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University of Pittsburgh, Ph.D., 1971
Chemistry, organic

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ELABORATION OF FUSED RING SYSTEMS BY THE AGENCY OF β-CHLOROETHYL VINYL KETONE

by

Lantz Stephen Crawley

B. S., American University, 1967

Submitted to the Graduate Faculty of Arts and Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy

University of Pittsburgh

1970

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UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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DEDICATION

I wish to dedicate this thesis to Dr. Mary Aldridge, who first stimulated my interest in organic chemistry.

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FOREWORD

To Dr. Samuel Danishefsky, teacher and friend, I express my sincere gratitude. His high standards and enthusiasm for the art of synthetic chemistry will remain an inspiration to me.

Gratitude is extended to Mr. Richard Montgomery for providing instruction in the operation of the LKB mass spectrometer and for determination of mass spectra. Recognition is given to Mr. John Naworal for determination of mass spectra and to Mr. Norbert Rattay for preparation of starting material.

Thanks are also extended to Dr. E. P. Oliveto and Hoffmann-La Roche for graciously supplying, without charge, the 2-methyl-1,3-cyclopentane dione used in this study.

A special thanks is extended to Miss Barbara Petersen for her assistance in obtaining pertinent literature both from within and outside of the university library system and for her invaluable contributions to the preparation of this thesis.

Acknowledgment is made to the University of Pittsburgh for a Graduate Teaching Assistantship and to the National Institutes of Health for financial aid in the form of a research grant.

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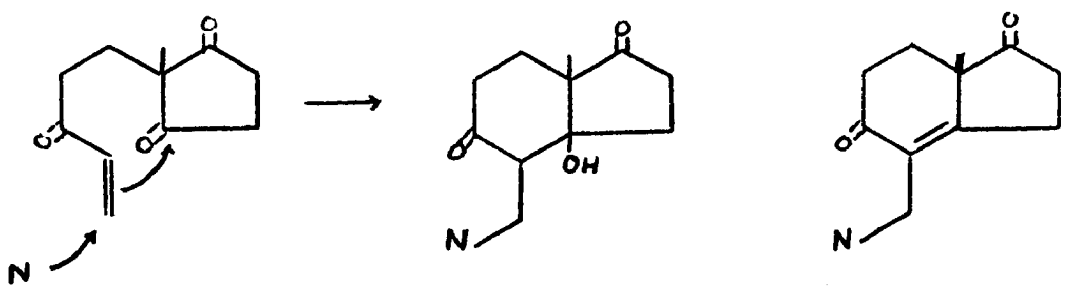
I. GENERAL OBJECT OF THE INVESTIGATION

The primary objective of the study was to explore the possibilities inherent in conjugate addition of a generalized nucleophile, N, to I. Subsequent aldolization of such adducts could give systems of relevance to steroid synthesis. The group N would be so selected as to allow for further buildup of the steroid, possibly in the same medium as it is produced. The envisioned reaction scheme is depicted in the following sequence.



I I_b I_c

Of major importance to the execution of this synthetic scheme, was the preparation of appropriately modified nucleophiles so as to allow for the construction, in a single reaction sequence, of a molecule which contains the requisite functionality for conversion to steroidal systems.

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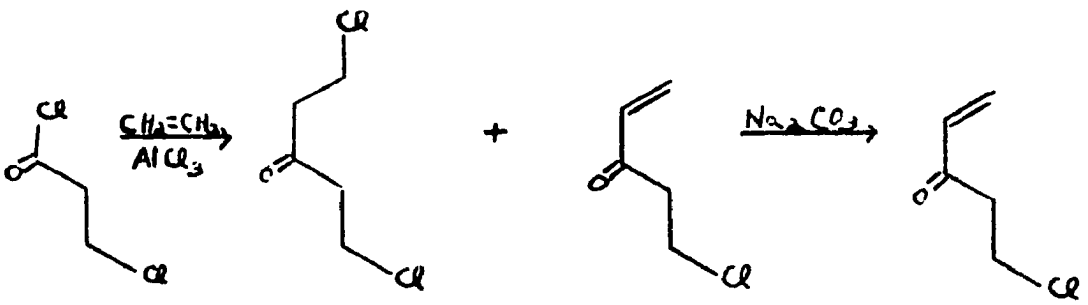
II. DISCUSSION OF PREVIOUS WORK

There are many fine reviews concerning the total synthesis of steroids,[1-6] and no attempt is made to cover the subject in a comprehensive fashion. Since this thesis is a continuation of the recent work of Migdalof[7] on a new approach to steroid synthesis, a review of that work and several related approaches seems in order.

In 1969, Danishefsky and Migdalof reported the preparation of a divinyl ketone equivalent, β-chloroethyl vinyl ketone (CVK)[8] by the following route:



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[1] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y. (1959).

[2] I. V. Torgov, Pure and Applied Chemistry, 6, 525 (1963).

[3] T. B. Windholz and M. Windholz, Angew. Chem. Intl. Ed., 3, 353 (1964).

[4] L. Velluz, J. Valls, and G. Nomine, ibid., 4, 181 (1965).

[5] P. Morand and J. Lyall, Chem. Rev., 68, 85 (1968).

[6] L. J. Chinn, J. S. Buran, P. D. Klimstra, and R. Pappo, Intra-Sci. Chem. Rep., 3, 1 (1969).

