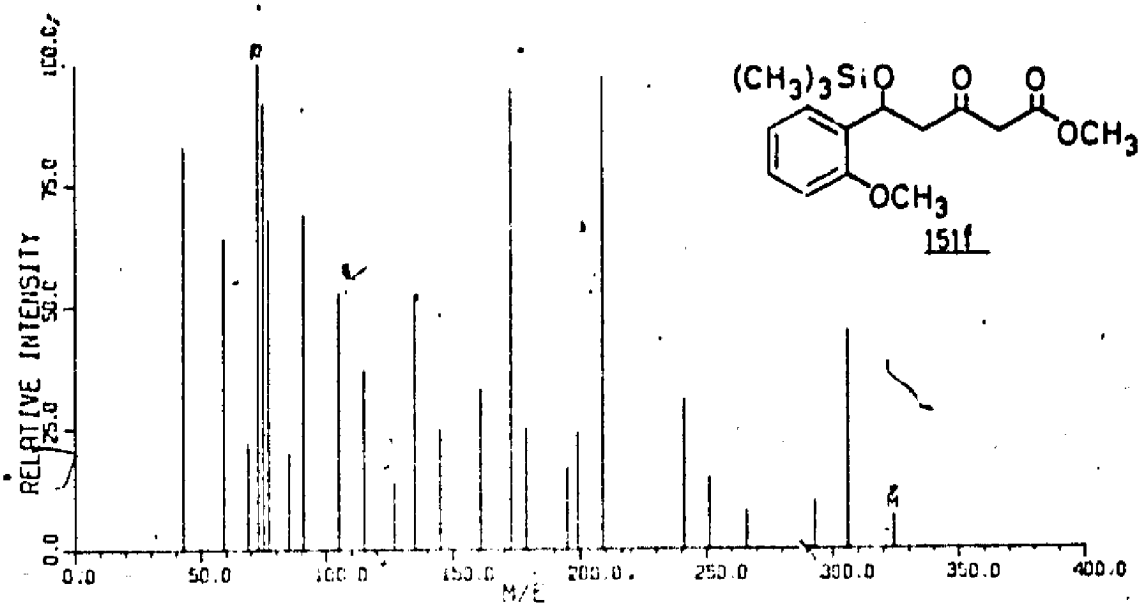

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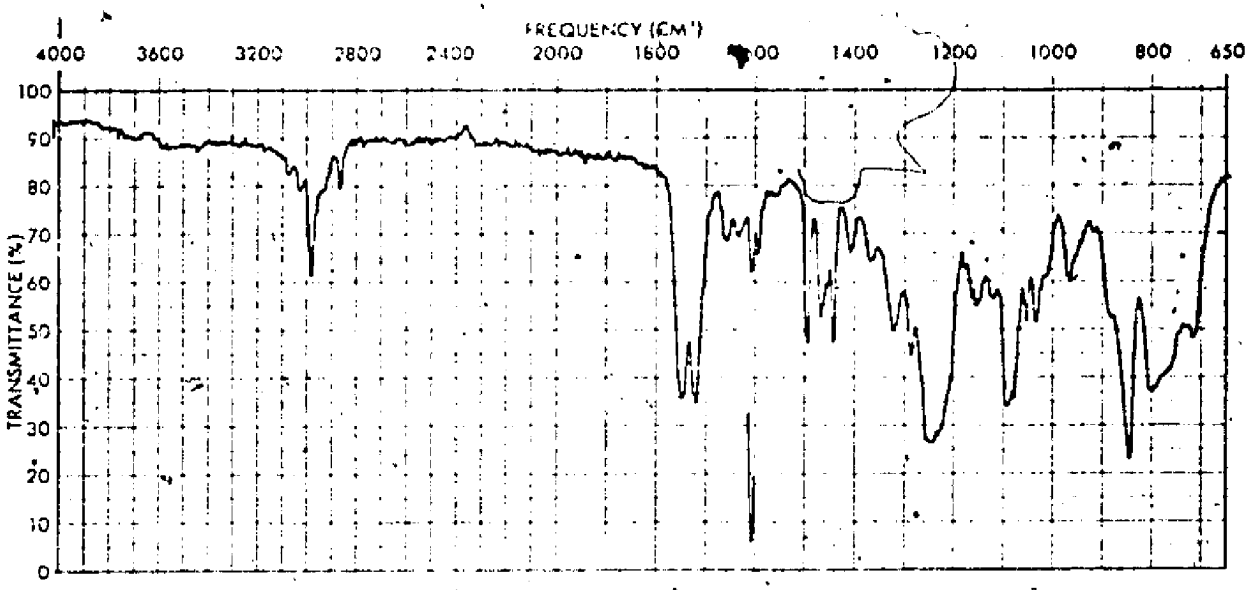

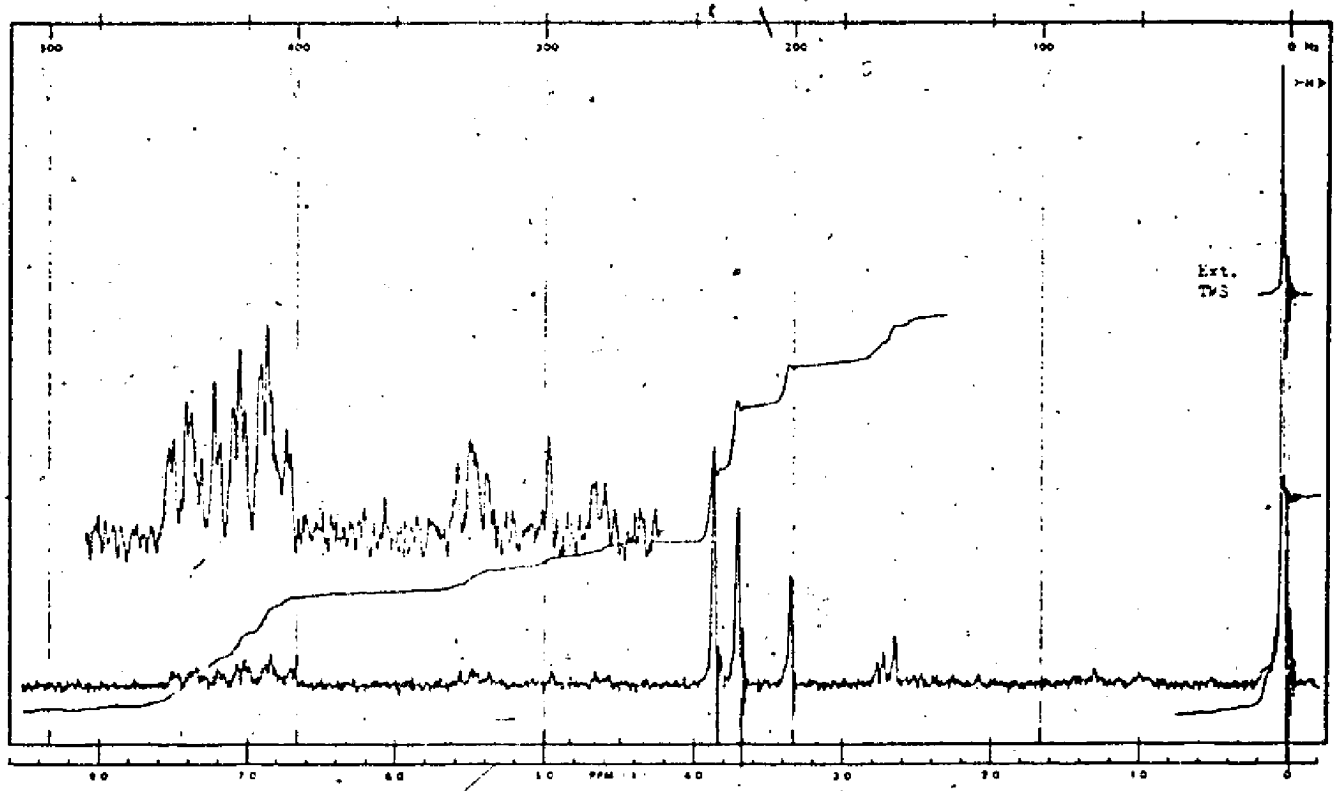

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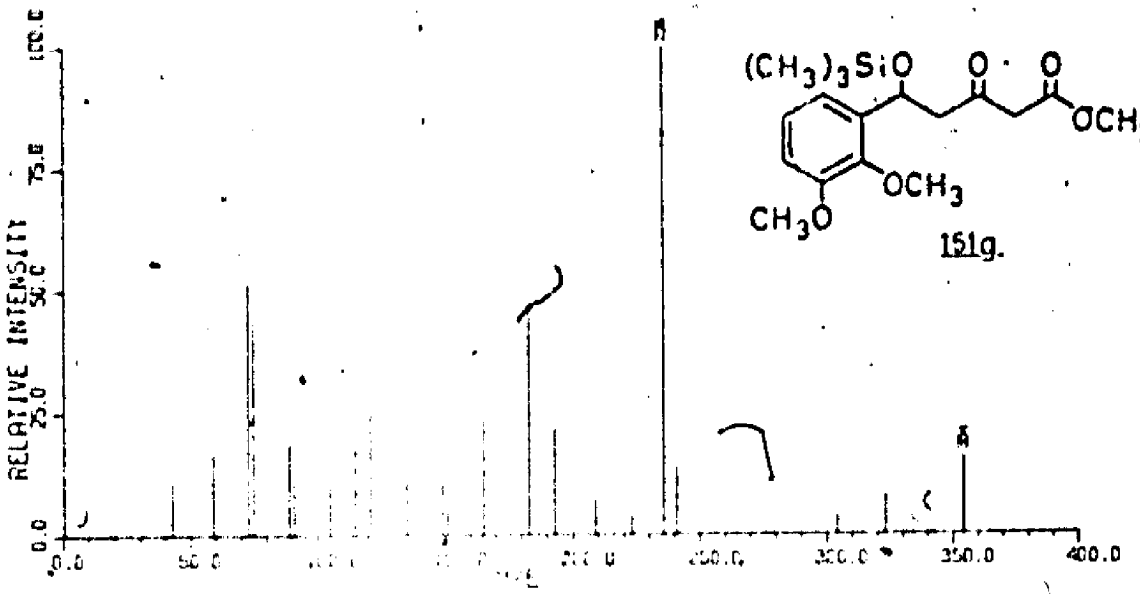

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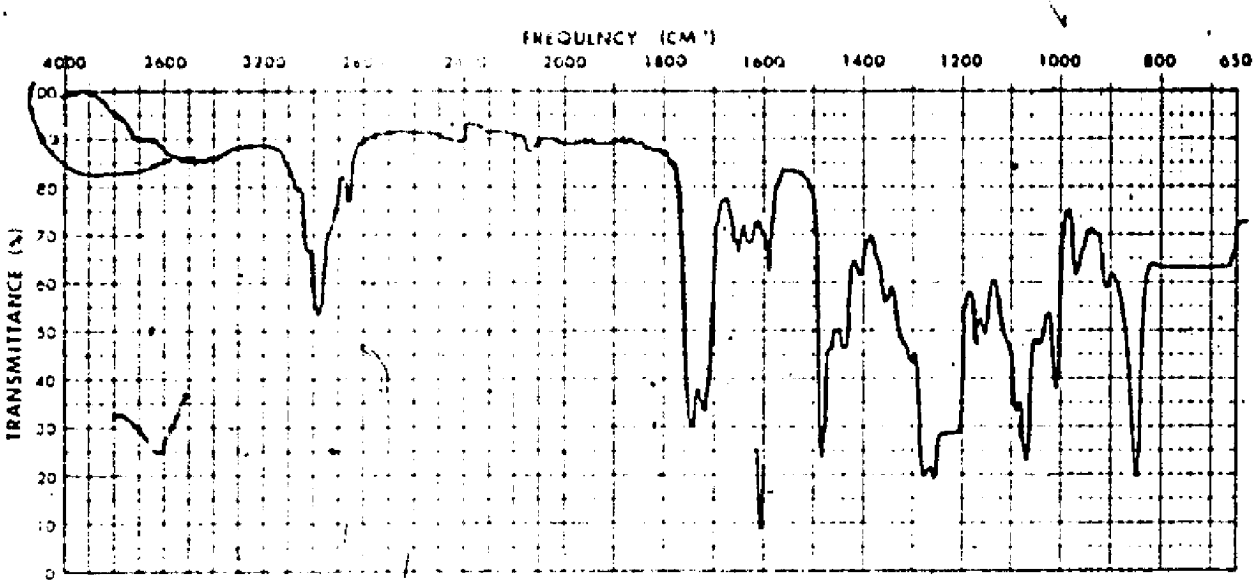

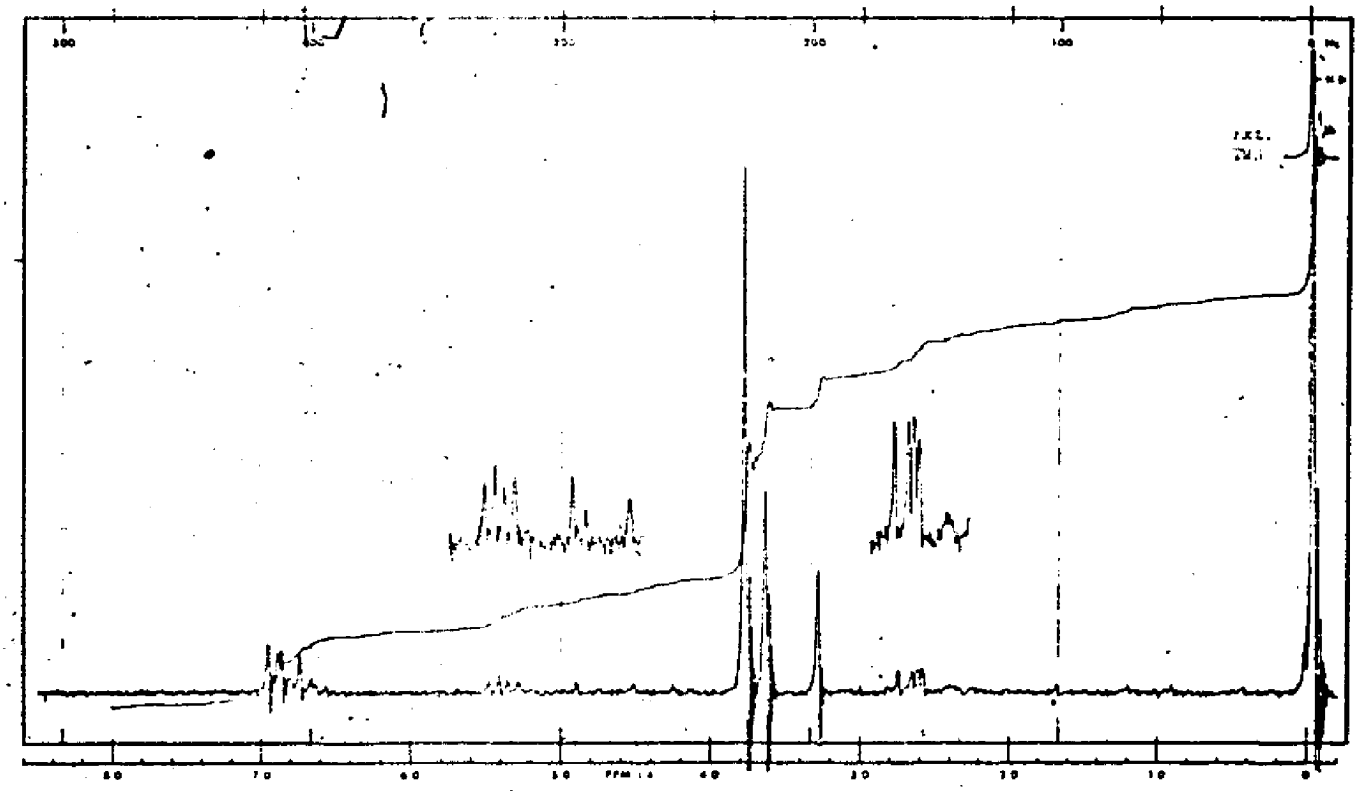

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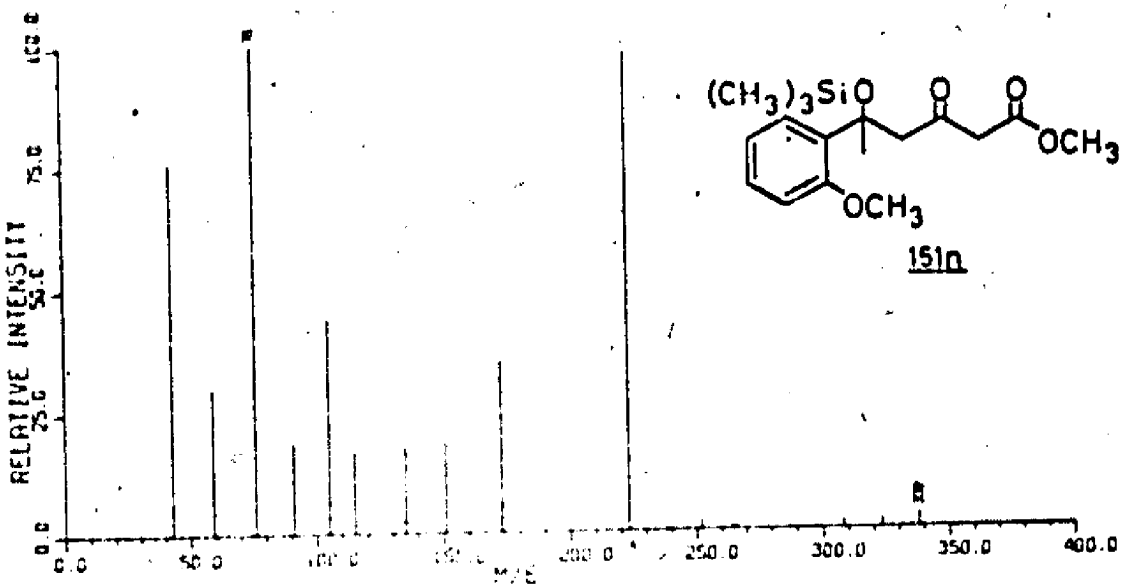

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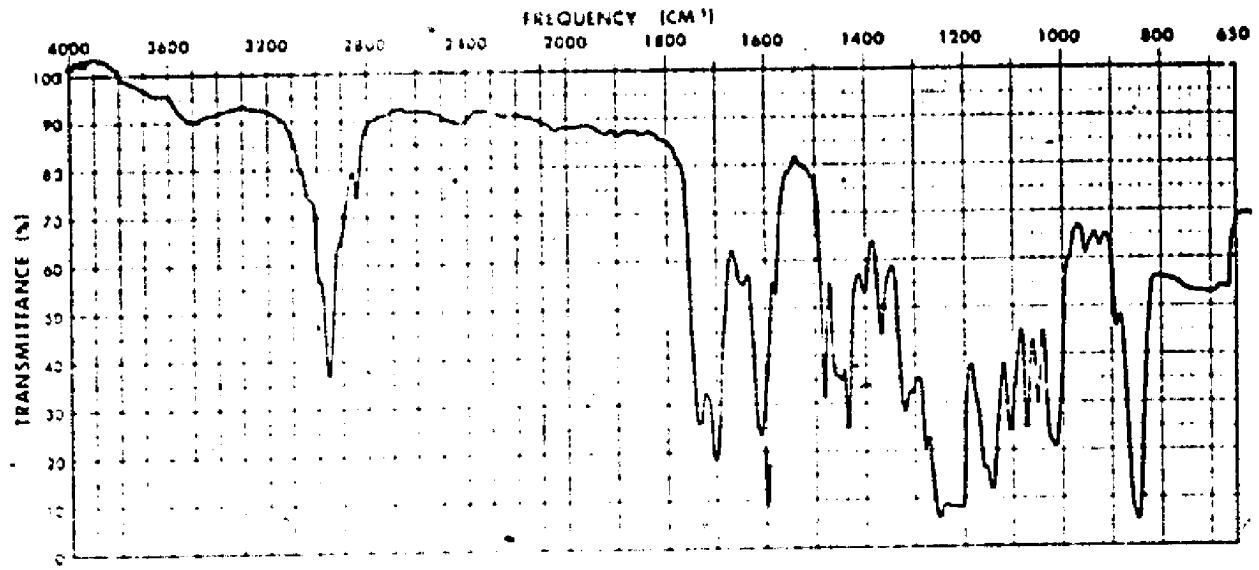