[7] B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

[8] S. Danishefsky and. B. Migdalof, J. Am. Chem. Soc., 91, 2806 (1969).

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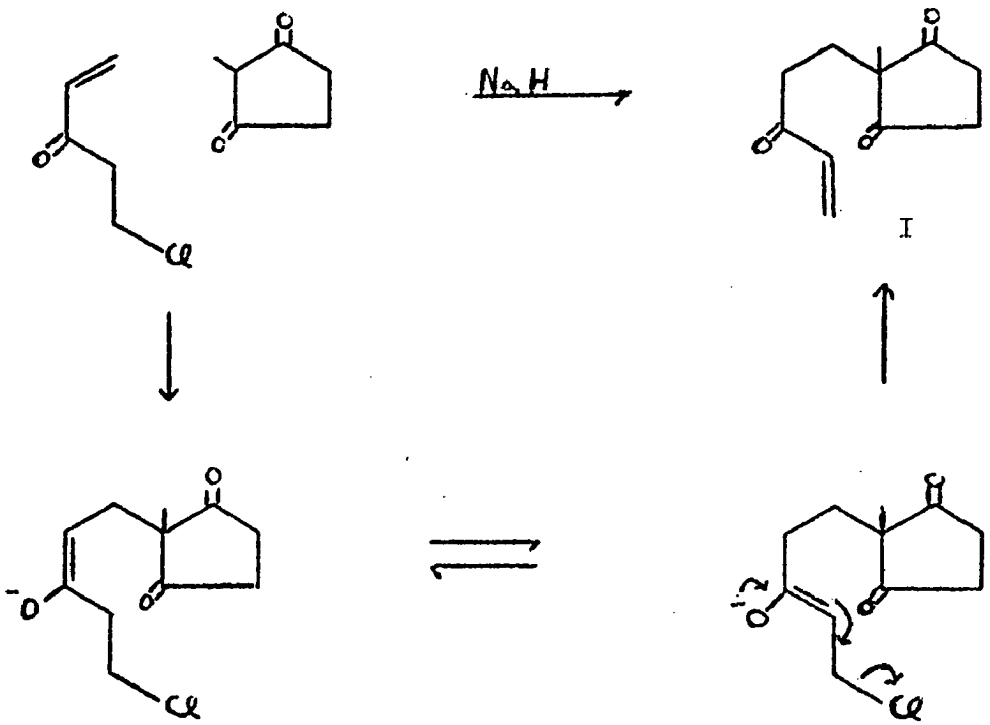
This compound condensed with 2-methyl-1,3-cyclopentanedione to give I. Suggestive evidence pointed to a sequence involving (i) Michael addition, (ii) proton transfer and (iii) β-elimination of chloride.[1] The reaction path is shown below.



The reactions of nucleophiles with compound I form the basis of this thesis. It will be noted that of the eleven carbons of I, three (methylene groups α to three ketones) are potentially nucleophilic and four (three carbonyl groups and the β-carbon of the enone) are potentially electrophilic. Addition of a nucleophile to the β-carbon of the enone also, in principle, generates nucleophilic activity at its α-carbon.

---

[1] S. Danishefsky and B. Migdalof, J. Am. Chem. Soc., 91, 2806 (1969).

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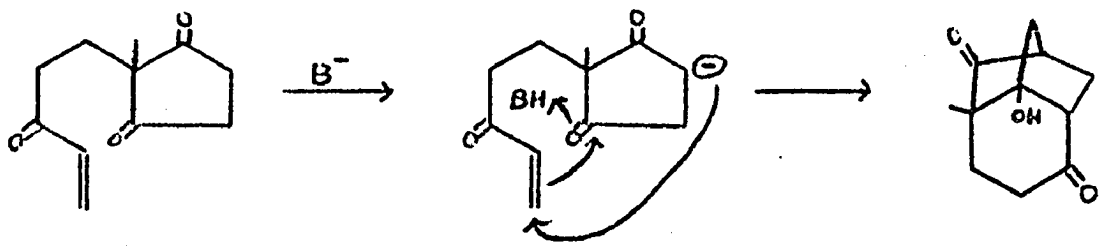
The interplay of this complex functionality is nicely seen in the result of treating compound I with base (potassium t-butoxide). The product obtained is the tricyclic hydroxydione, II.[1] A plausible mechanism is shown below.



I II

Fortunately for our purposes, this intramolecular condensation is not a serious deterrent to effecting base catalyzed intermolecular attacks on I at least when the nucleophile is a relatively non-basic anion of the type derived from β-dicarbonyl systems. This is illustrated in the reaction of I with t-butyl acetoacetate (1 eq.), potassium t-butoxide (0.2 eq.) in t-butyl alcohol. The mixture resulting from this reaction was treated with p-toluenesulfonic acid in acetic acid at 90° for 3 hours. The three products are shown below. It may be reasonably assumed that they are all formed by conjugate addition, aldolization and decarbo-t-butoxylation. Compound III, so produced, can cyclize in two alternate ways to give IV (major) and V (minor).[2]

---

[1] S. Danishefsky and B. Migdalof, Tet. Letters, 4331 (1969).

[2] B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

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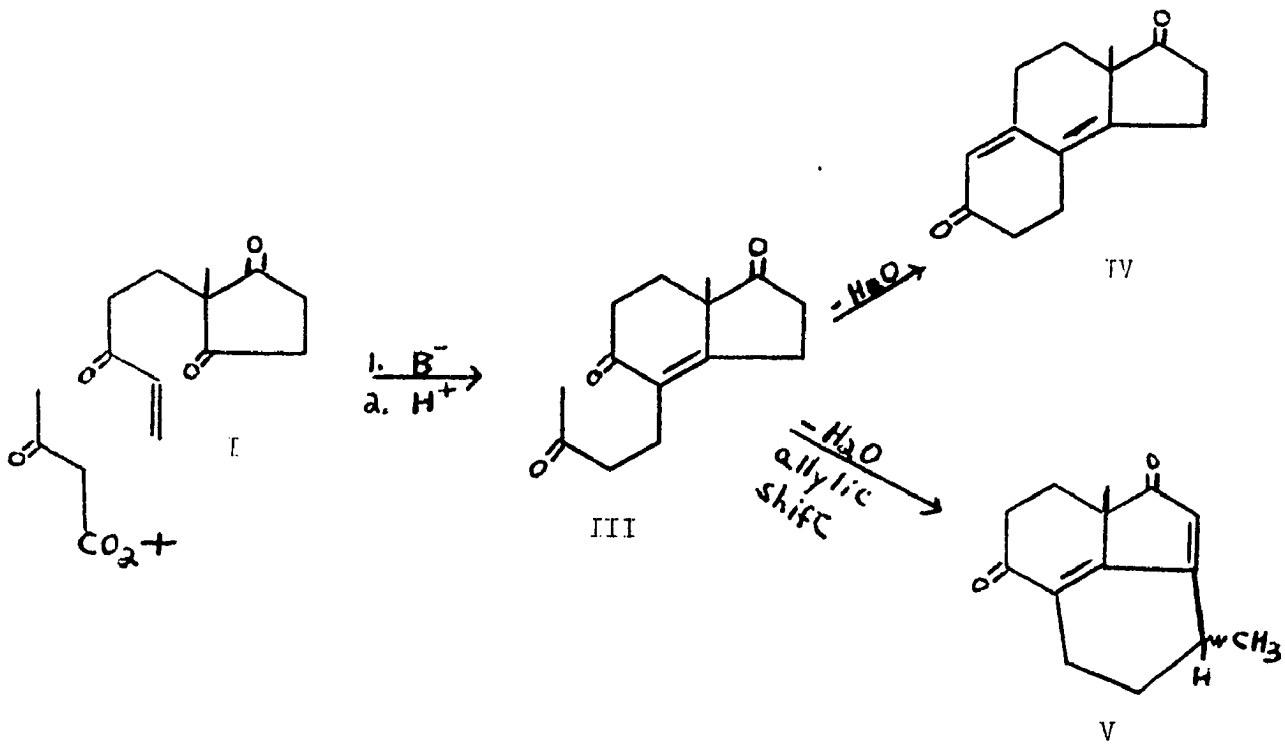

It is instructive to compare this approach to a tricyclic dienone system such as IV with previous methodology.

A. The Swiss Approach

The key step in this approach is 1,6-addition of the conjugate base of a cyclic β-diketone to a 3-vinylcyclohexenone. The latter is prepared by addition of vinyl Grignard to the corresponding β-alkoxy enone which in turn arises from O-alkylation of the β-diketone. Serious difficulties are encountered during the vinylogous aldol condensation. Nevertheless, this method has been applied with some success to the construction of 6[1] and 5[2] D ring precursors.

---

[1] A. Eshenmoser, J. Schreiber and S. A. Julia, Helv. Chim. Acta., 36, 482 (1953).

[2] A. Frey, Promotionsarbeit, ETH, Zürich (1954).

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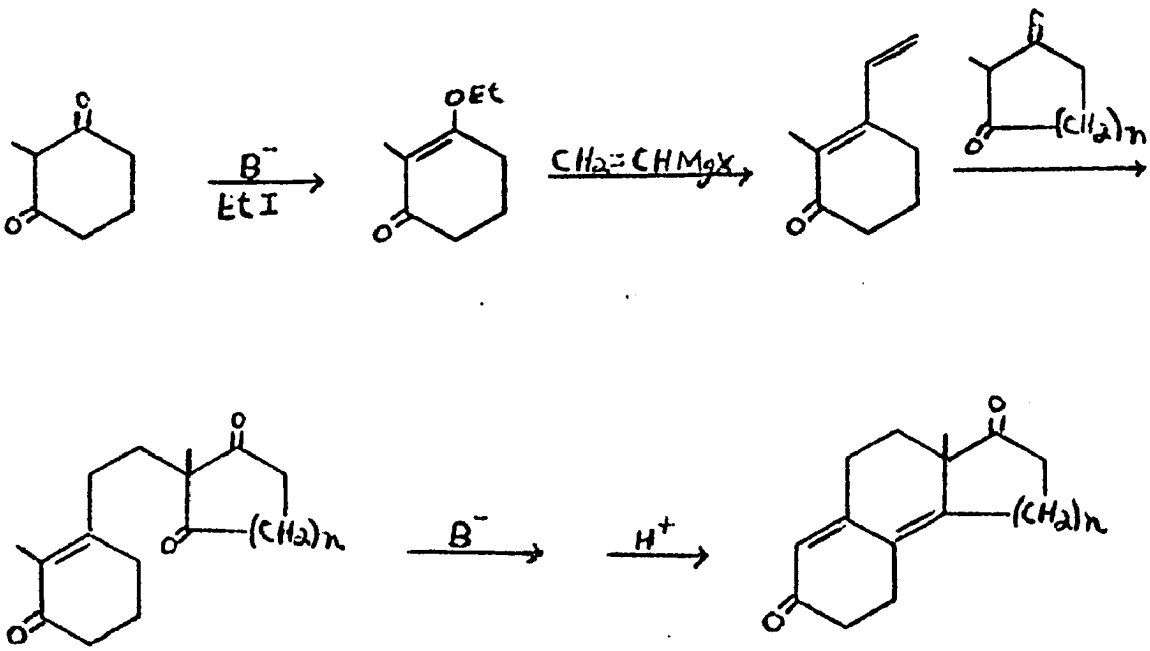