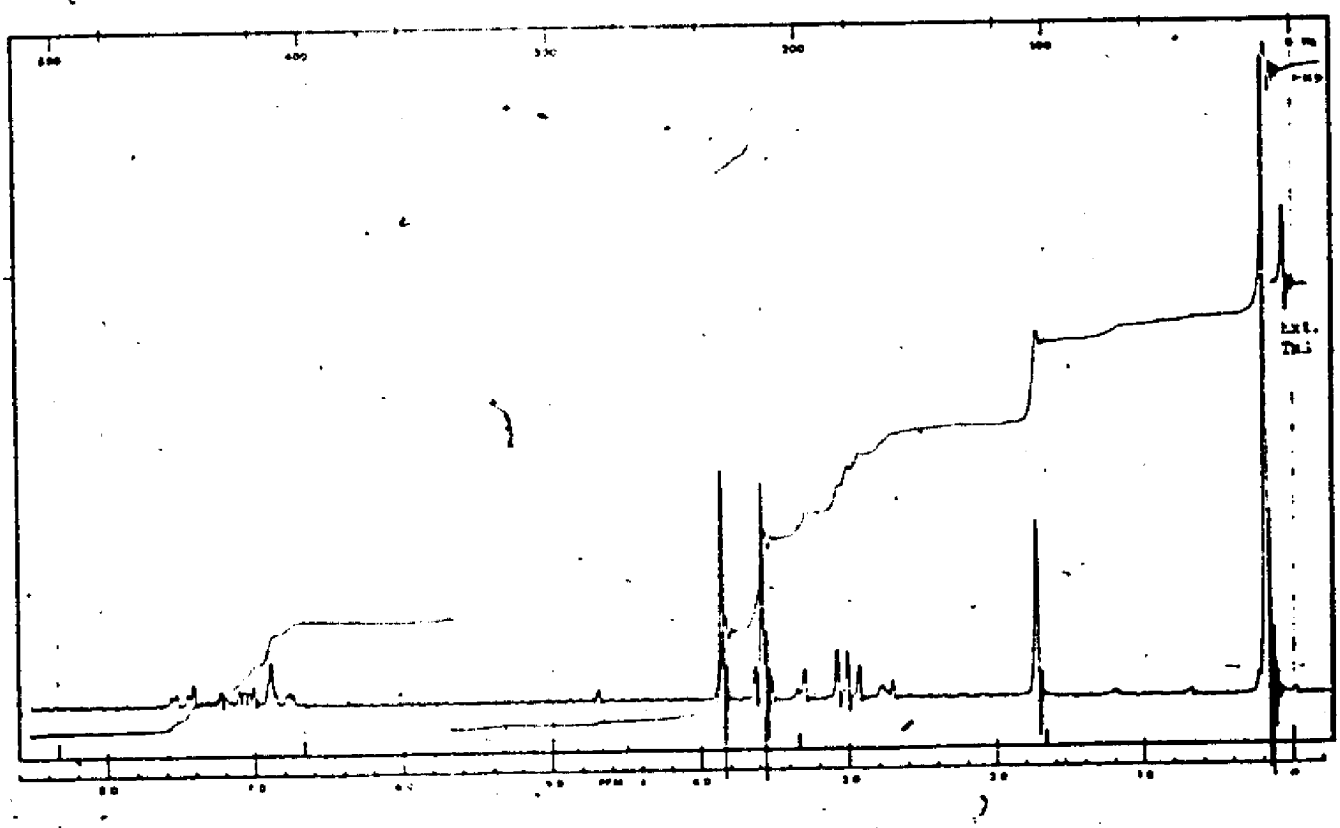

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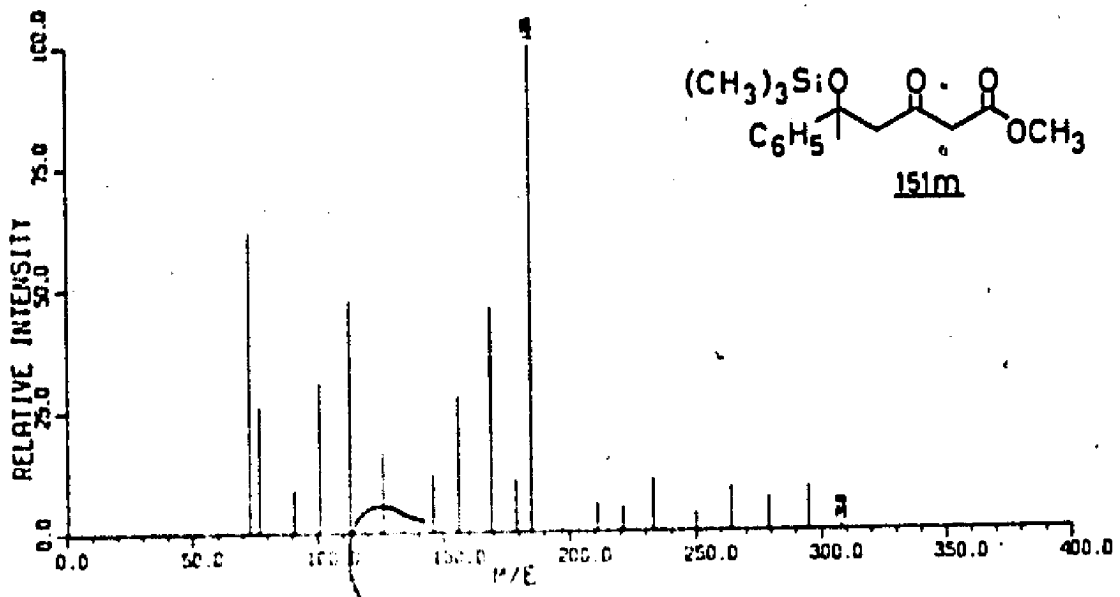

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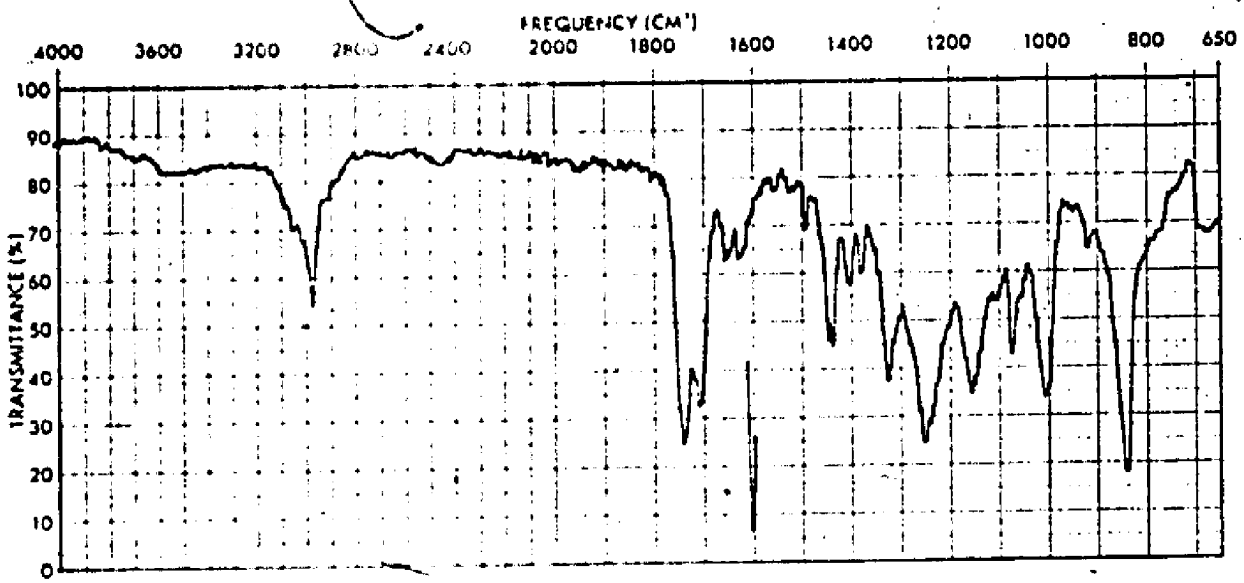

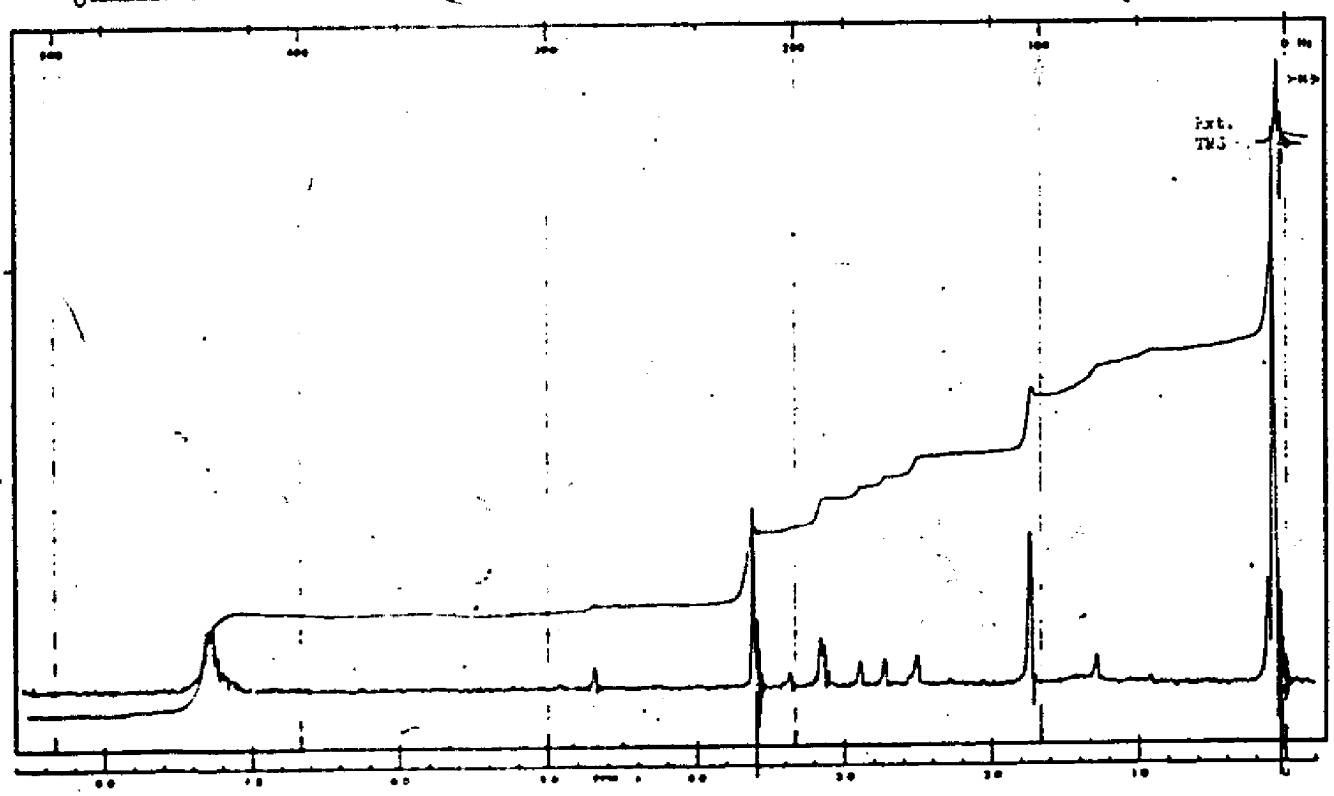

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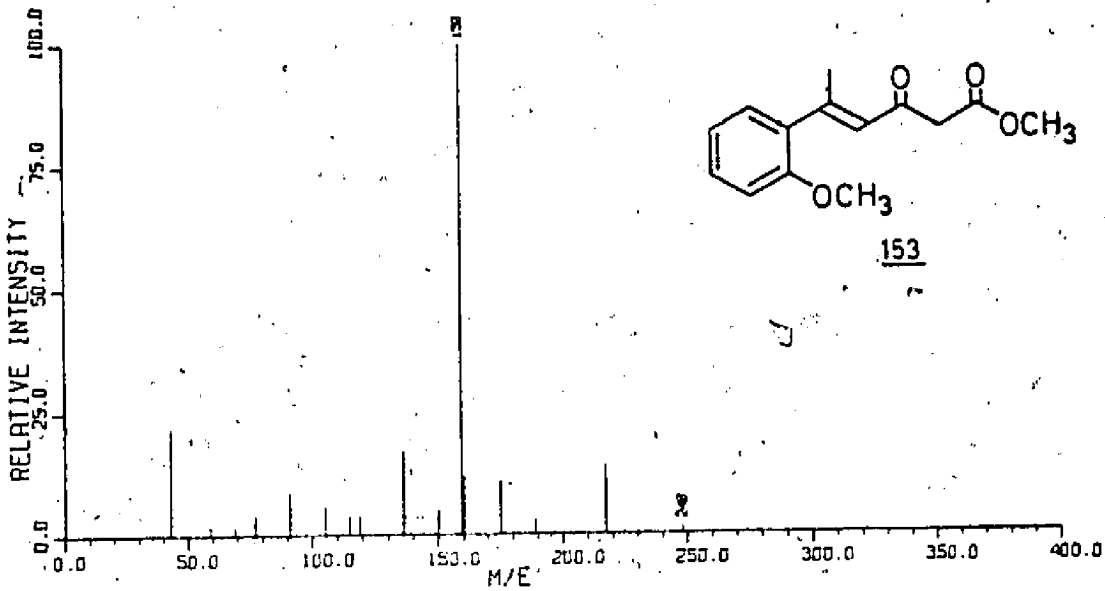

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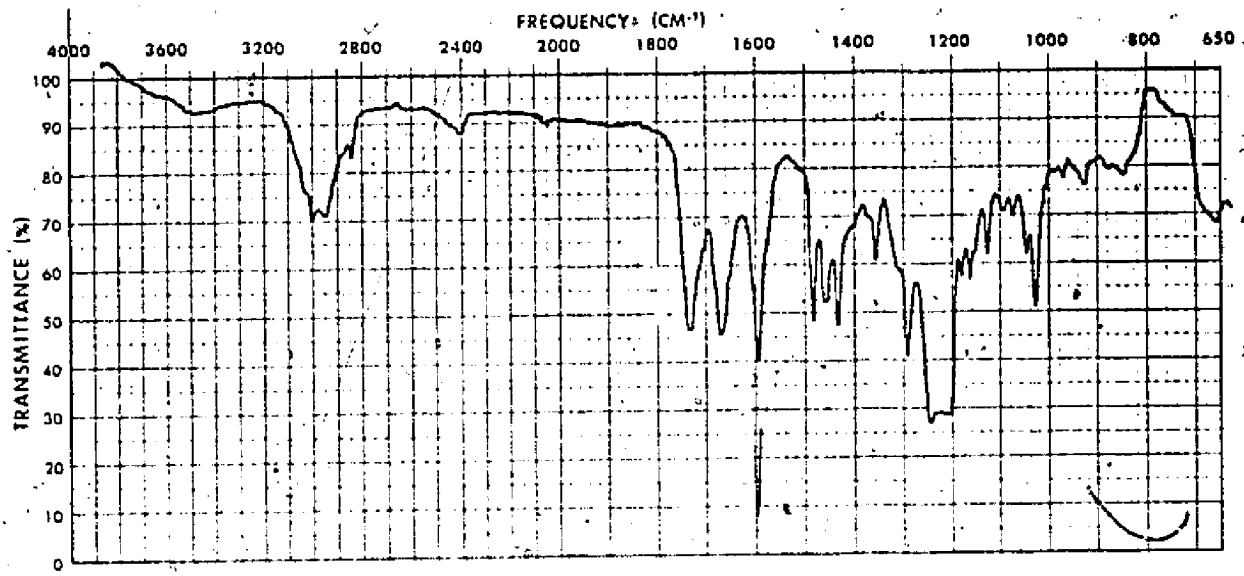

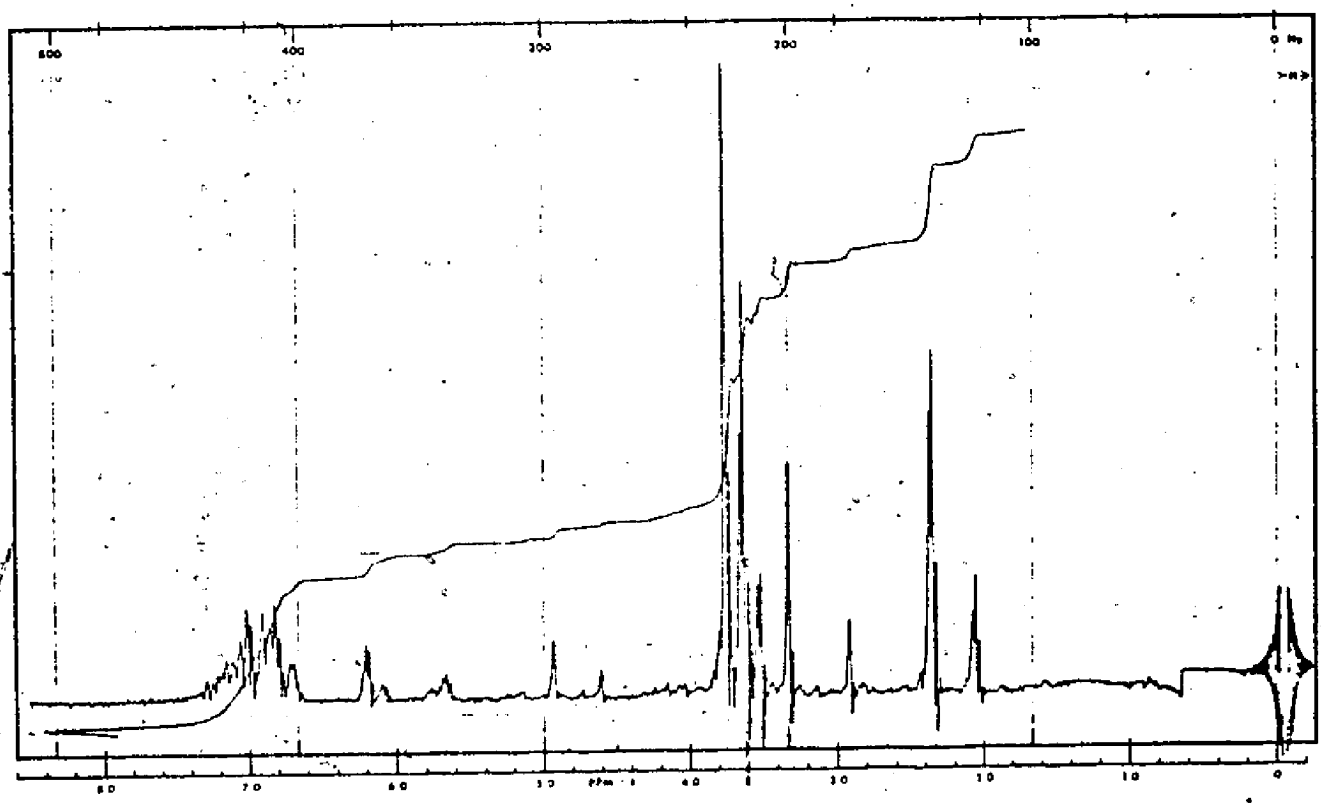

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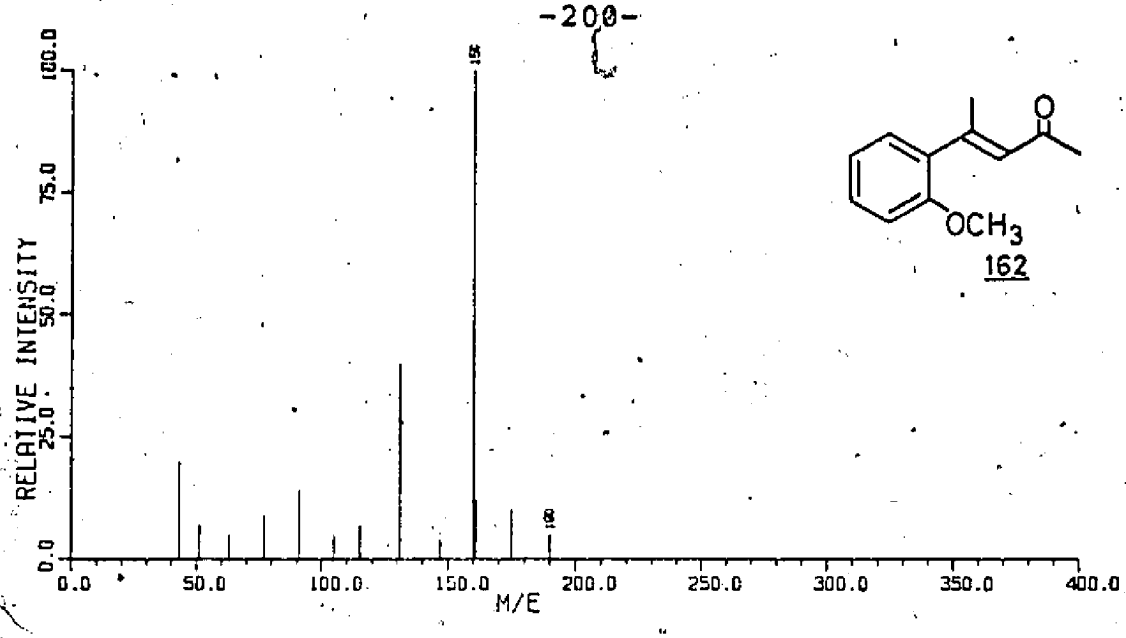

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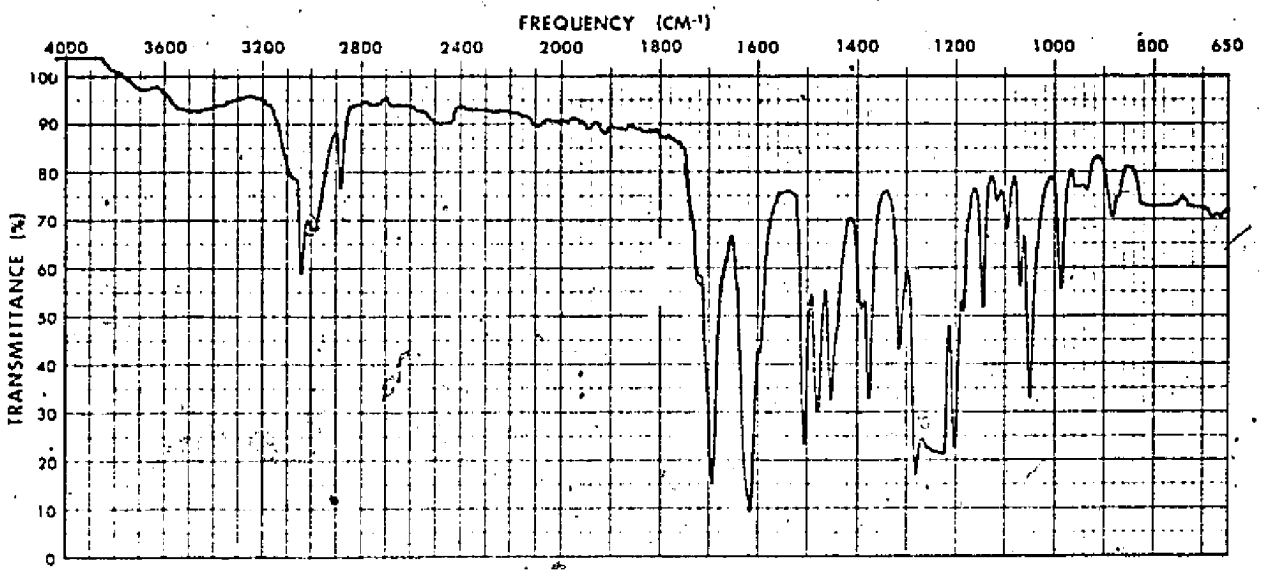