$n = 1$ or 2

Some improvement was realized by Panouse[1] who effected a one step closure of the seco system with p-toluenesulfonic acid in acetic acid.

B. The Russian Approach[2,3]

This involves a two-stage annelation of 2-methylcyclopentane-1,3-dione. The first annelation is conducted according to Boyce and Whitehurst.[4] Enamine alkylation of the hydrindenedione with

---

[1] J. J. Panouse and C. Sannie, Bull. Soc. Chim. France, 1435 (1956).

[2] O. I. Fedorova, G. S. Grinenko and V. I. Maksimov, J. Org. Chem. USSR, 4, 597 (1968).

[3] O. I. Fedorova, G. S. Grinenko and V. I. Maksimov, ibid., 4, 600 (1968).

[4] C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 4547 (1960).

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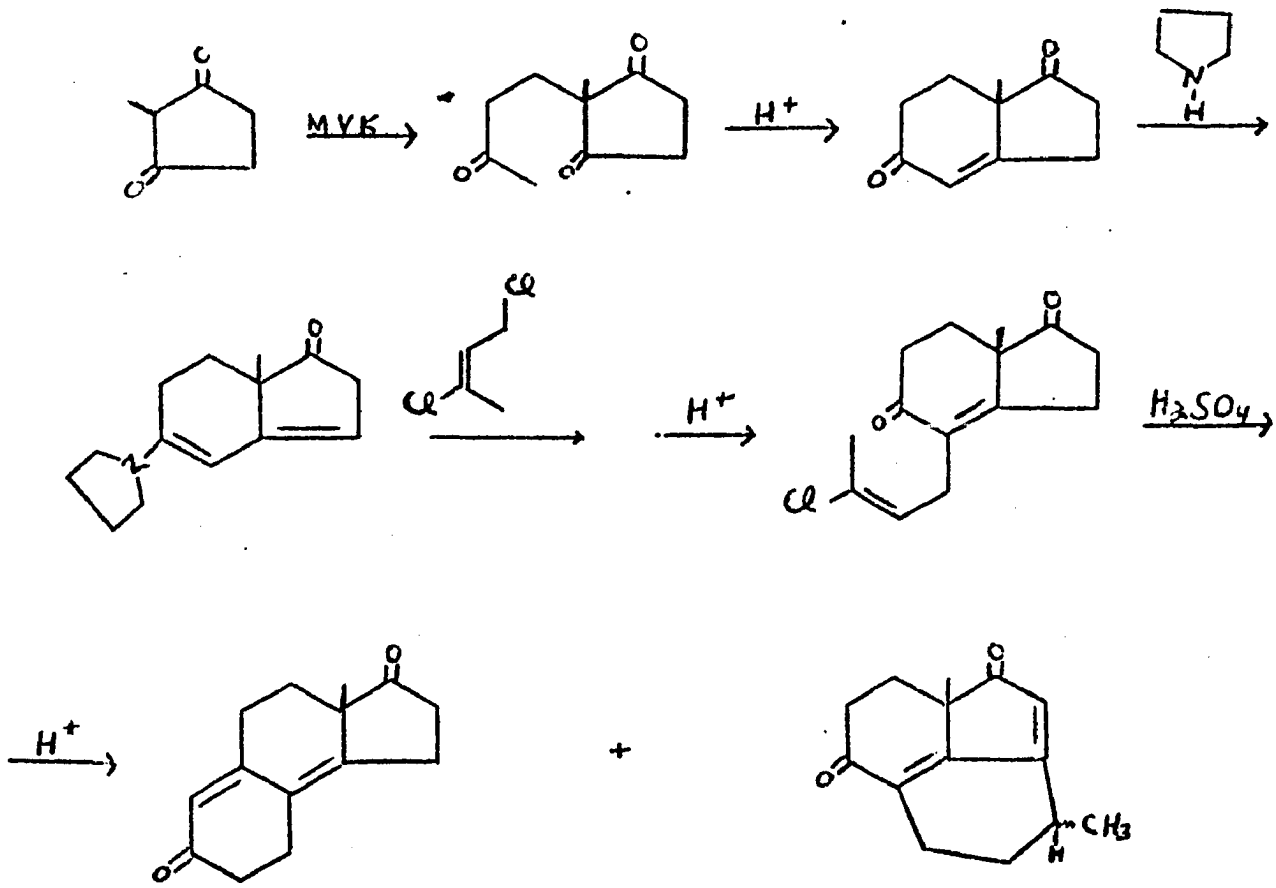
Wichterle's[1] reagent occurs in poor yield. Cleavage of the enamine and then of the chloride (conc. H_2SO_4) gave IV and V, although IV was not obtained in crystalline form.