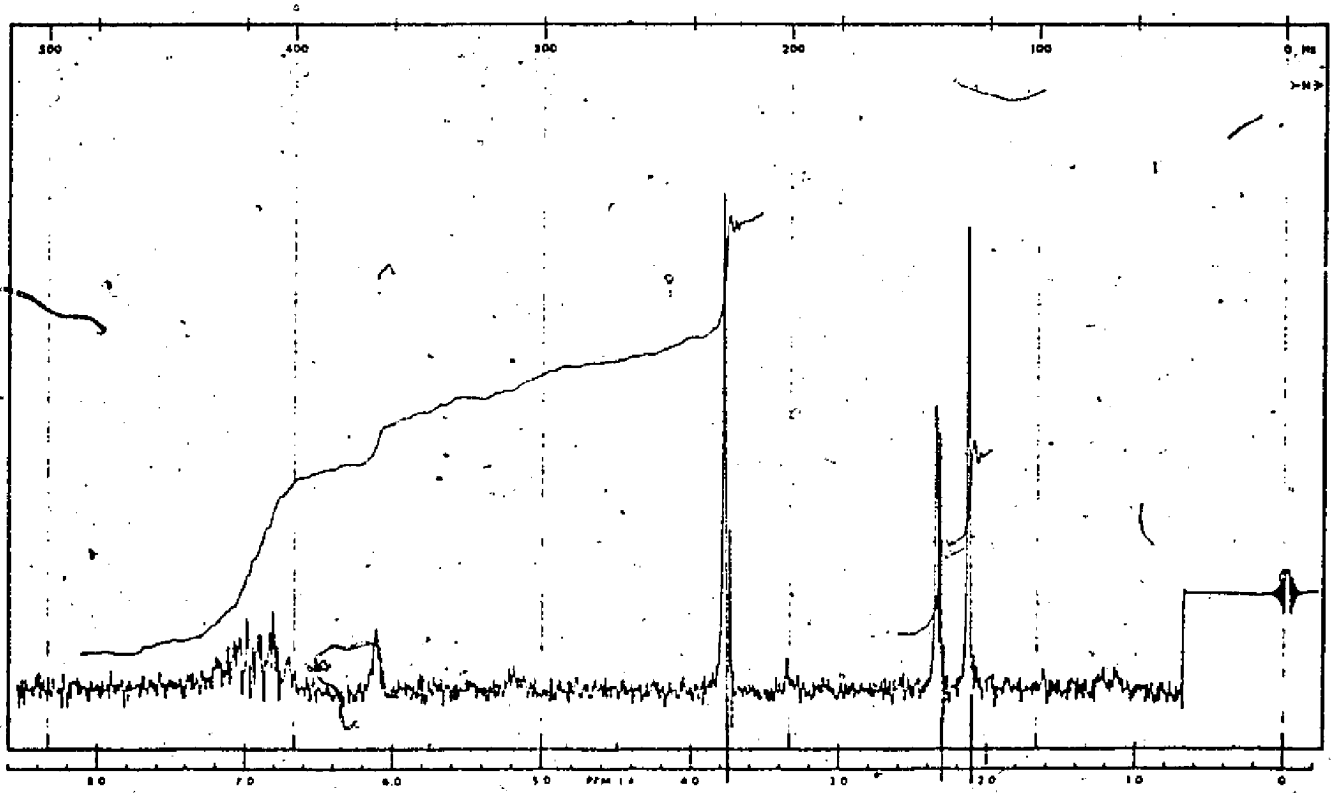

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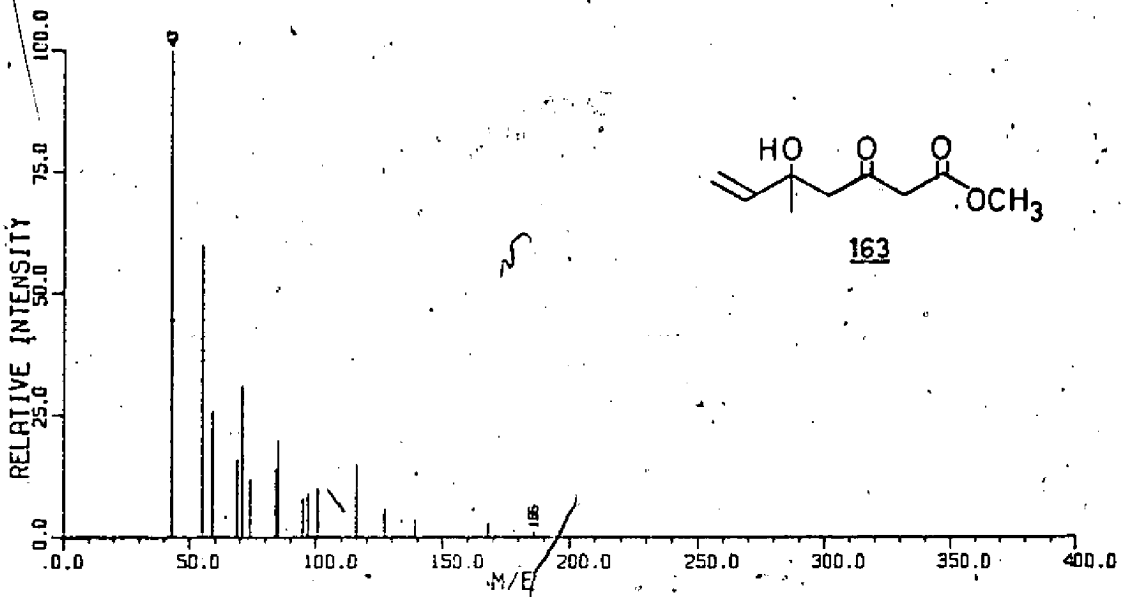

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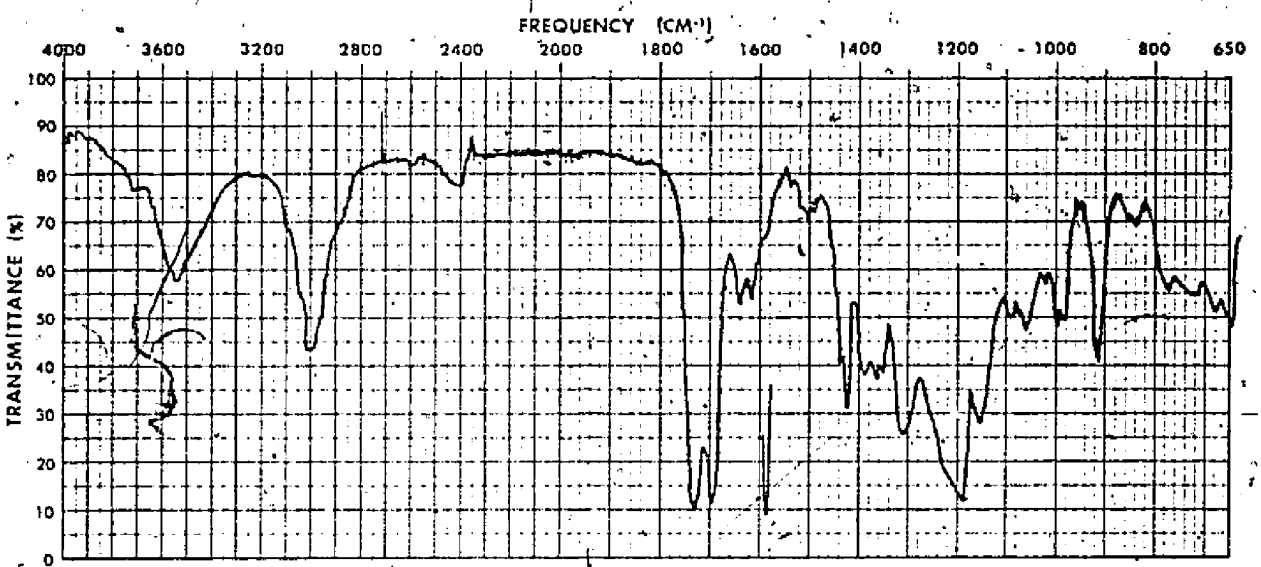

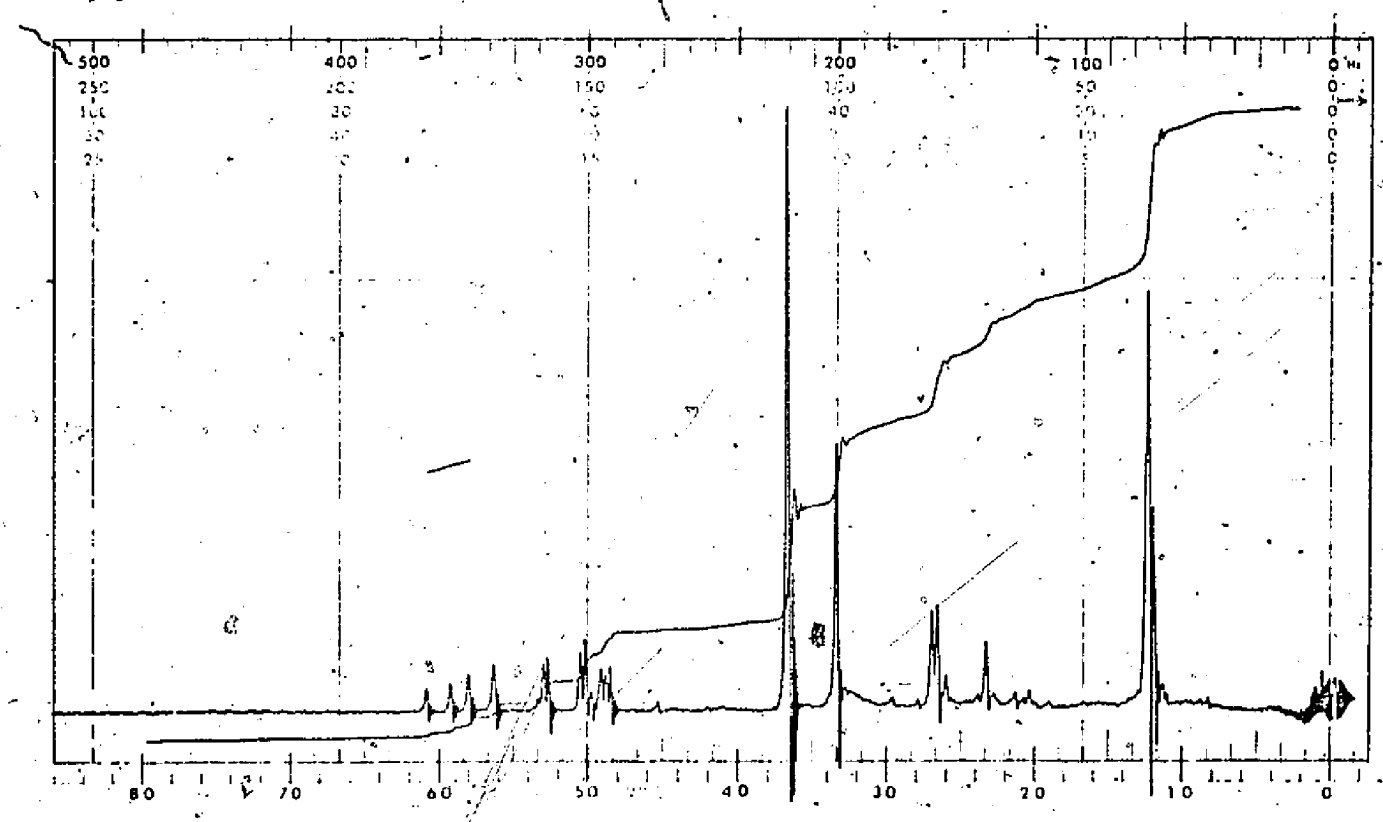

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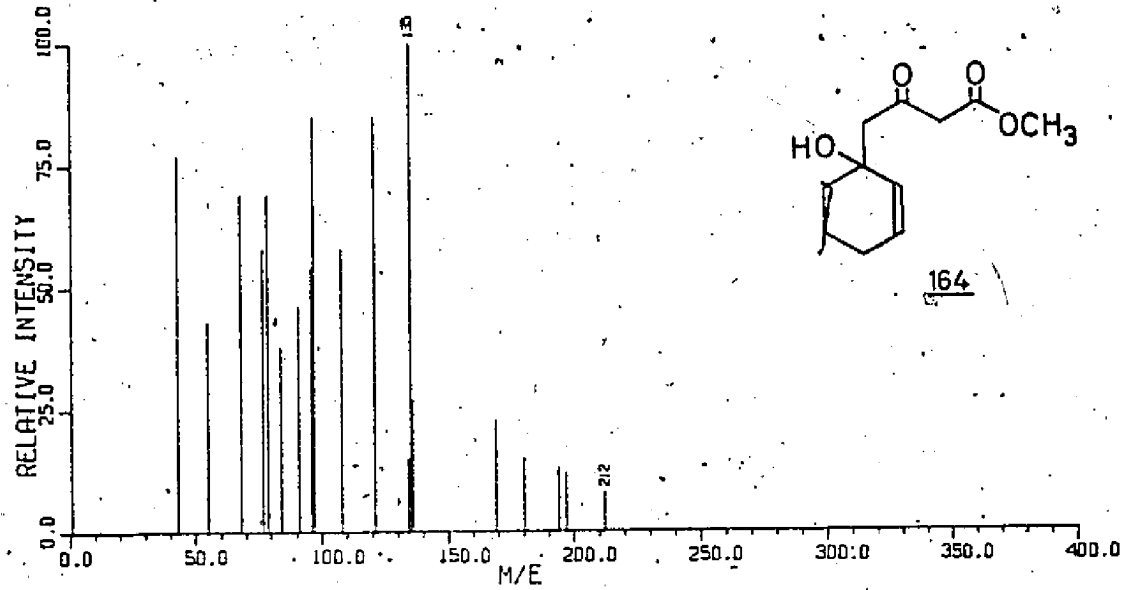

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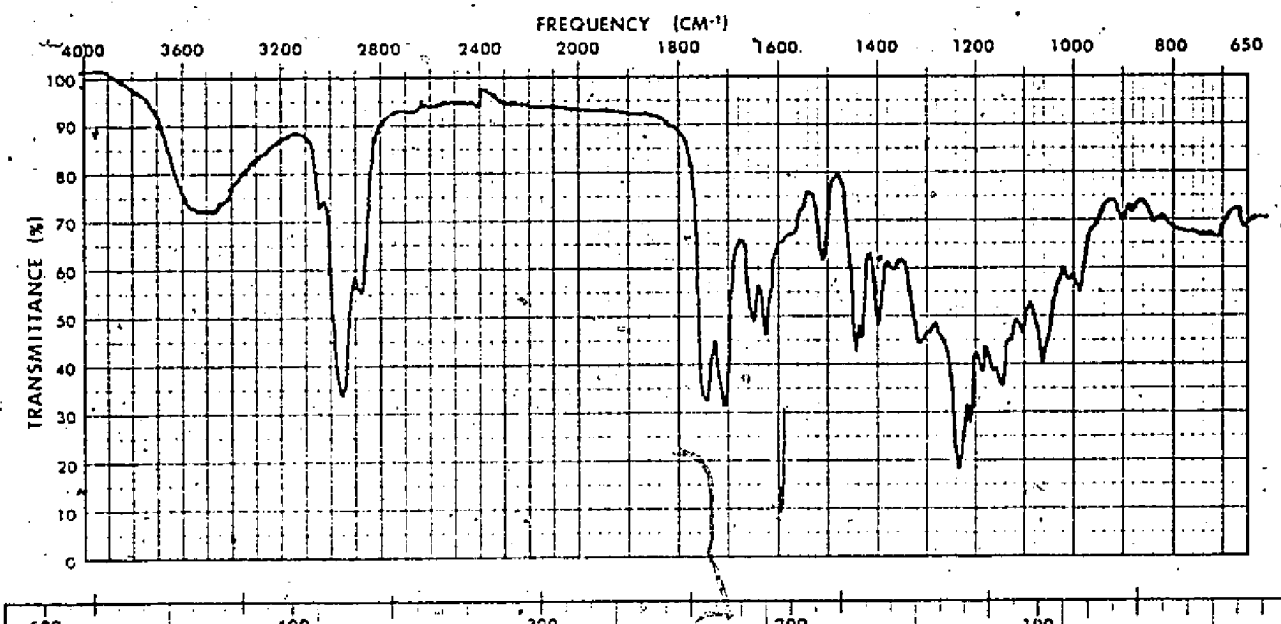

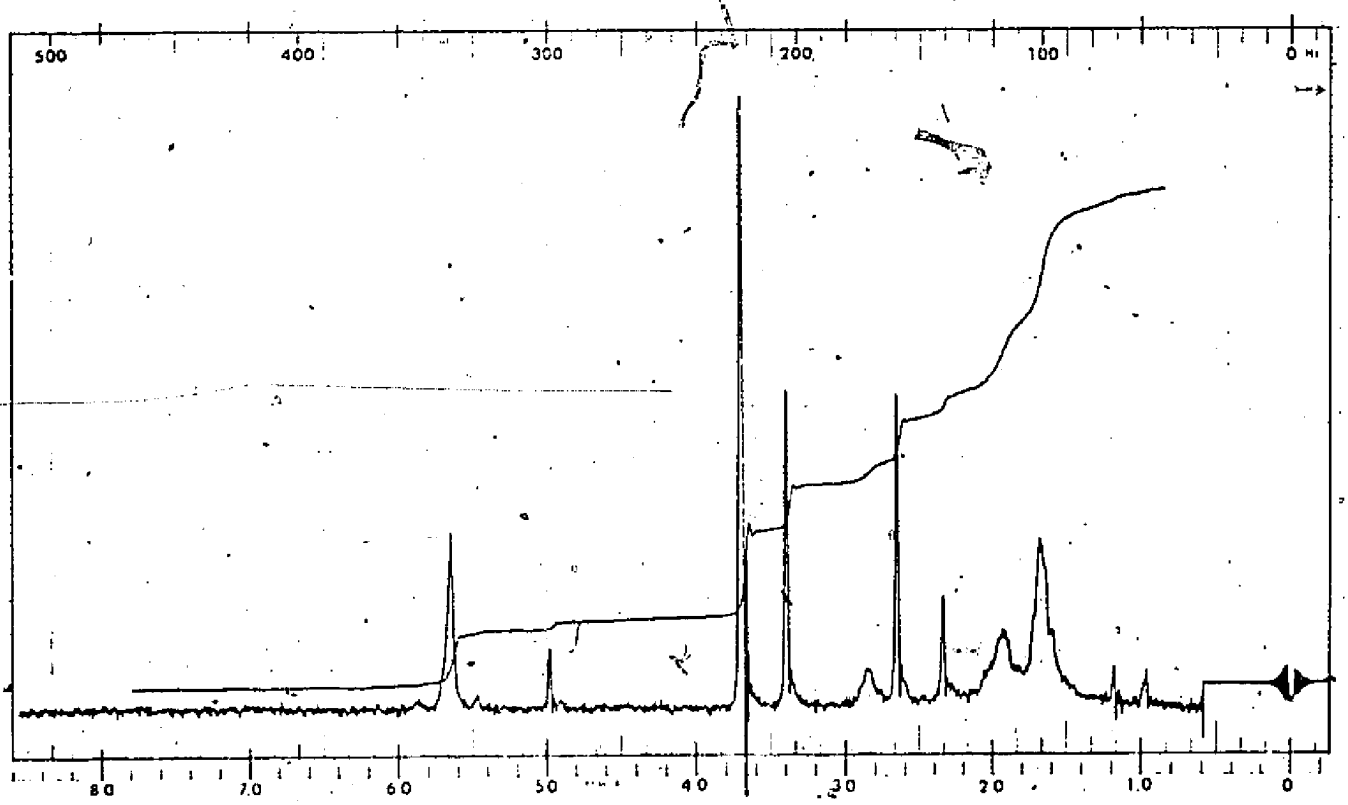

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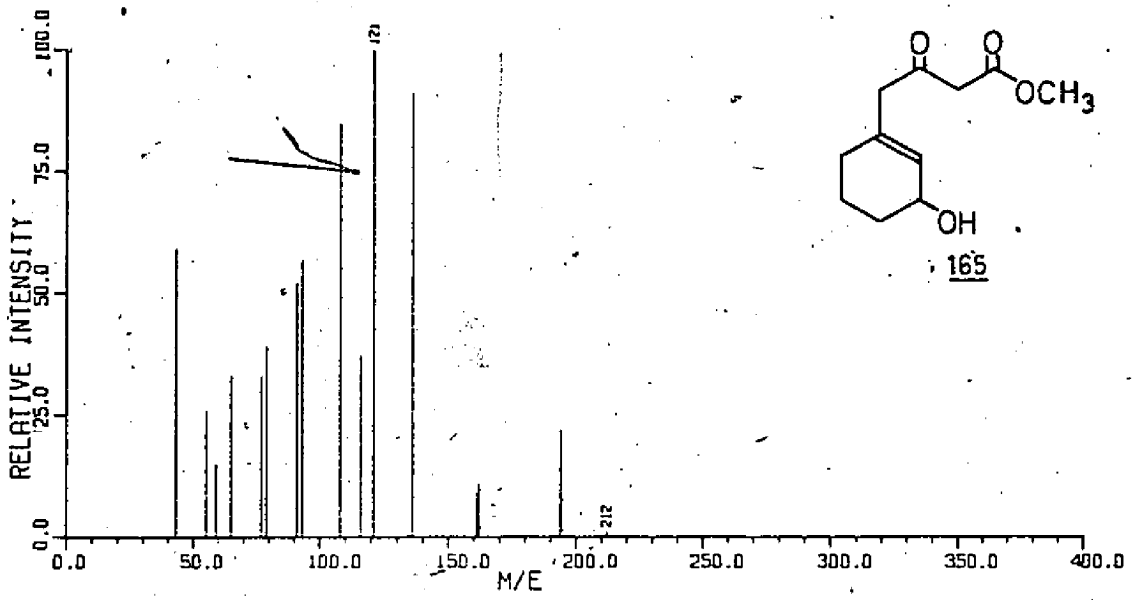

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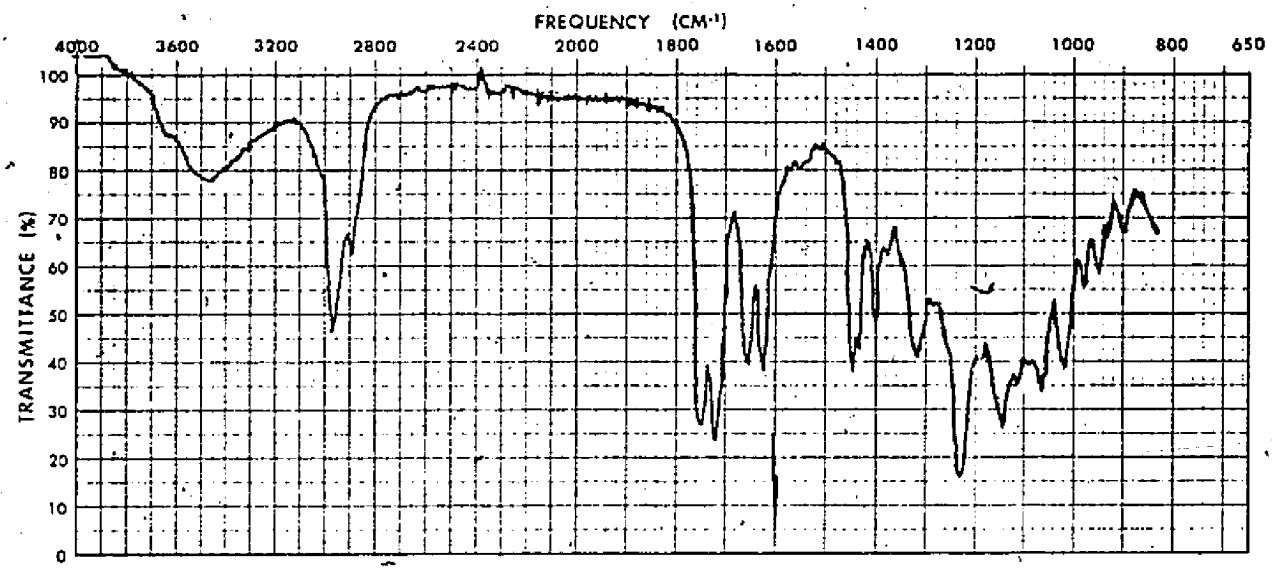

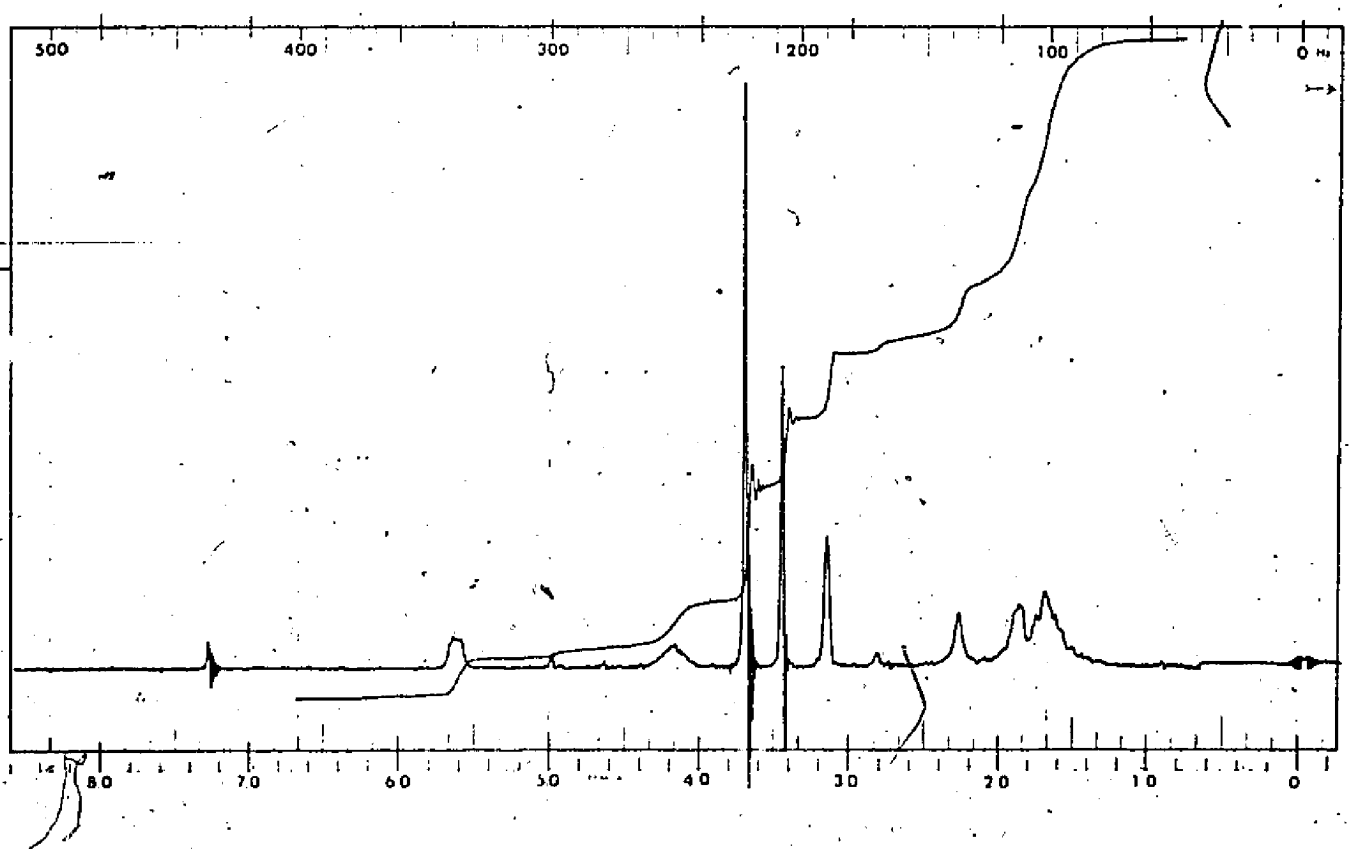

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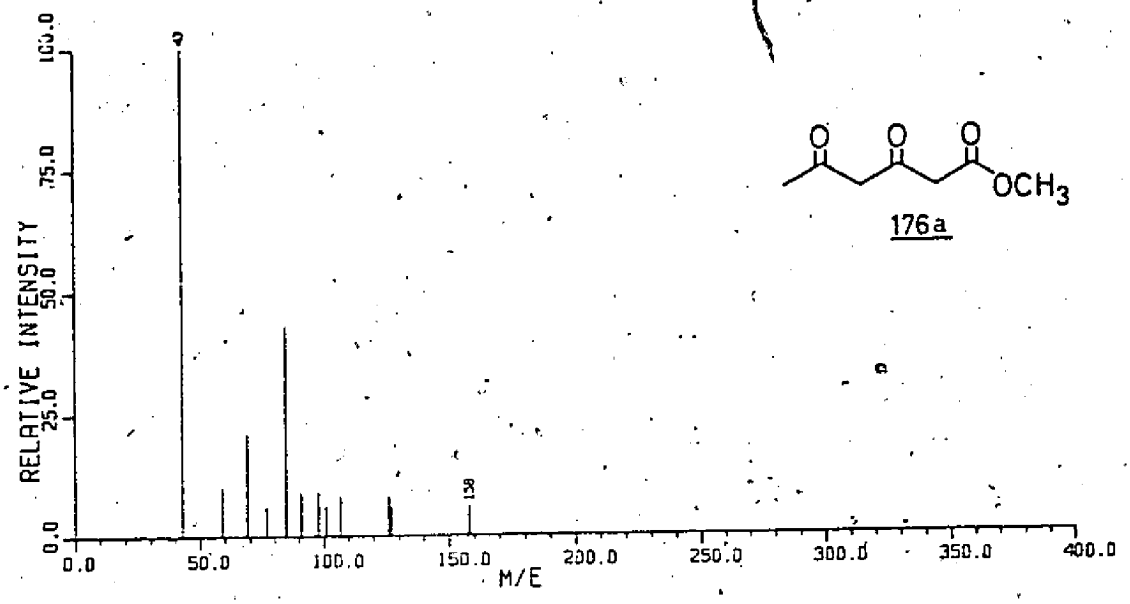

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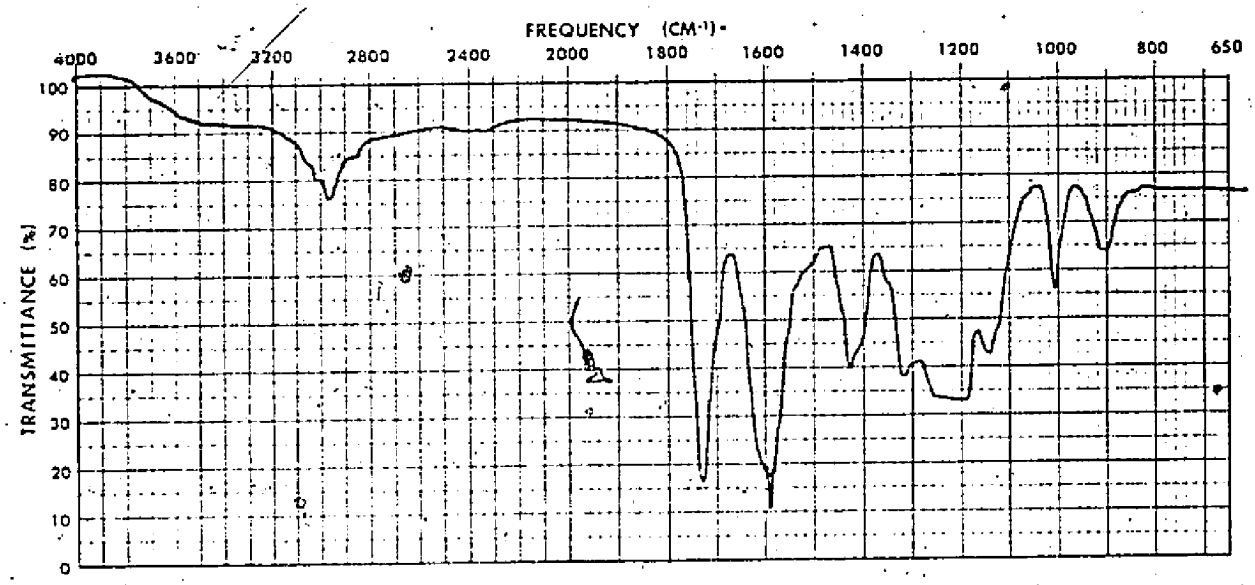

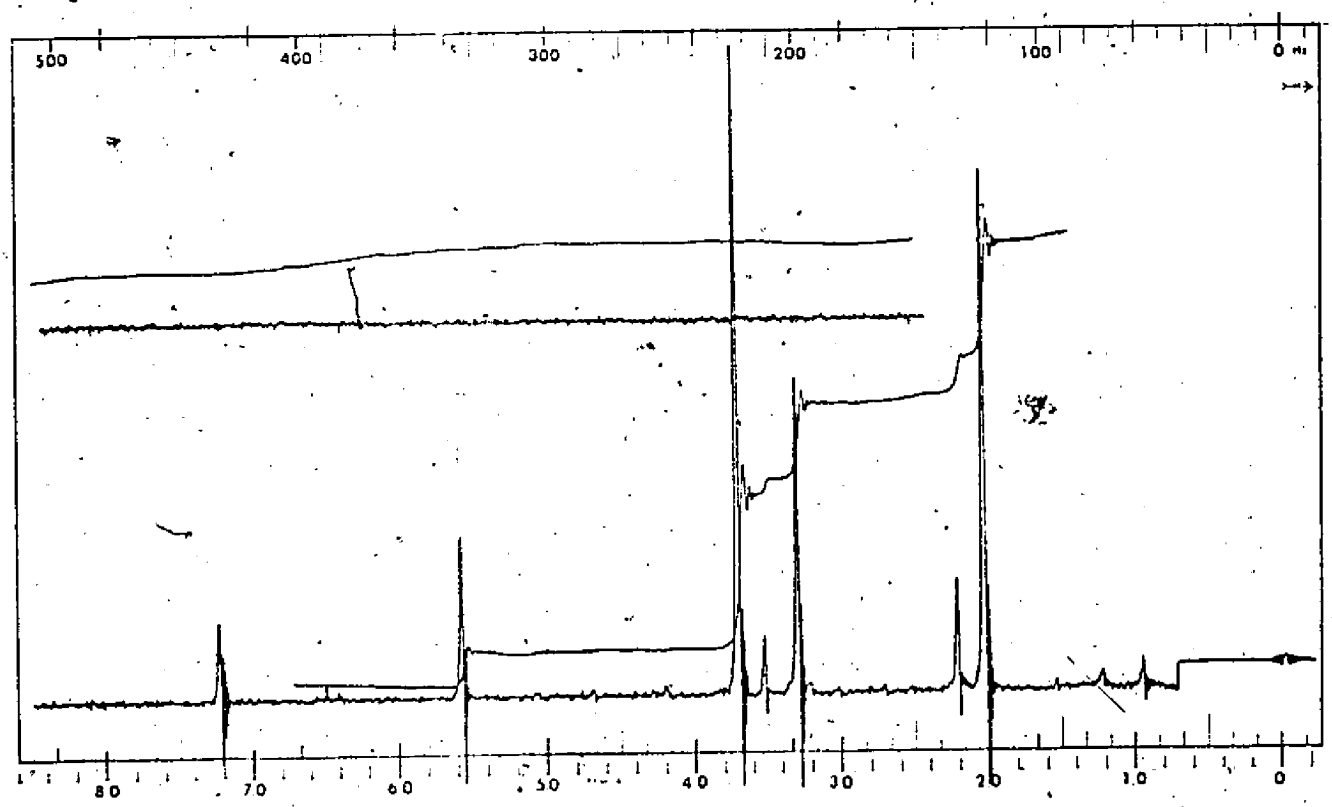

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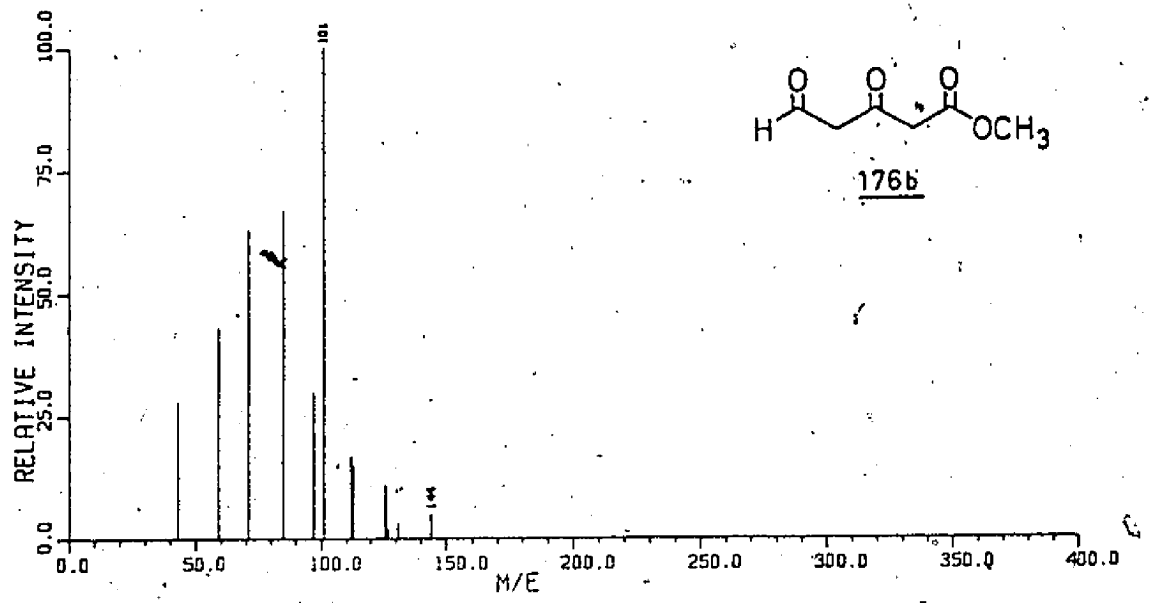

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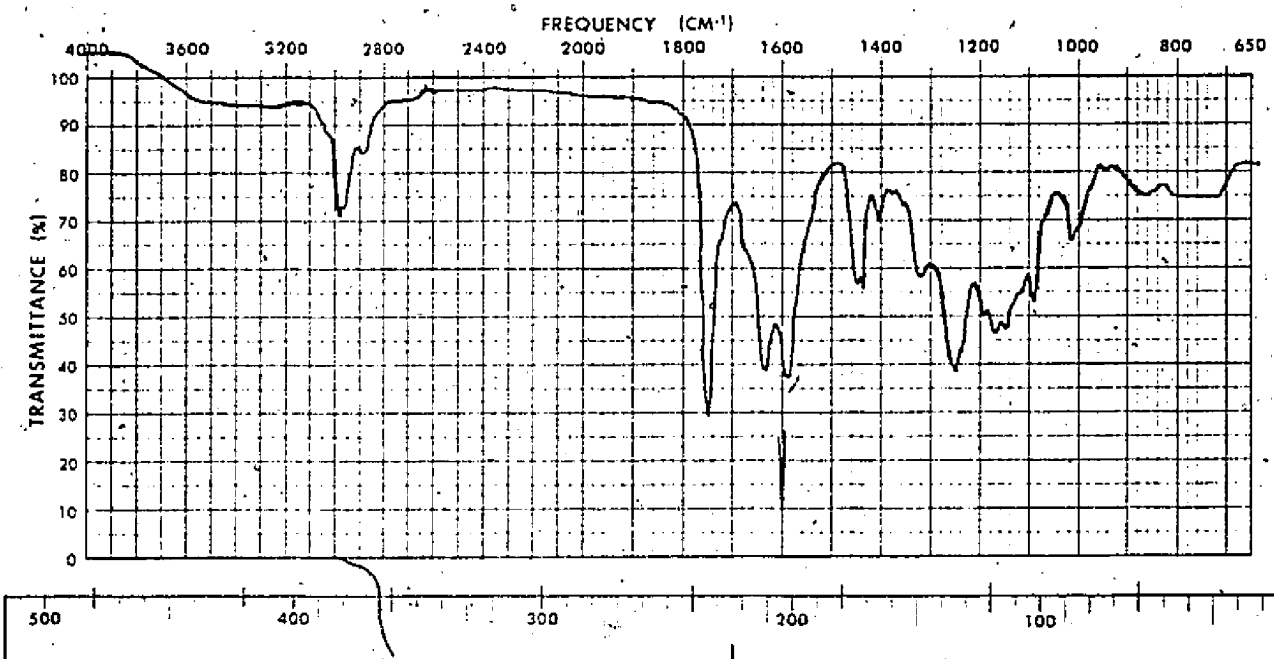

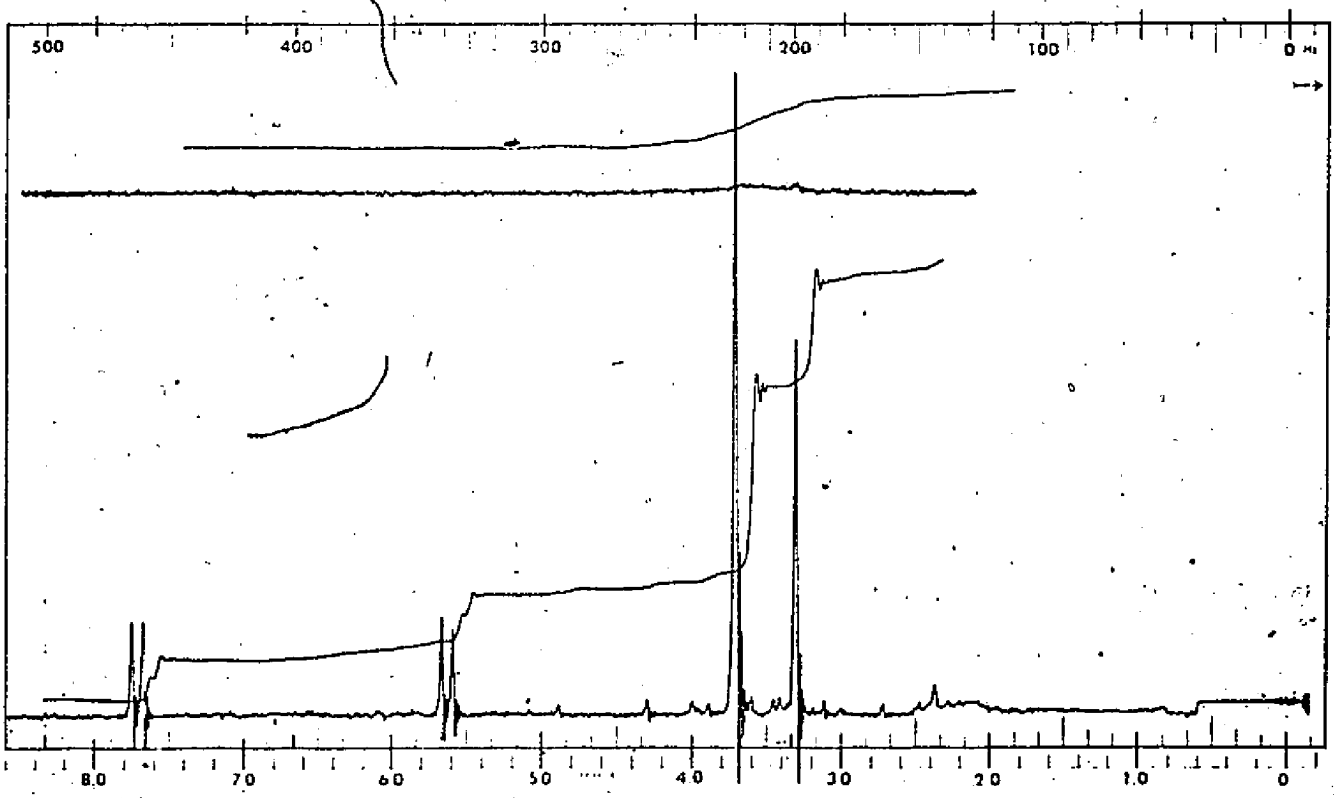

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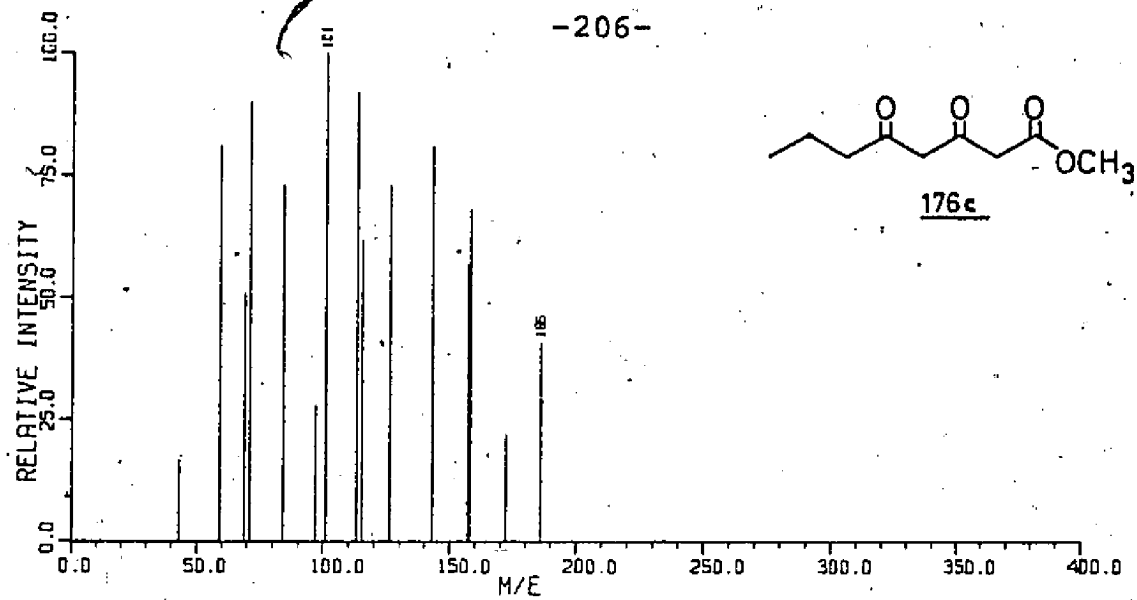