IV V

While this approach has little merit for producing systems such as IV, it does have the advantage of allowing for the preparation of an intermediate III which can be exploited for stereochemical purposes. Thus VI can be converted to III. The latter was subjected to catalytic hydrogenation to give, with unspecified stereoselectivity, VII. The latter was converted by standard means to VII-A which is the basic intermediate in the French synthesis.[2]

---

[1] O. Wichterle, Coll. Czech. Chem. Communs., 12, 93 (1947).

[2] I. Velluz, G. Nomine and J. Mathieu, Angew. Chem., 72, 725 (1960).

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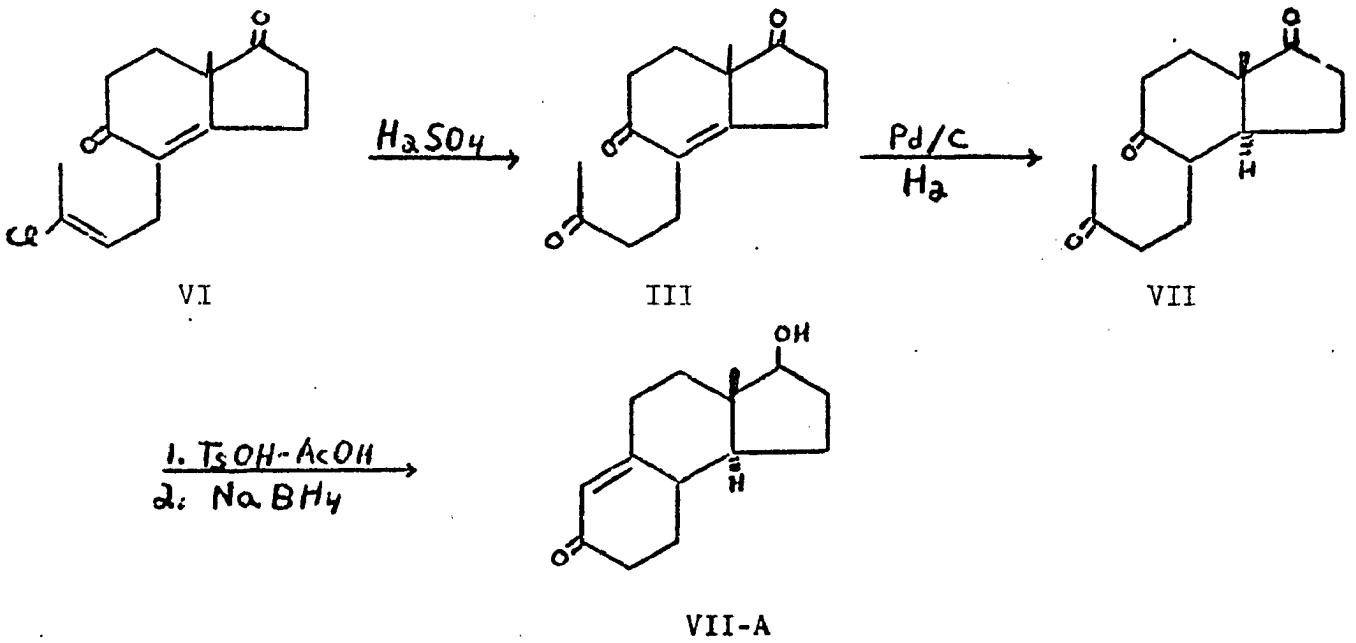
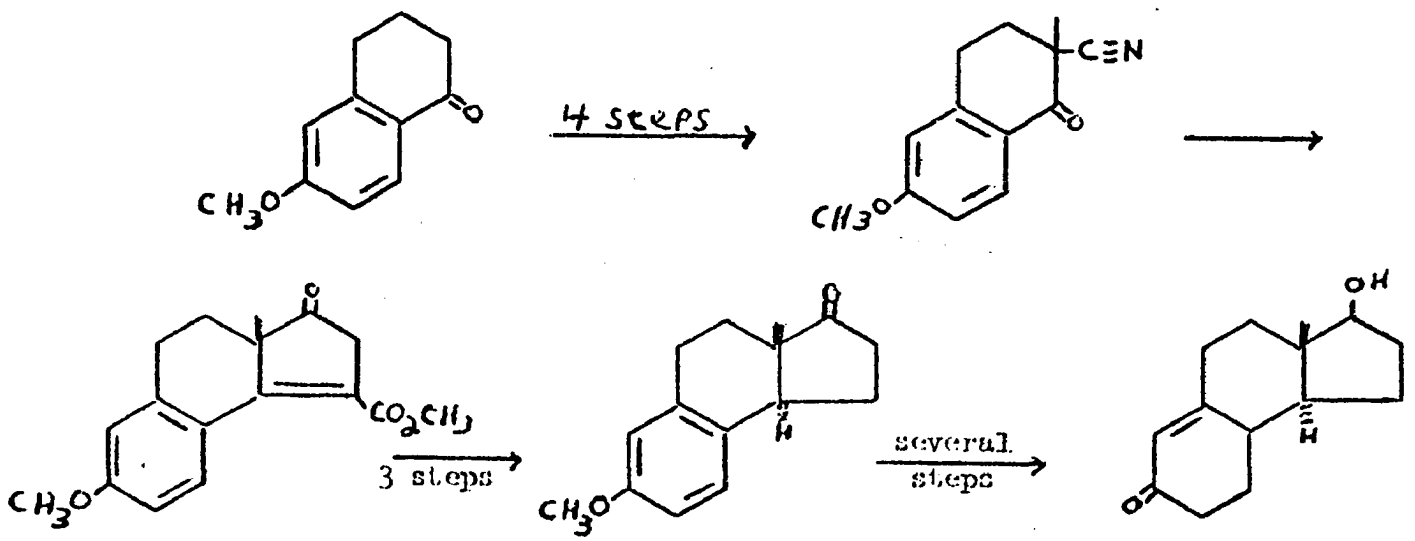