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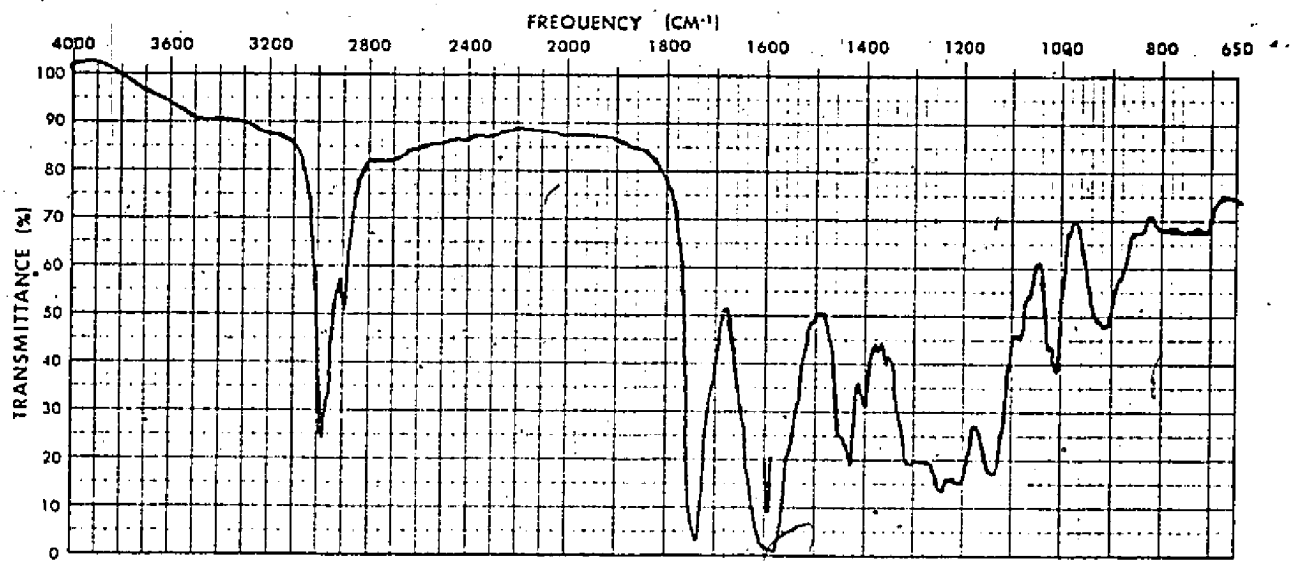

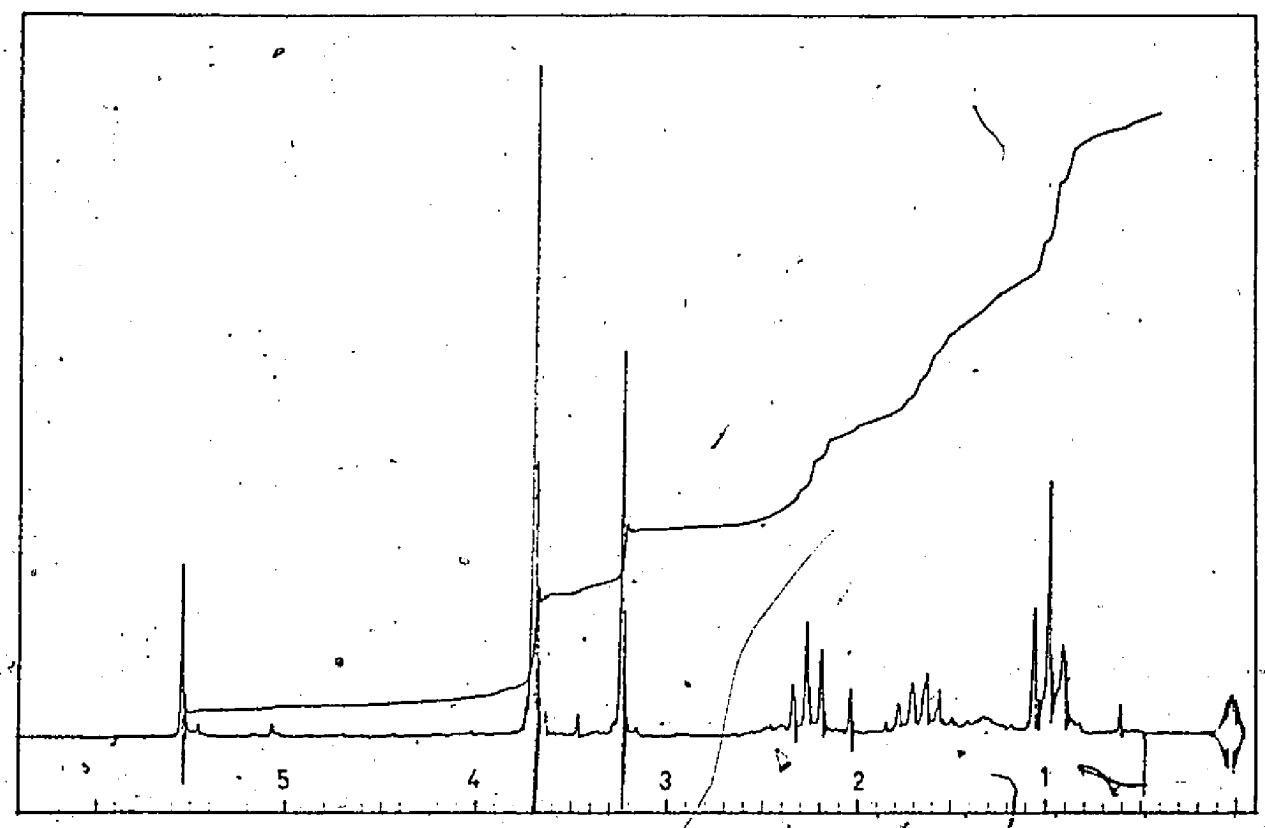

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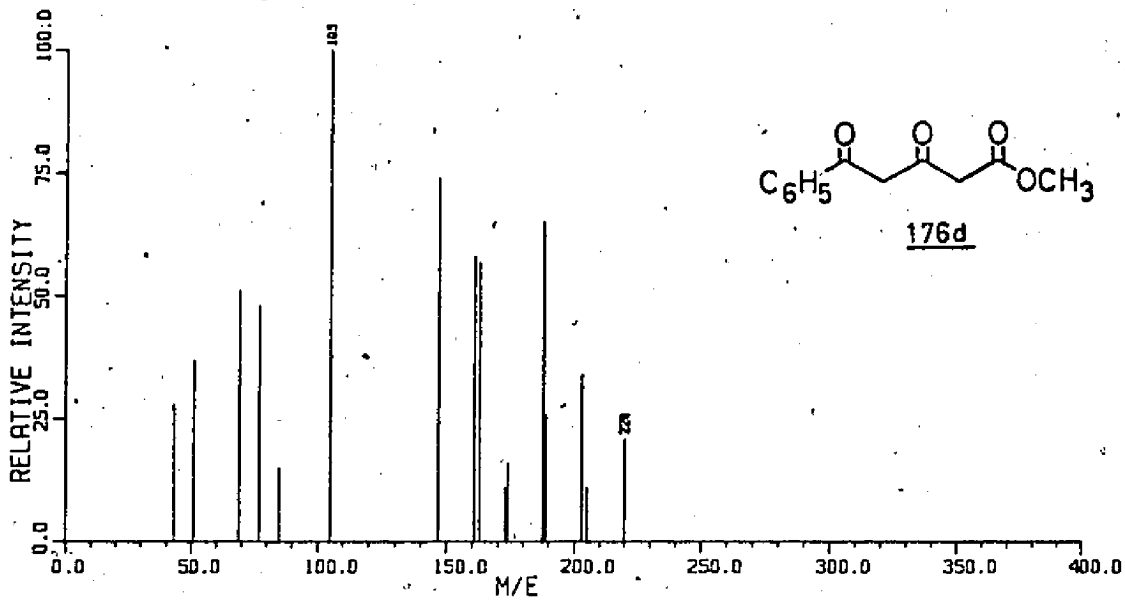

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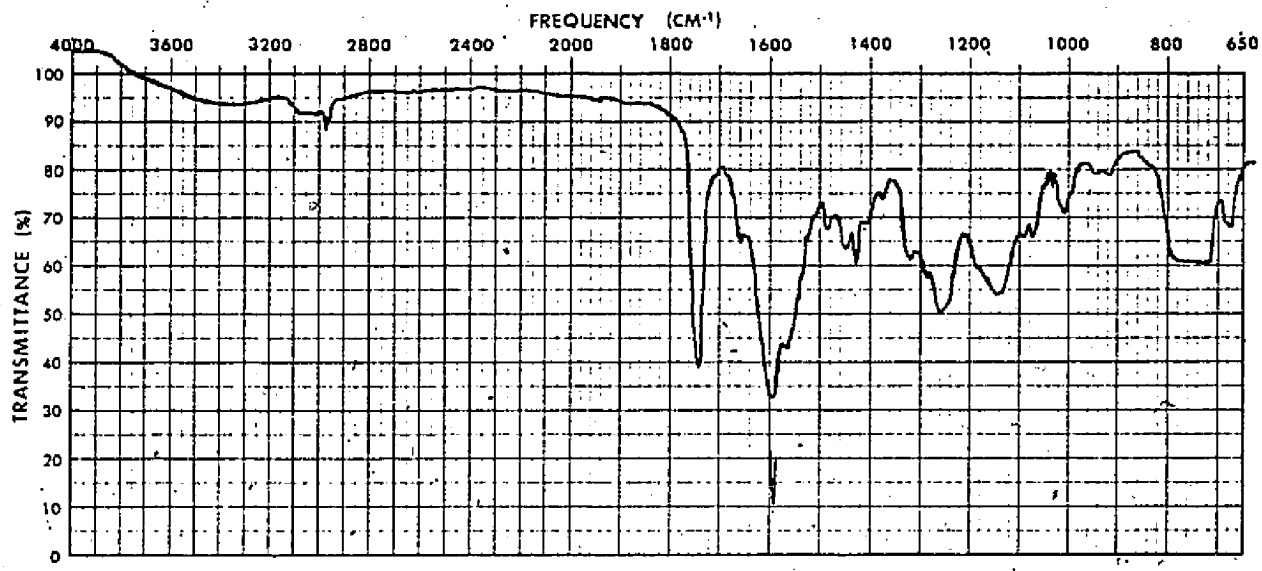

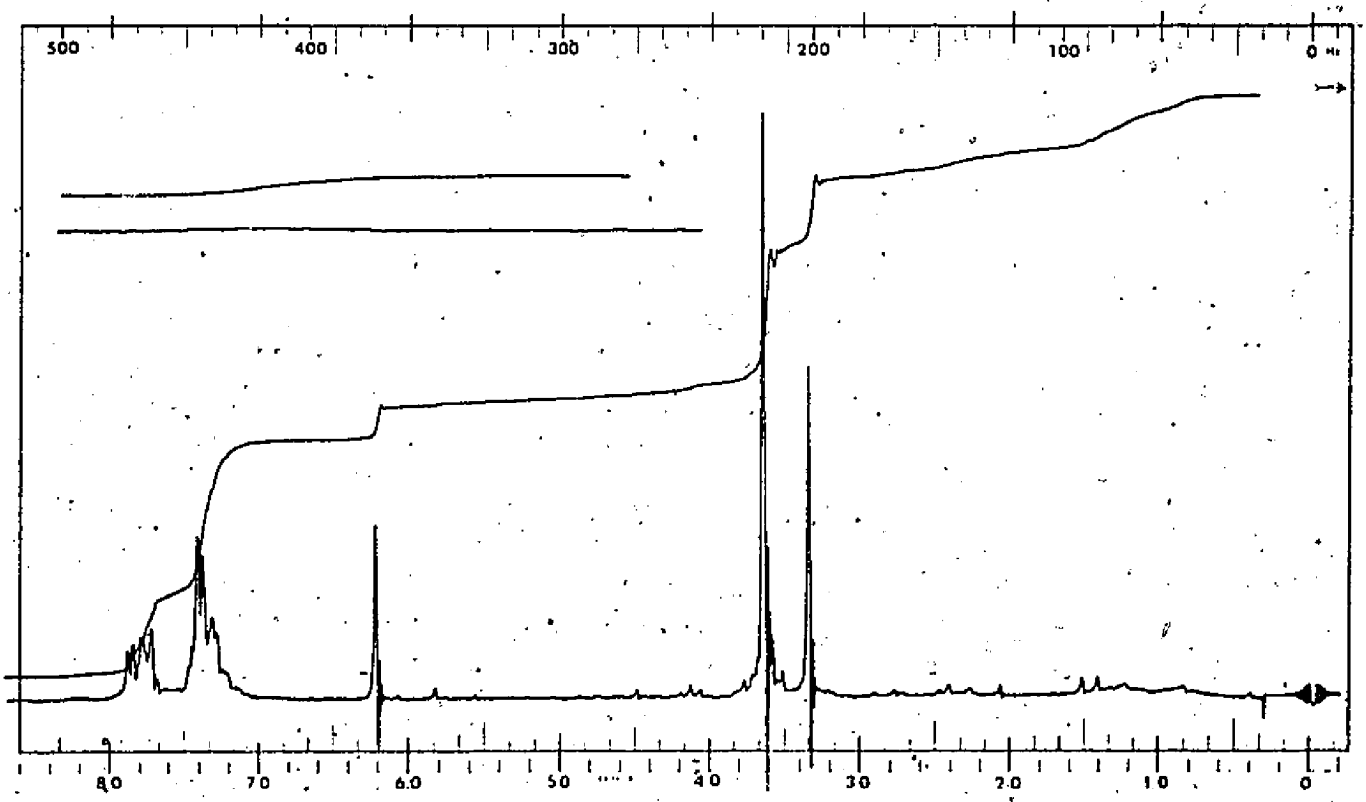

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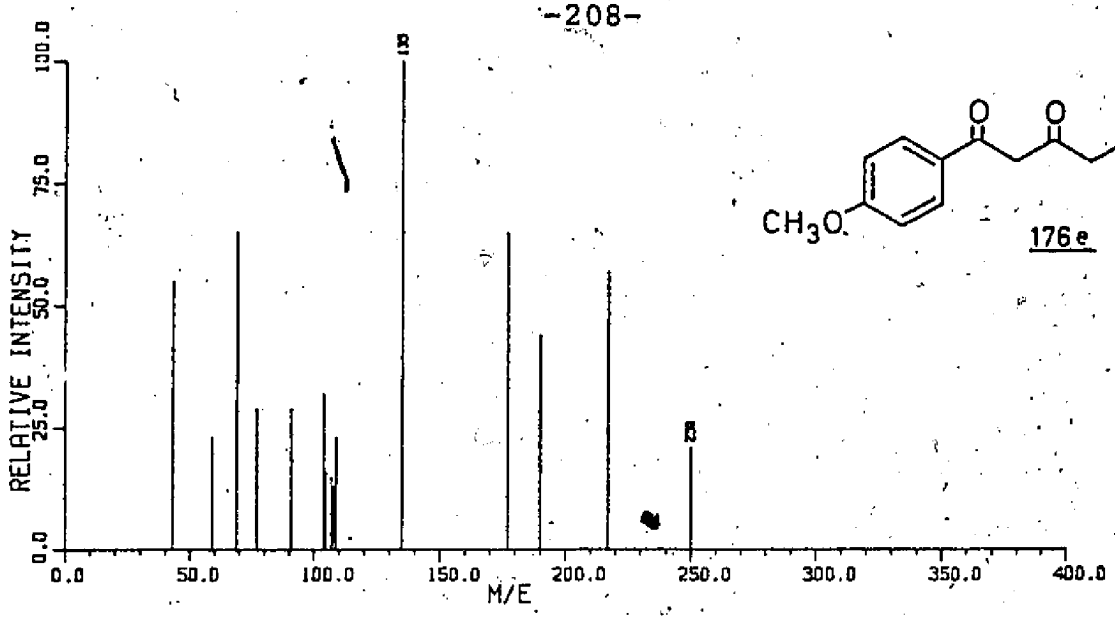

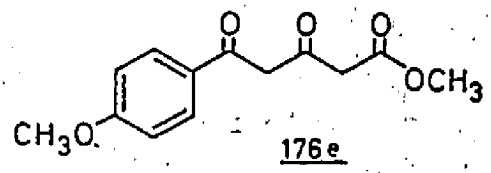

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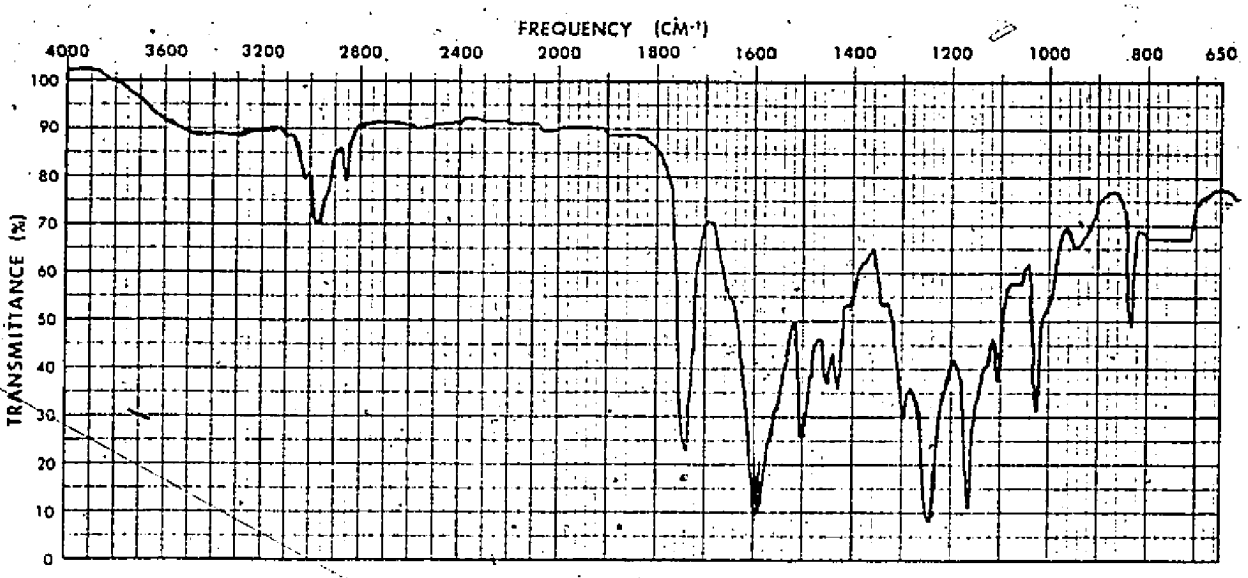

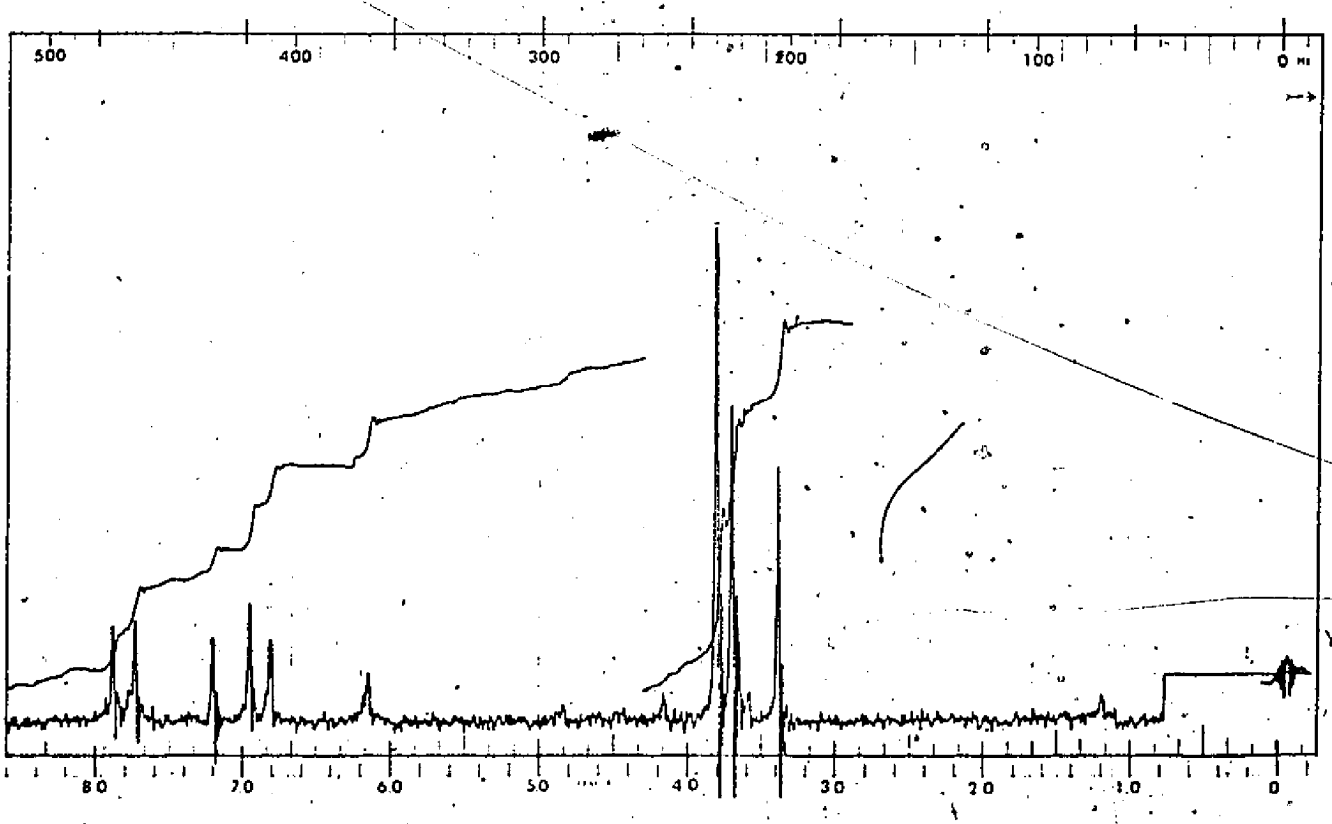

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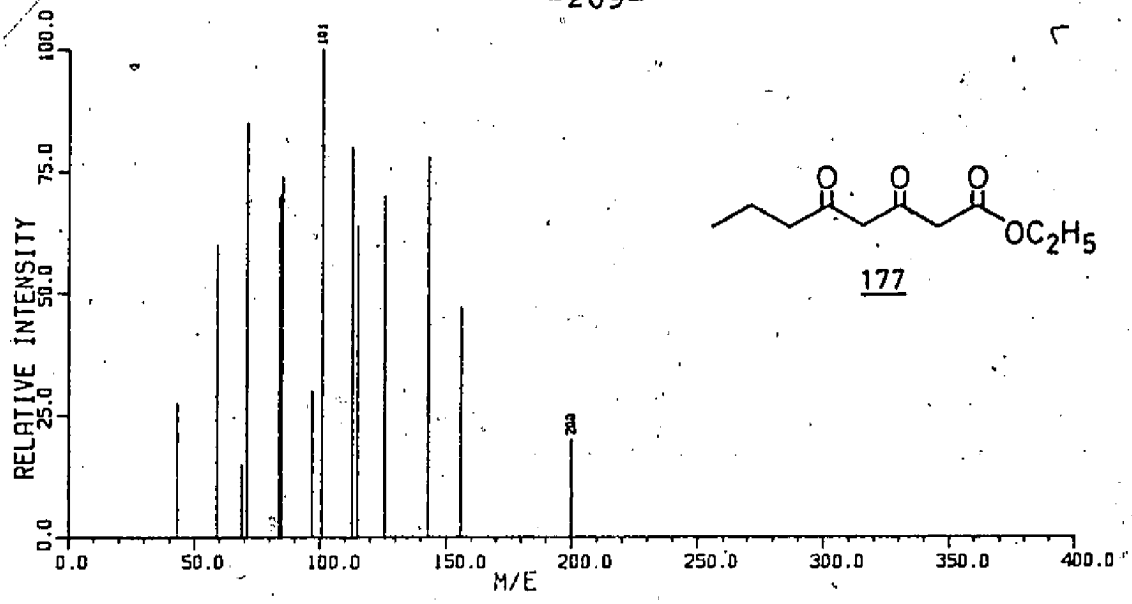

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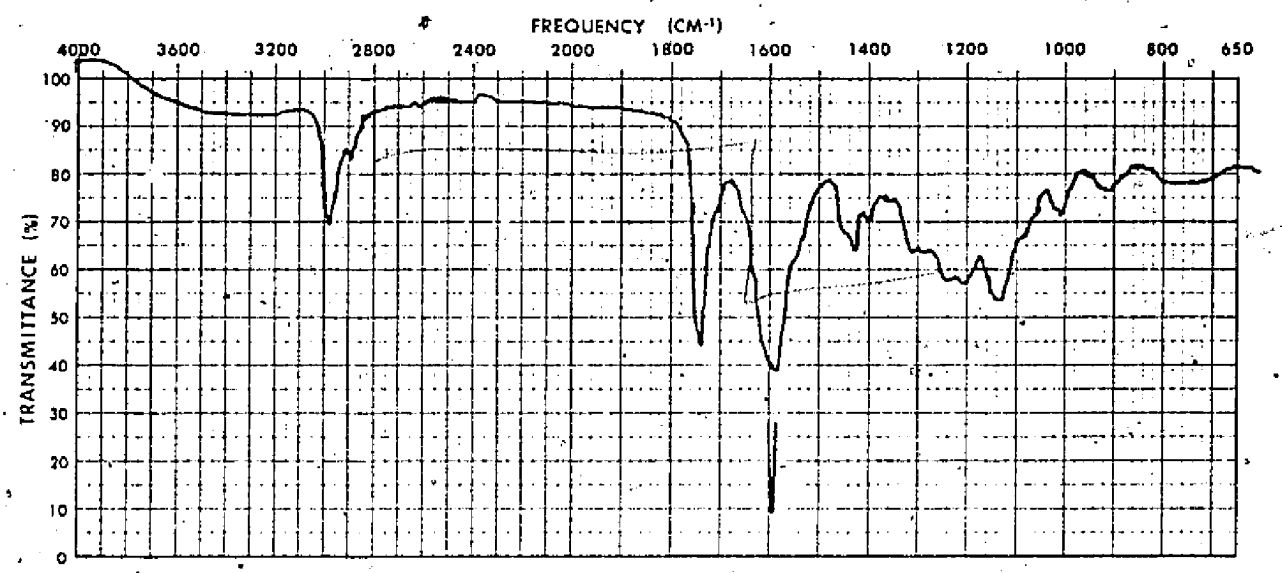

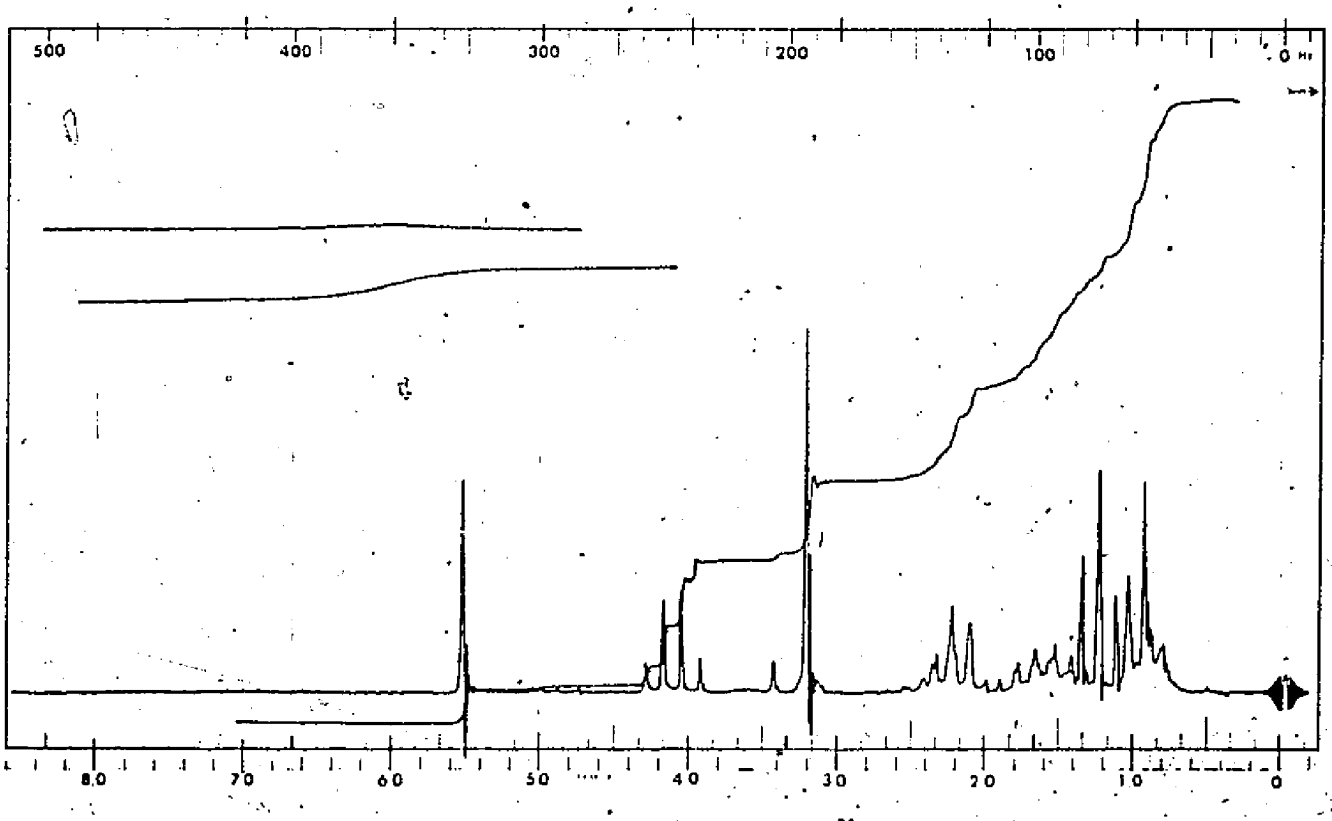

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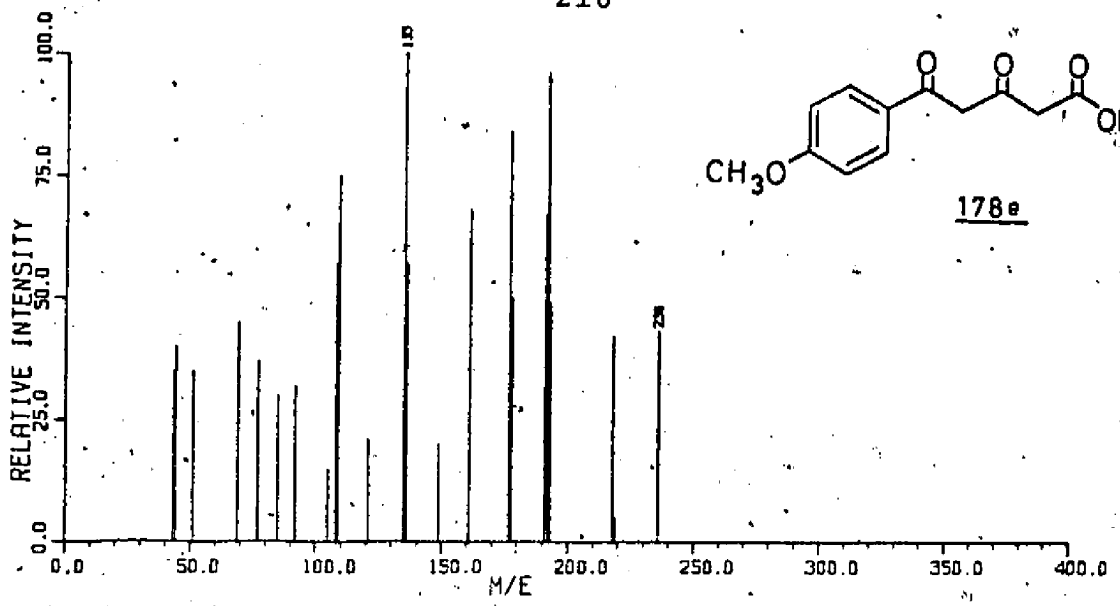

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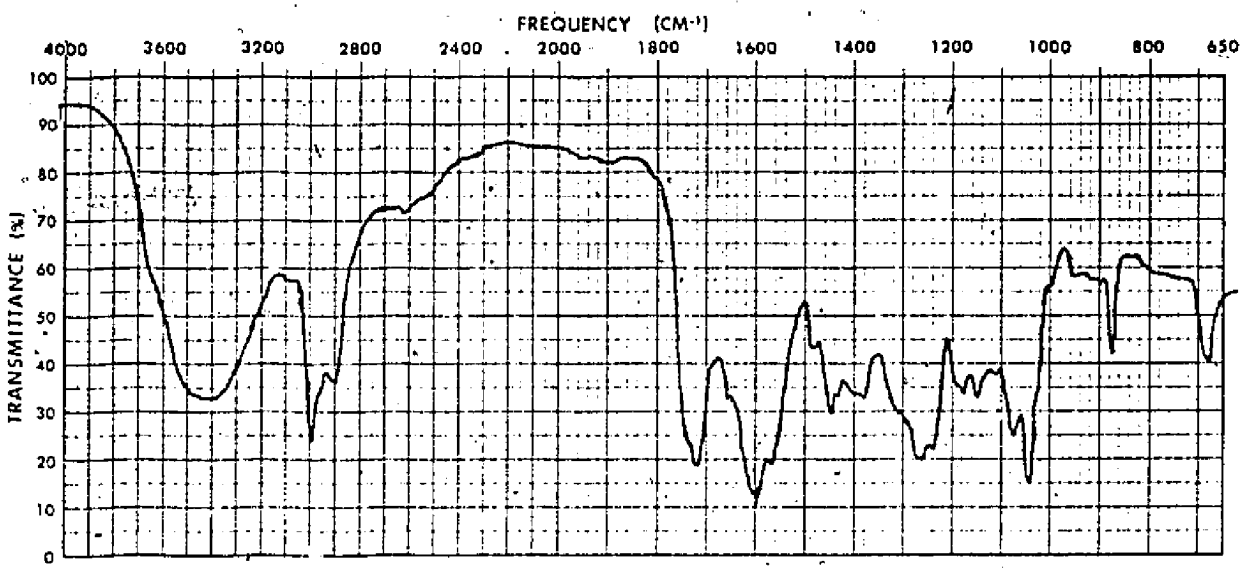

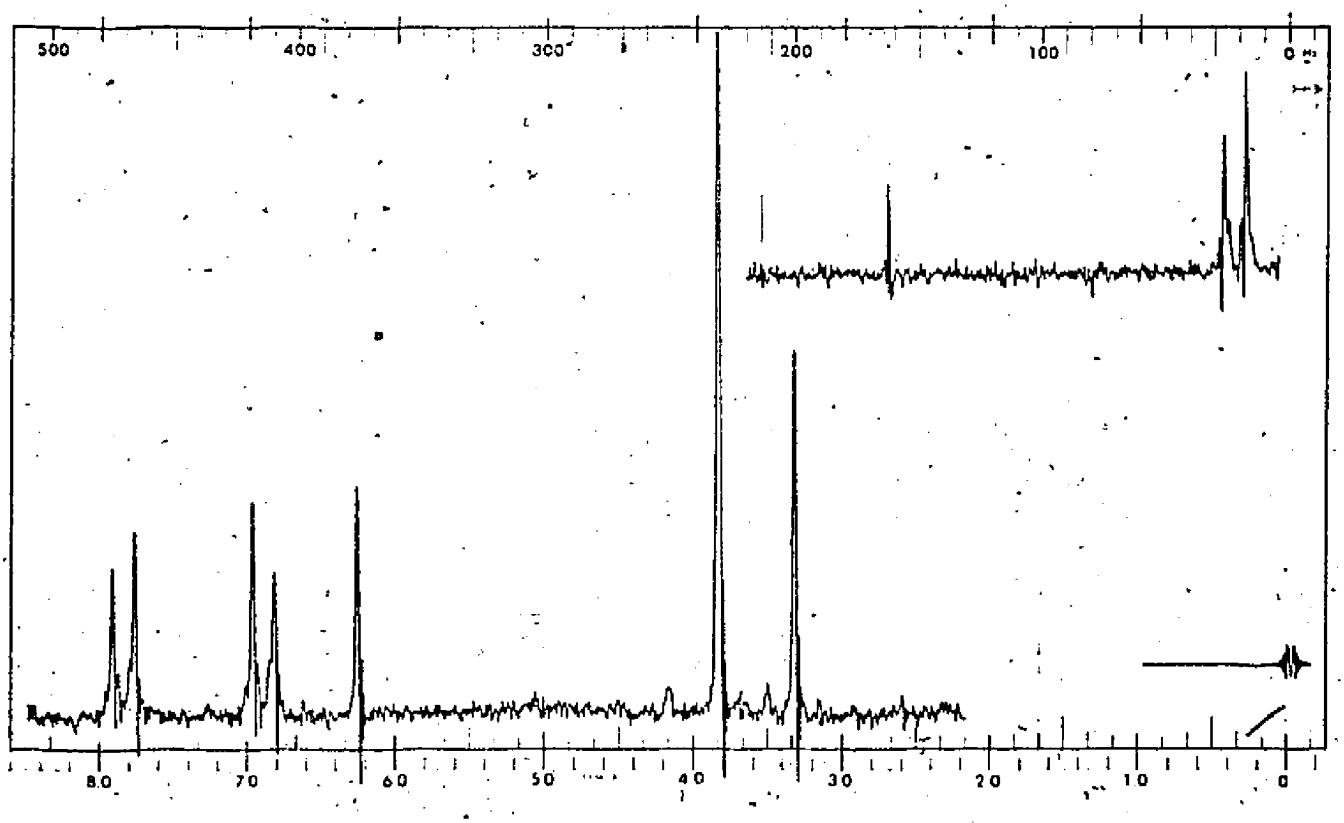

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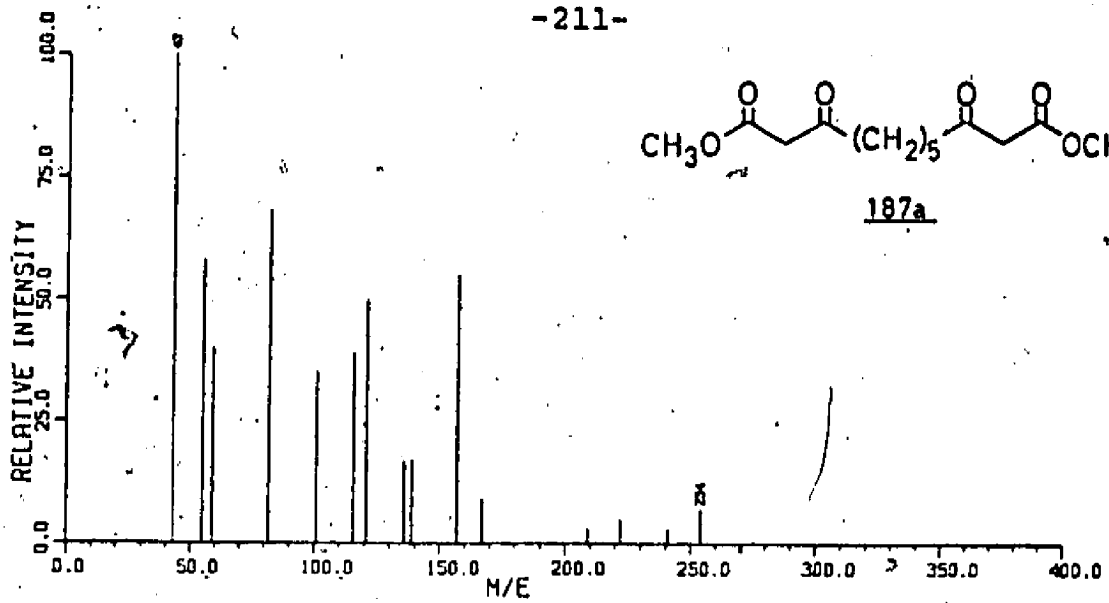

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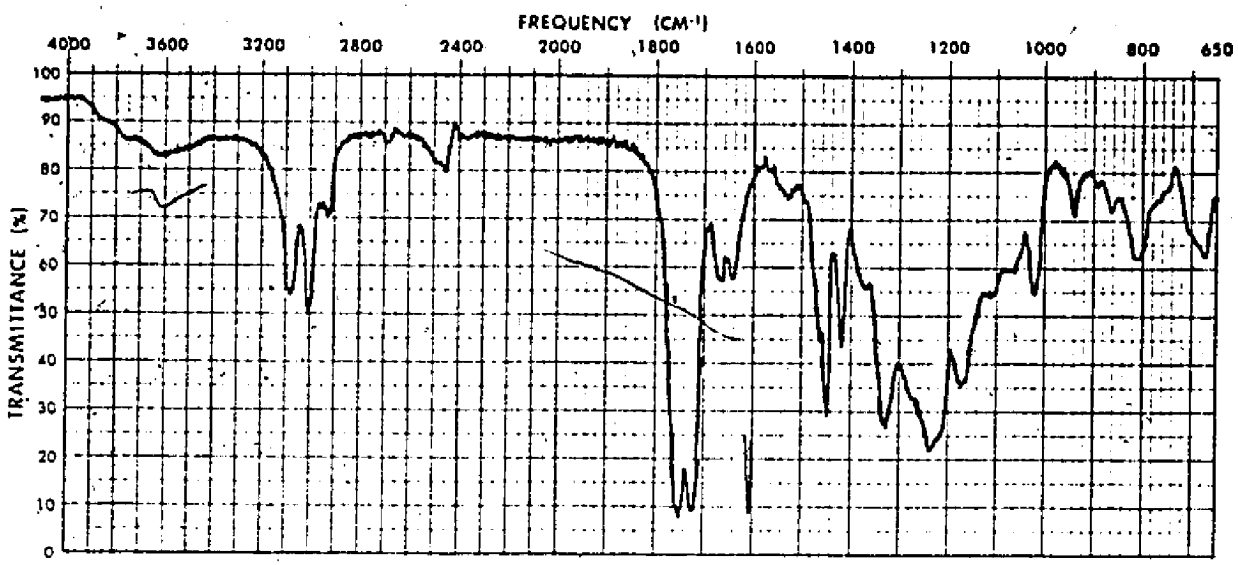