VI III VII

VII-A

C. The French Synthesis[1]



[1] L. Velluz, G. Nomine and J. Mathieu, Angew. Chem., 72, 725 (1960).

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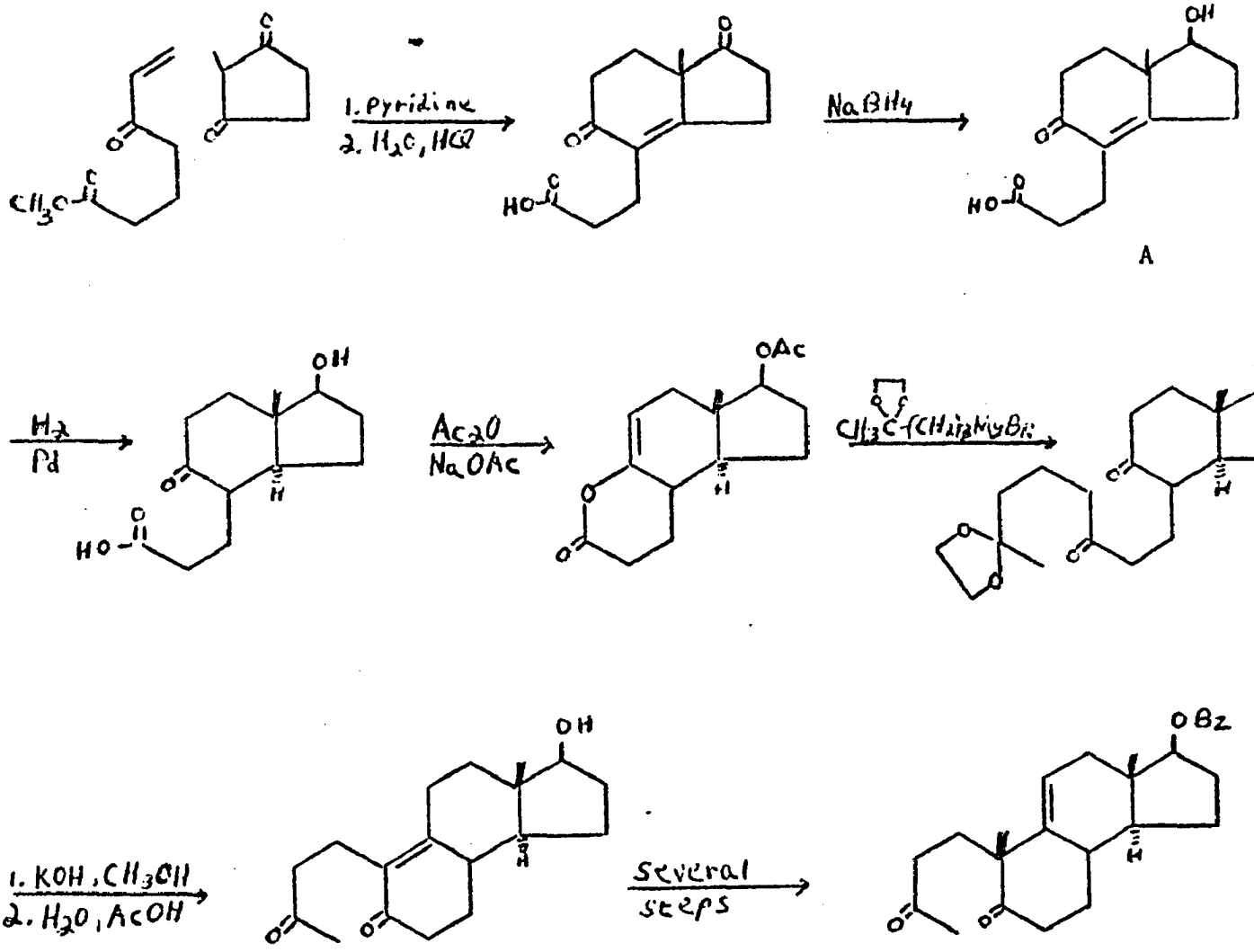
It is now appropriate to consider an alternate French synthesis of steroids.[1] The basic stereochemical discovery is that reduction of A gave predominantly the trans fused ring junction.[2]



[1] L. Velluz, G. Nomine, G. Amiard, V. Torelli and J. Cerede, Compt. Rend., 257, 3086 (1963).

[2] A recent review on the effect of substitution at C-4 on the stereochemistry of the reduction has appeared: G. Nomine, G. Amiard and V. Torelli, Bull. Soc. Chim., 3664 (1968).