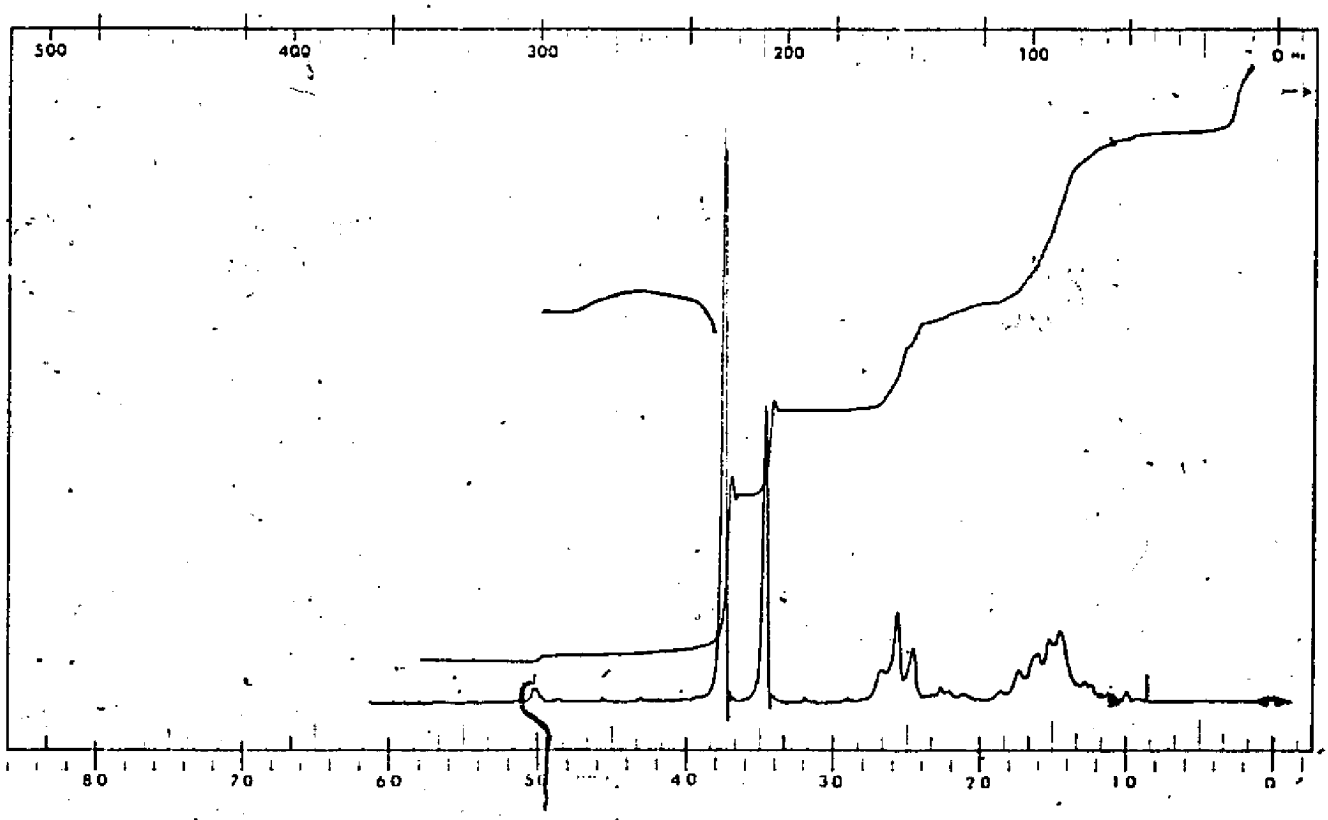

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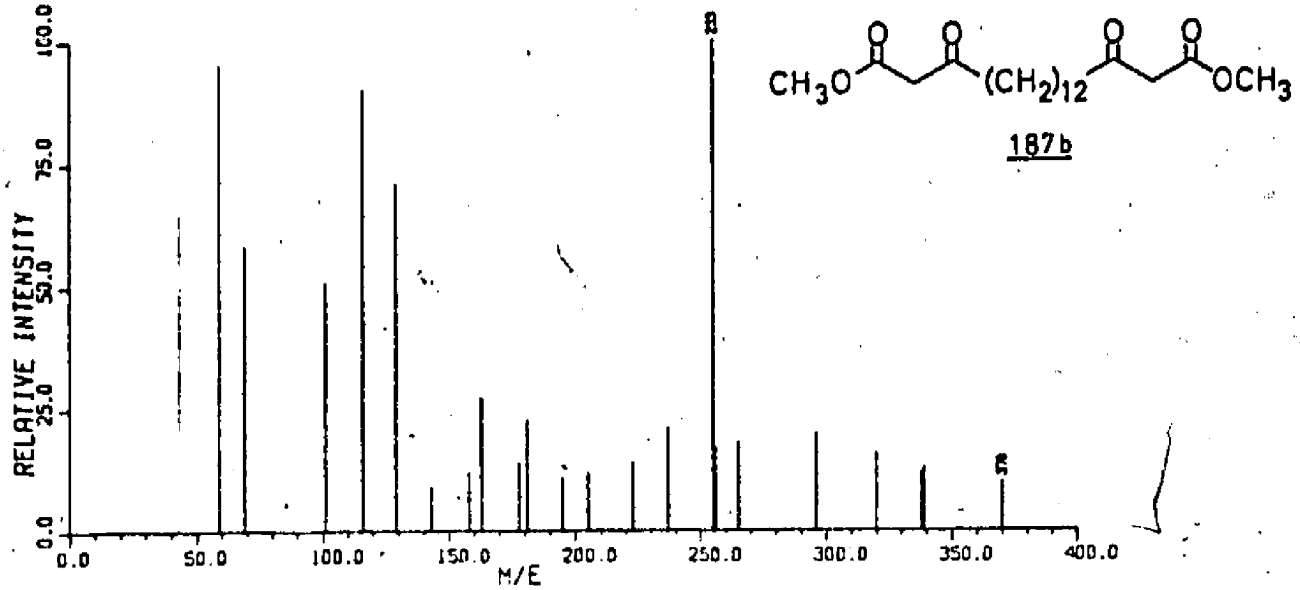

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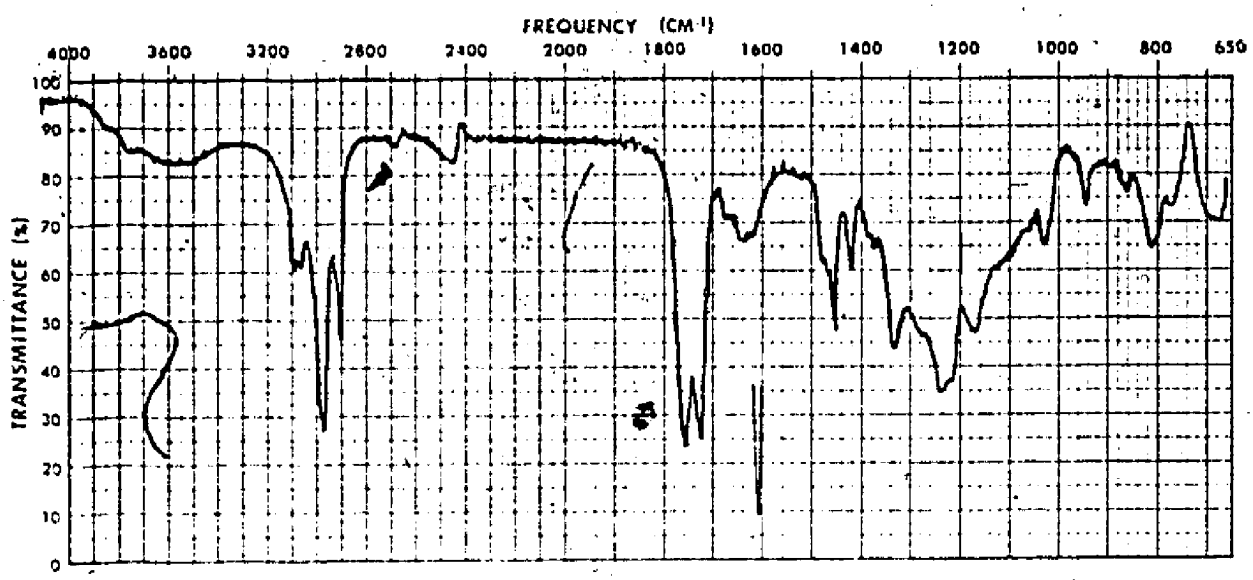

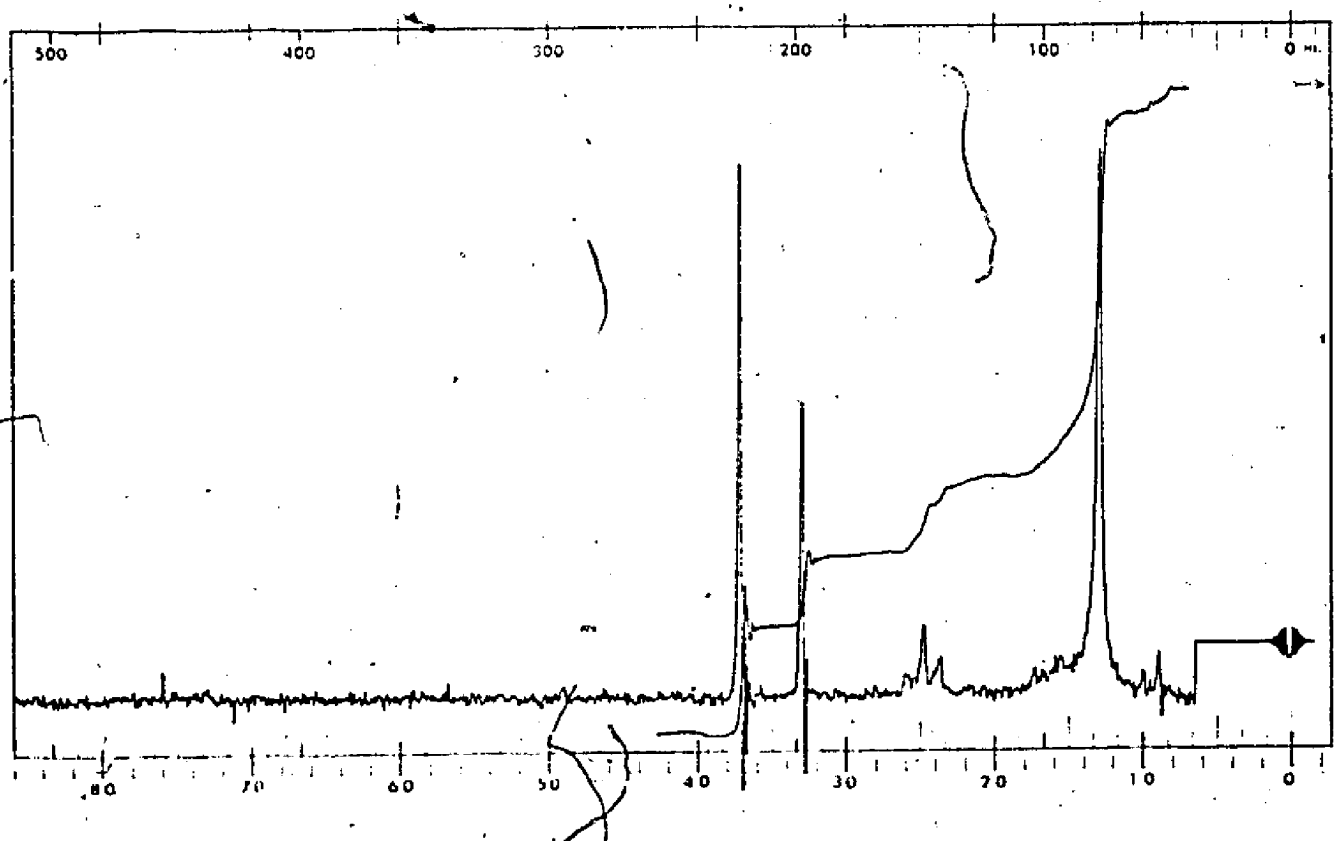

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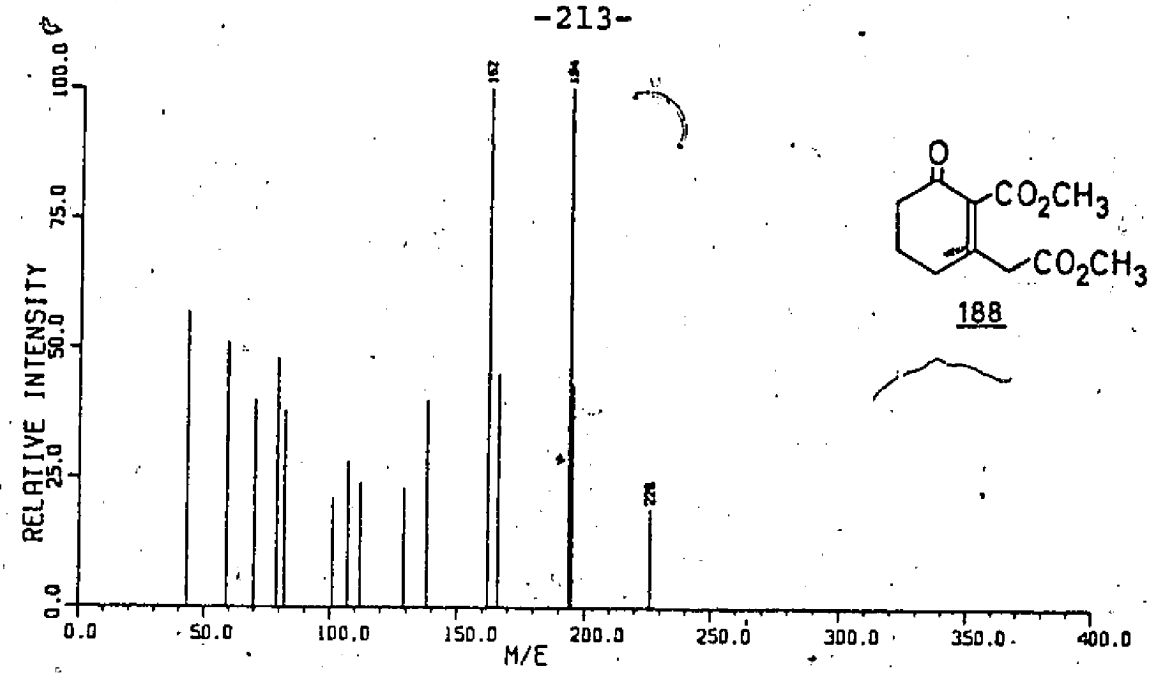

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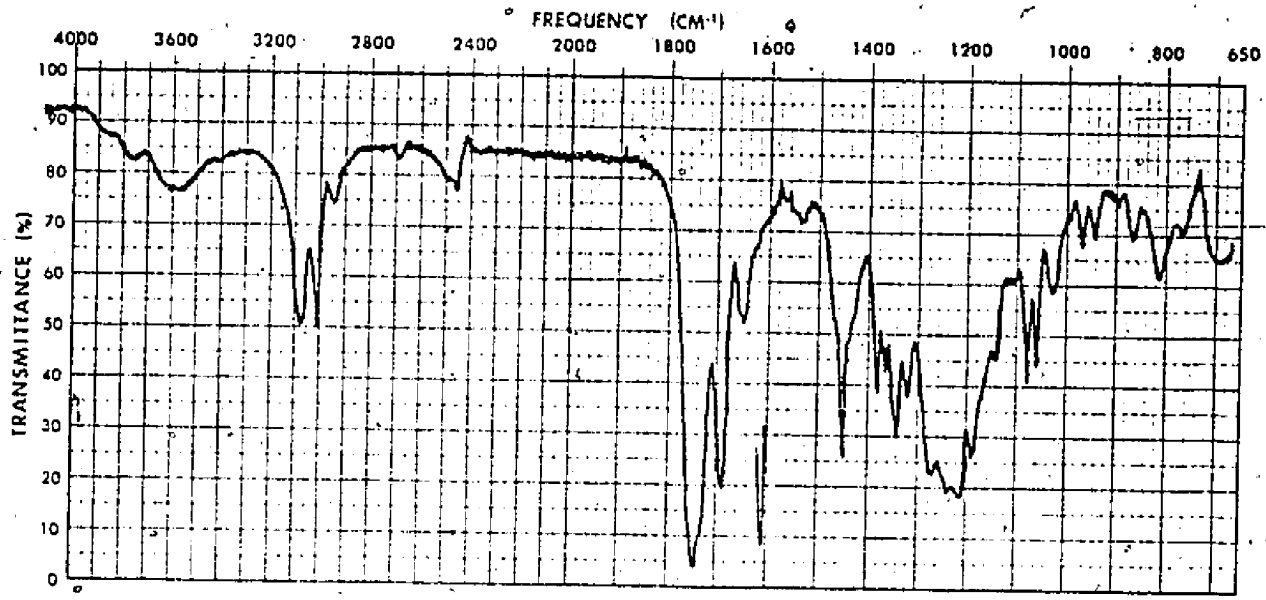

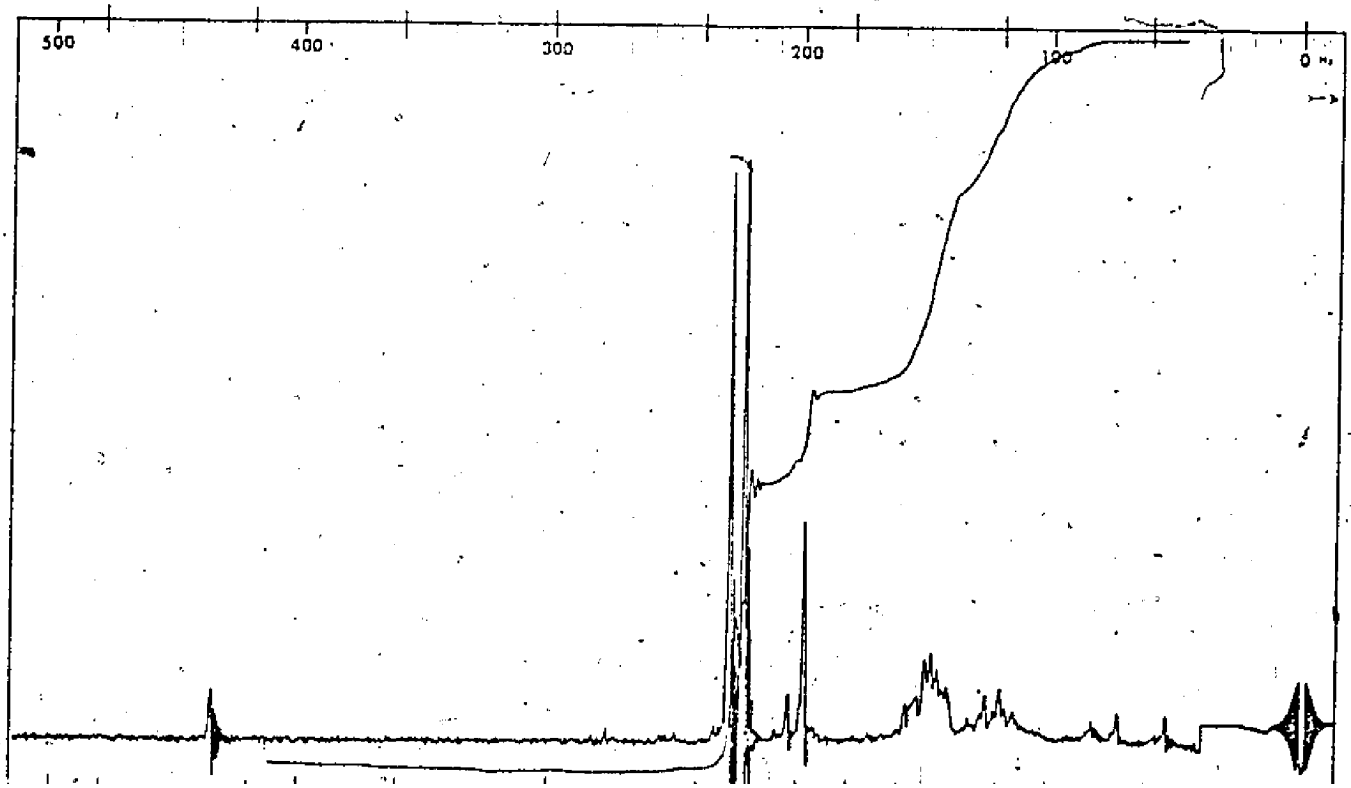

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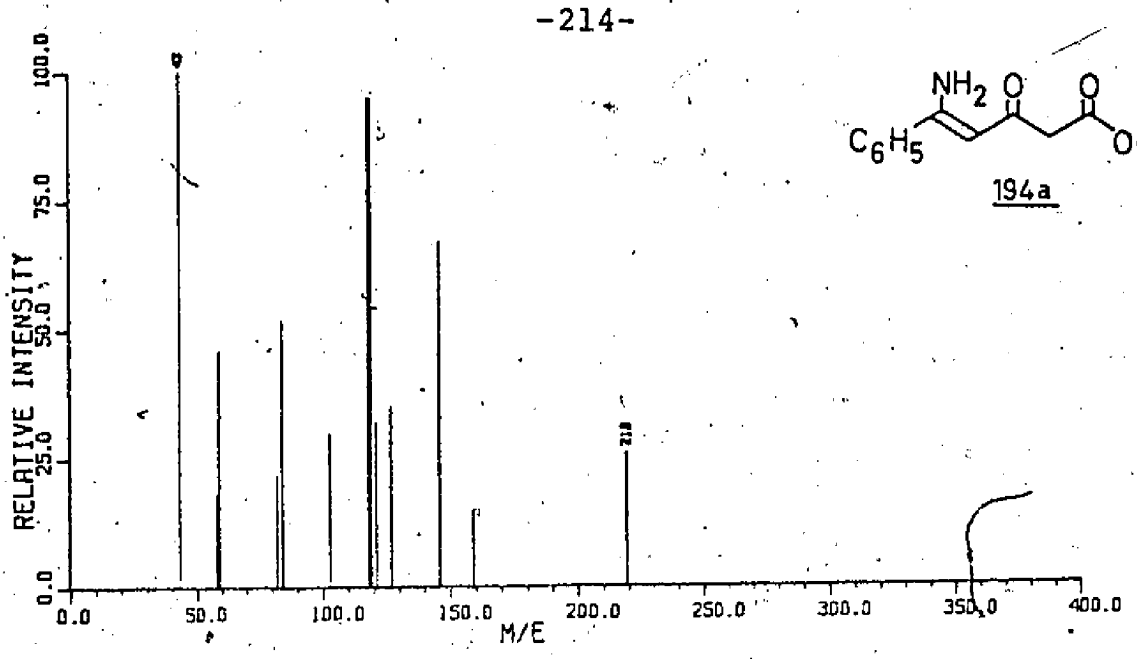

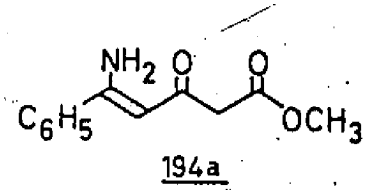

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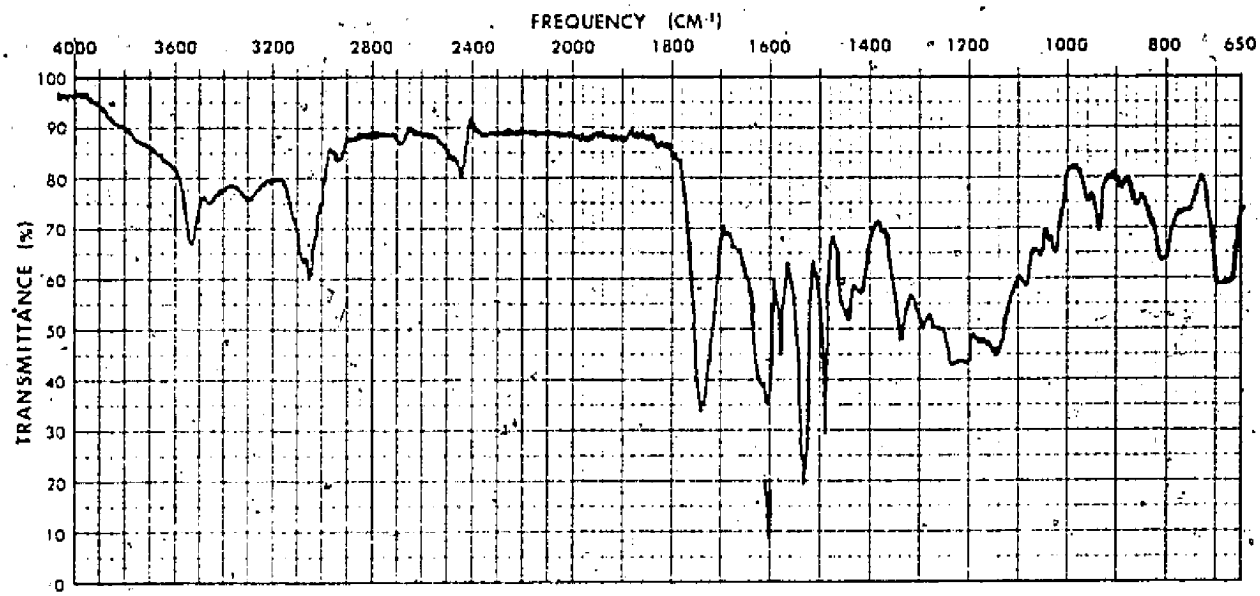

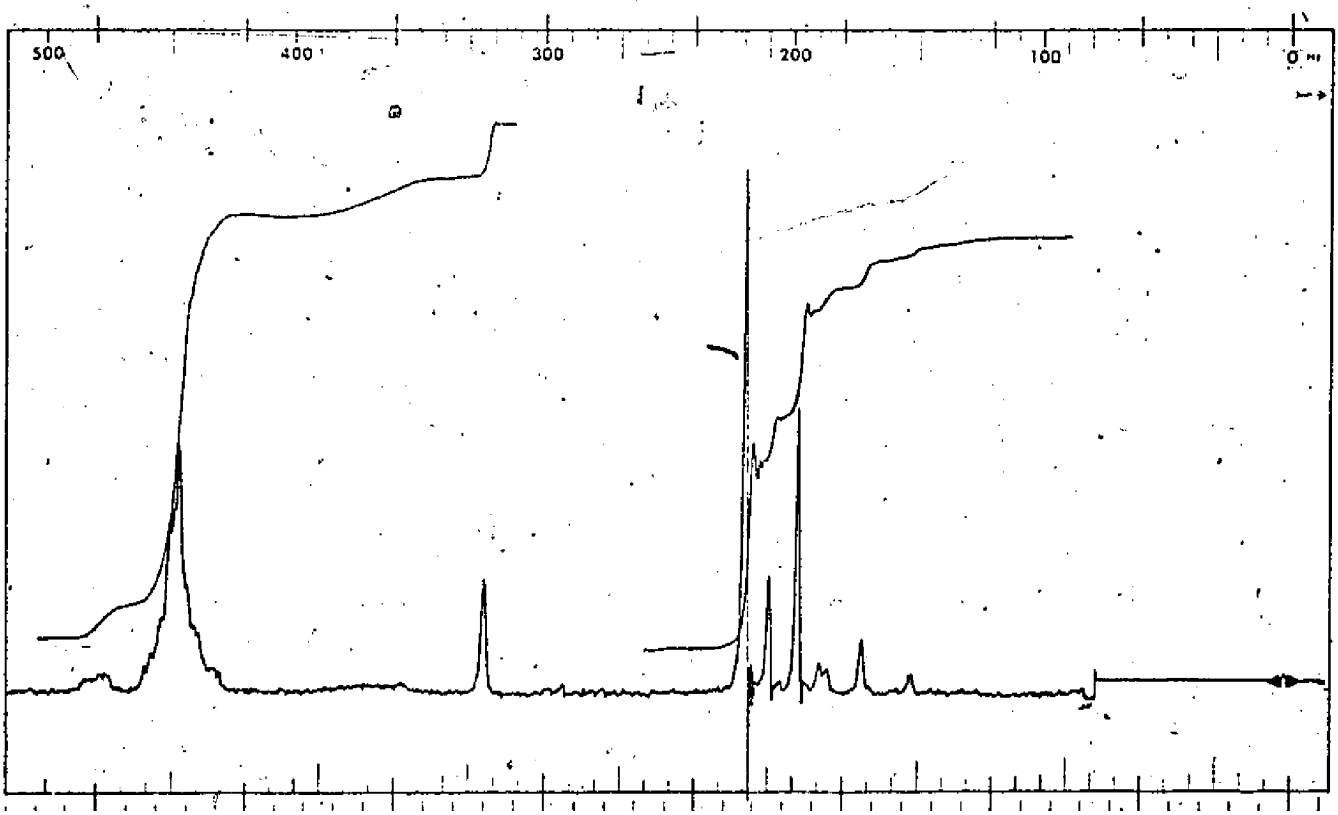

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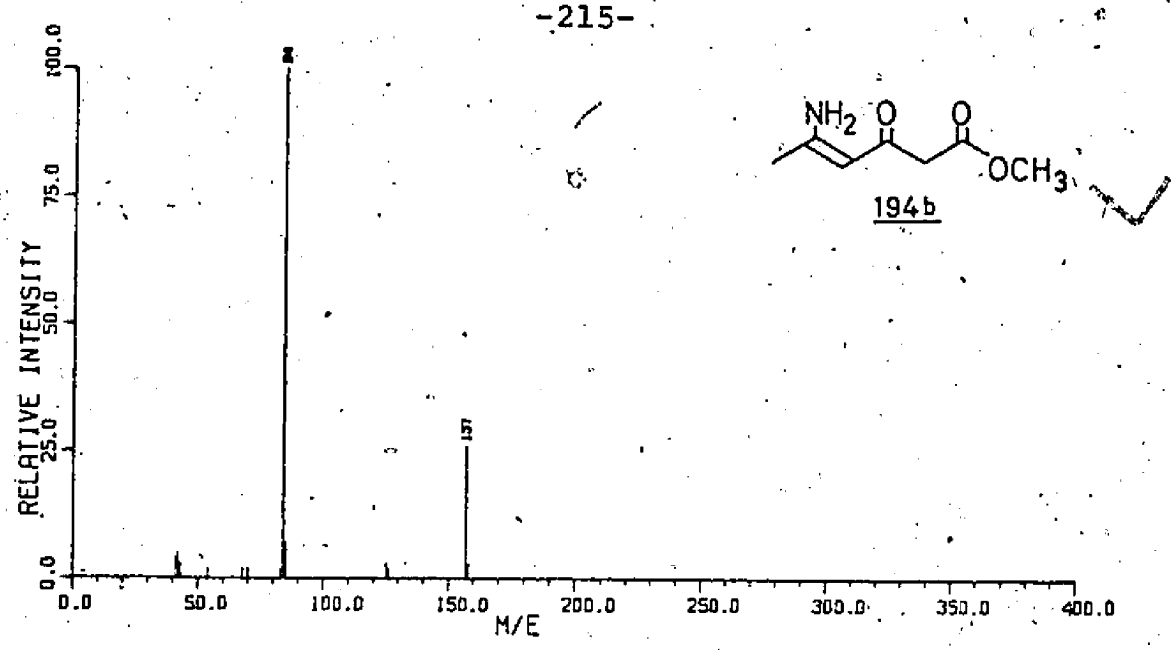

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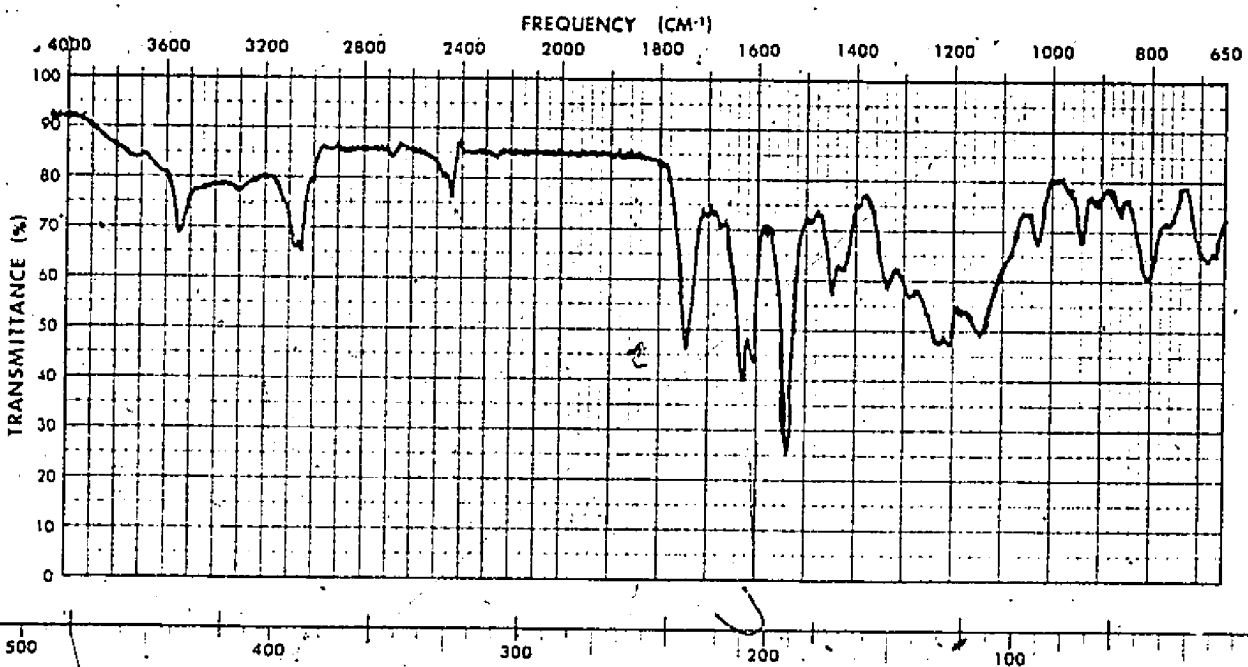

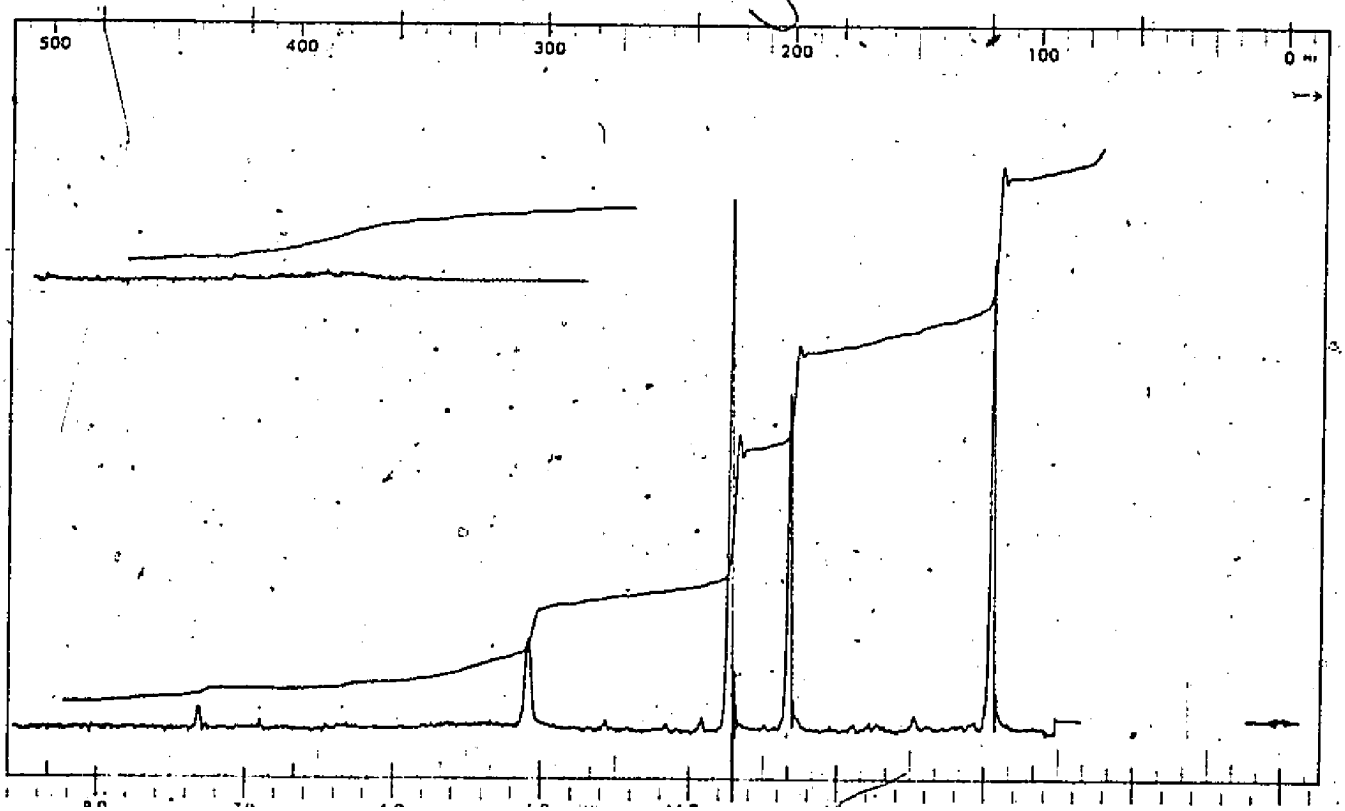

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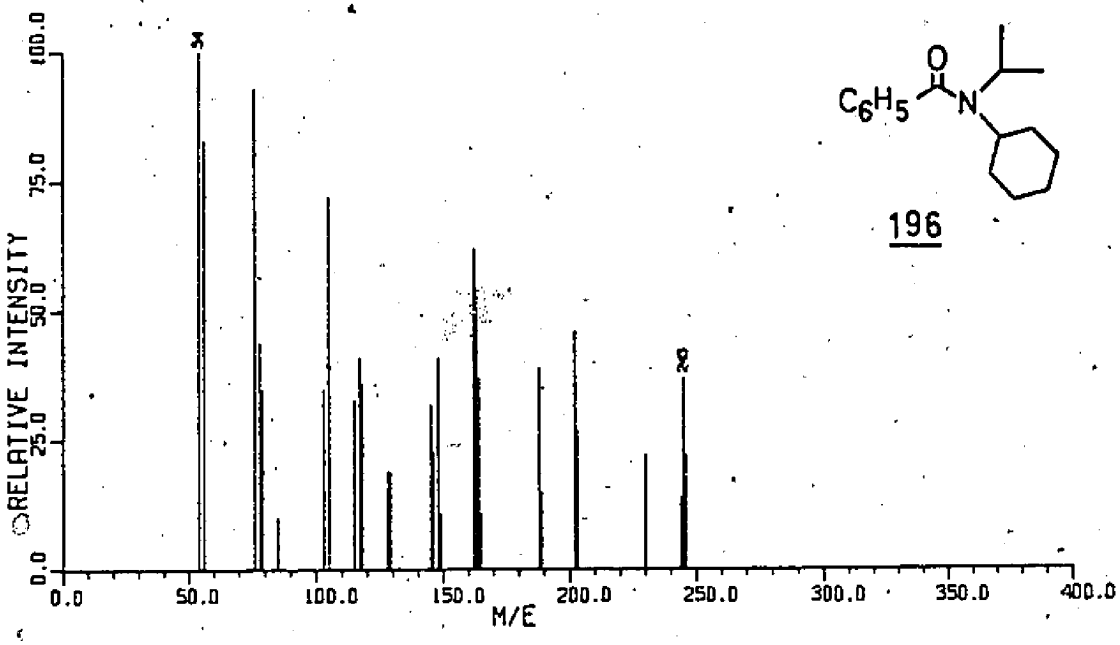
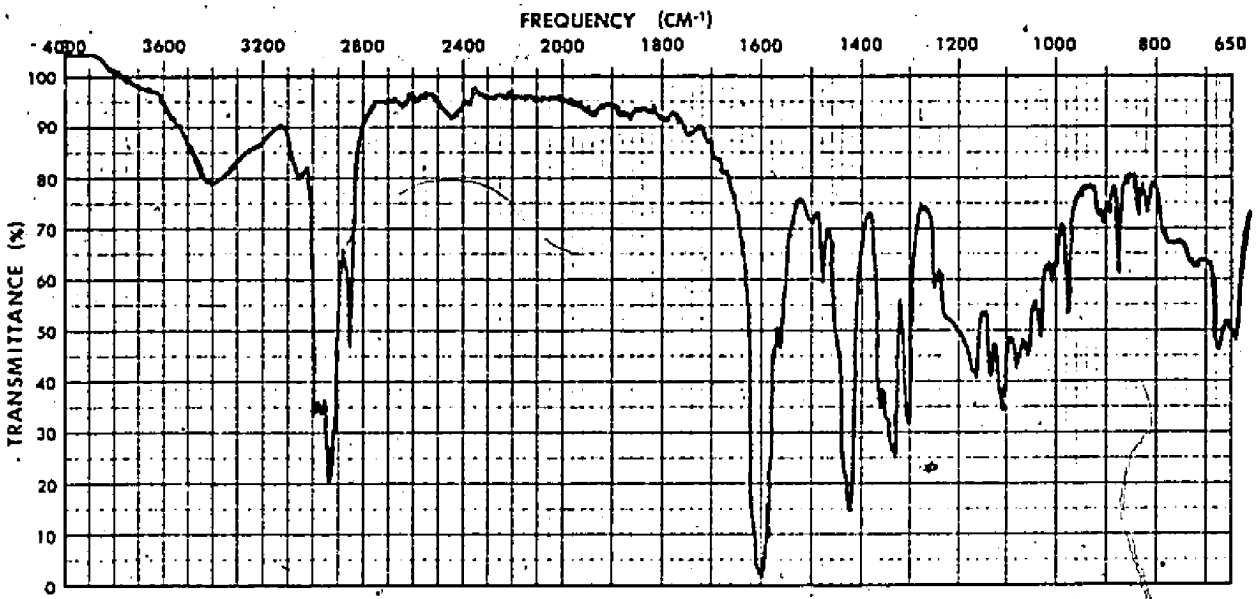
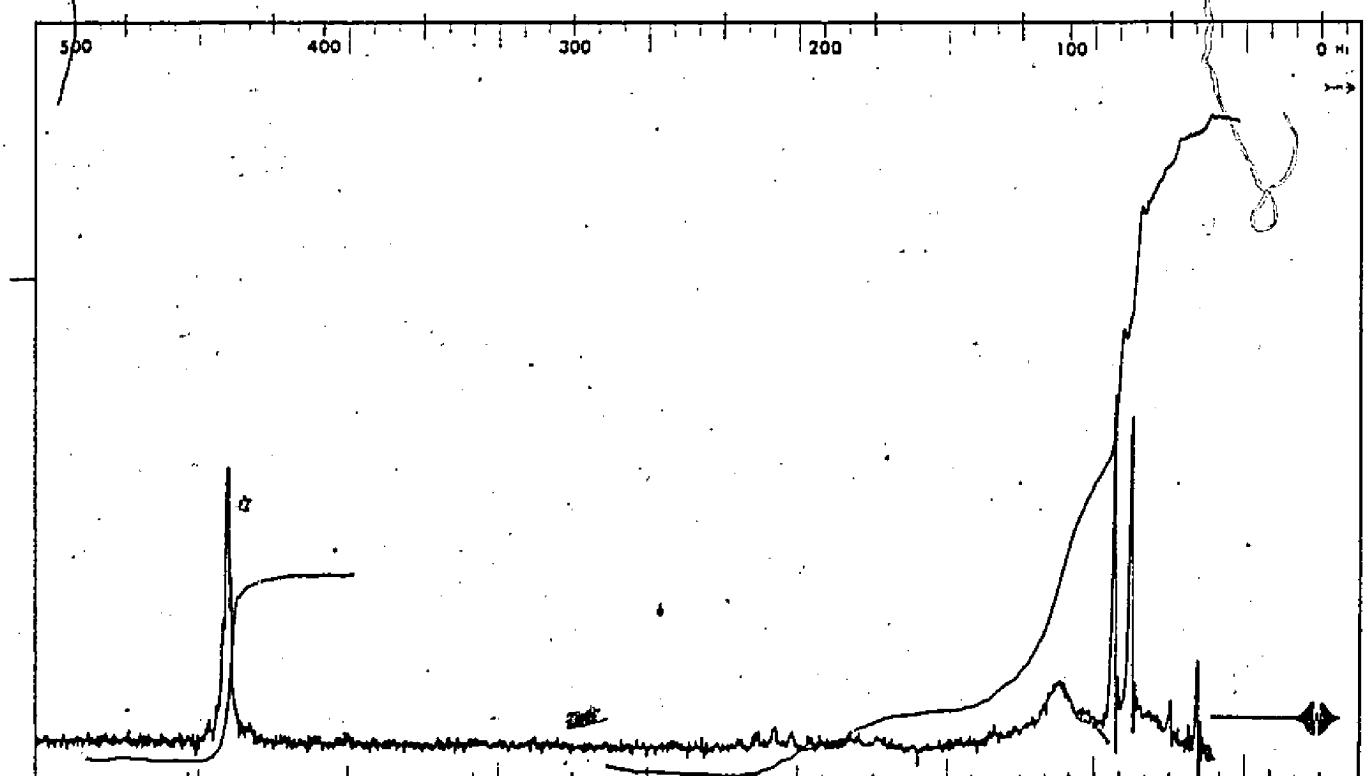


196





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PUBLICATIONS:

S. Huckin and L. S. Weiler, Tetrahedron Letters 2405 (1972).

S. Huckin and L. S. Weiler, Tetrahedron Letters 4835 (1971).

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