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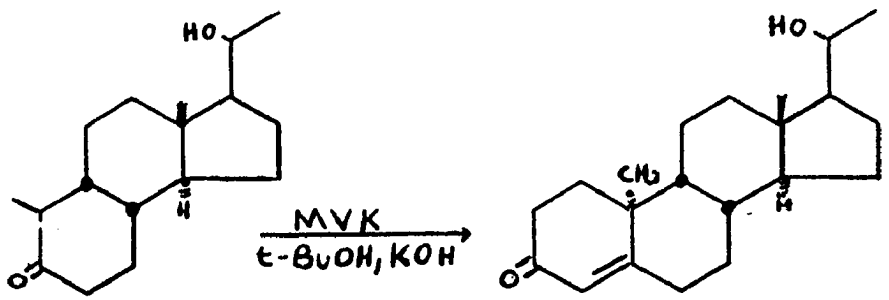
One advantage of this approach is that it allows for the stereoselective introduction of the C-19 methyl group.[1] However, the claim that only the desired β-methyl compound is obtained has been disputed by Stork.[2]

In contrast to these results is the synthesis of retrosteroids by the Hoffmann-LaRoche group.[3,4,5] The key step is a Robinson annellation which results in a compound with an α C-19 methyl group.



---

[1] L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, R. Bucourt and J. Tessie, Compt. rend., 250, 1293 (1960).

[2] G. Stork and J. E. McMurry, J. Am. Chem. Soc., 89, 5464 (1967).

[3] Z. G. Hajos, R. A. Micheli, D. R. Parrish and E. P. Oliveto, J. Org. Chem., 32, 3008 (1967).

[4] Z. G. Hajos, D. R. Parrish and E. P. Oliveto, Tetrahedron, 24, 2039 (1968).

[5] A. M. Krubiner, G. Saucy and E. P. Oliveto, J. Org. Chem., 33, 3548 (1968).

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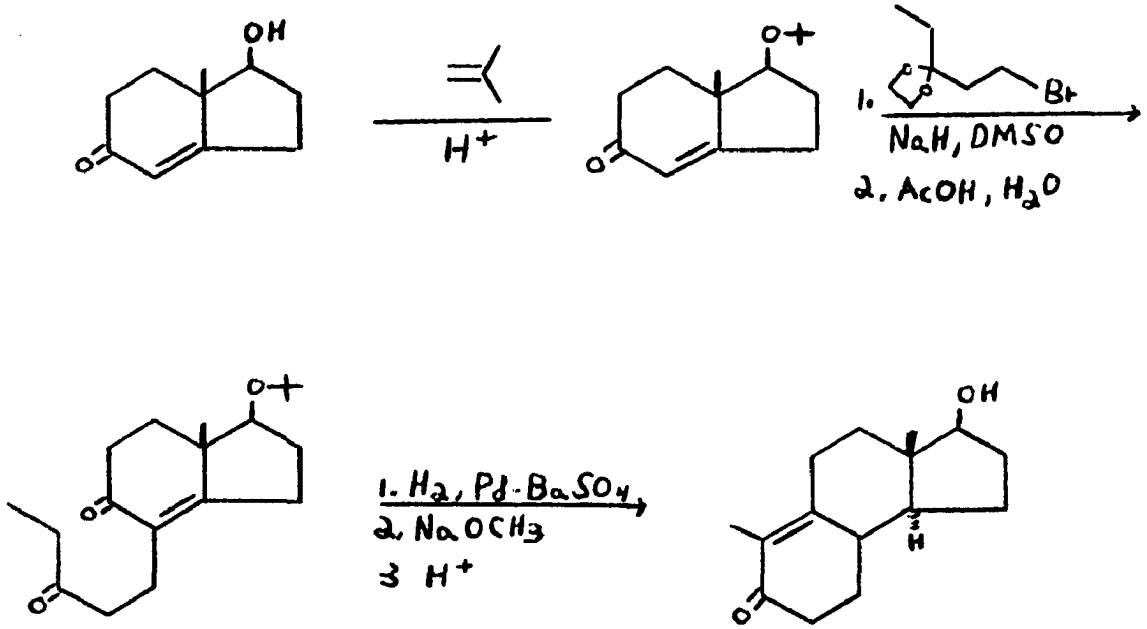
D. Oliveto's Approach[1,2]

The following scheme is another illustration of the synthesis of a tricyclic compound capable of elaboration to steroidal systems.



This synthesis, which starts with the previously prepared bicyclic hydroxy ketone,[3] has the advantage of being brief, but suffers from low yield. The alkylation step gives considerable O-alkylated product, which must be chromatographically separated. The three-step

---

[1] Z. G. Hajos, R. A. Micheli, D. R. Parrish and E. P. Oliveto, J. Org. Chem., 32, 3008 (1967).

[2] J. N. Gardner, B. A. Anderson and E. P. Oliveto, J. Org. Chem., 34, 107 (1969).

[3] C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 4547 (1960).

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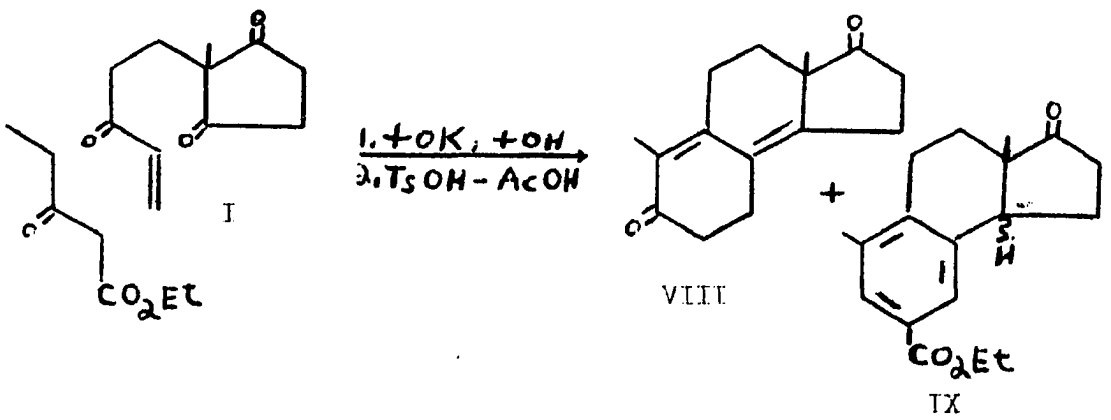
conversion of the enedione to the tricyclic compound also occurs in low yield (ca. 50%). Interestingly, hydrogenation gave, as the major product, the desired trans C/D ring junction. Previous attempts to produce the trans isomer of the bicyclic hydroxy ketone starting material gave, under a variety of hydrogenation conditions, only the thermodynamically more stable C/D cis isomer.[1] Only those bicyclic systems containing a large substituent at C_4 give respectable amounts of trans junction.

E. Migdalof's Approach

Condensation of I with ethyl propionylacetate gave the desired tricyclic compound VIII, but only as a minor product. The major product was the aromatic compound IX.



Compounds VIII and IX arise from conjugate addition of the anion of the β-ketoester, followed by acid catalyzed hydrolysis, decarboxylation and bis cyclodehydration on one operation. The unfortunate genesis of the undesired salicylate, IX, is presumed to occur

---

[1] C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 4547 (1960).

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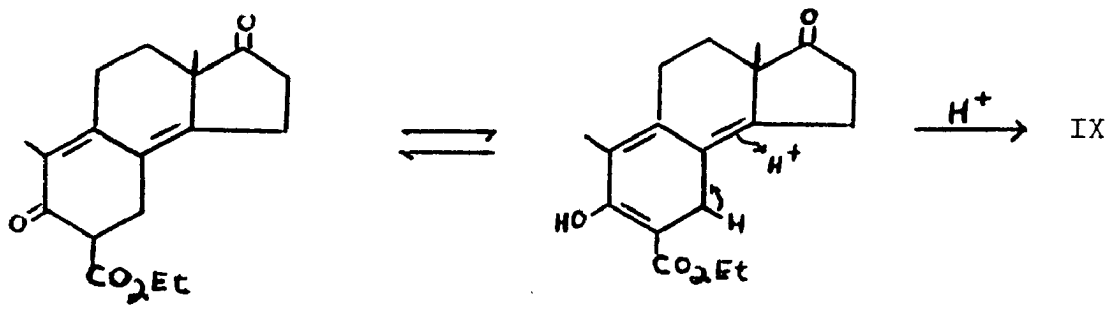
because bis cyclodehydration precedes ester hydrolysis. This would produce the intermediate X, whose enolic form could readily aromatize to IX.[1]



X

This route could lend itself to a more aggressive approach to steroid synthesis if the esters were modified to contain functionality for construction of the A ring. Methylation of the reaction products from condensations of these esters with I should then lead to the desired epimer β at C_{10}.[2,3]

---

[1] J. J. Panouse and C. Sannie, Bull. Soc. Chim. France, 1435 (1956).

[2] L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, R. Bucourt and J. Tessie, Compt. rend., 250, 1293 (1960).

[3] G. Stork and J. E. McMurry, J. Am. Chem. Soc., 89, 5464 (1967).

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III. DISCUSSION OF RESULTS

Migdalof's[1] work suggests that the products which results from the two-stage condensation of β-ketoesters with I may be dependent on the nature of the alkyl group of the esters, and/or the substitution pattern at C_4. In order to properly sort out these effects, it was necessary to study the reaction of the "complimentary" compounds, (i.e., t-butyl propionylacetate and ethyl acetoacetate), with I.

The commercial preparation of t-butyl acetoacetate consists of the reaction of t-butyl alcohol with diketene.[2] Since no equivalent method exists for the preparation of t-butyl propionylacetate, the Hauser[3] dianion method was used for the terminal methylation of t-butyl acetoacetate. Treatment of the latter with 2 eq. of potassium amide in liquid ammonia followed by addition of methyl iodide gave a serious mixture of mono and polyalkylated products, from which X was separated by preparative glc, although in only 5% yield. The infrared spectrum contained maxima at 5.75μ (ester carbonyl), and at 5.85μ (acyclic ketone). The nmr contained a triplet (3H) at τ 8.15 and a quartet (2H) at τ 7.45 (ethyl group), a singlet (9H) at τ 8.53 (t-butyl group) and a singlet (2H) at τ 6.71 (methylene of β-dicarbonyl).

---

[1] B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

[2] S. O. Lawesson, S. Grönwall and R. Sandberg, Org. Syn., 42, 28 (1962).

[3] J. Wolfe, T. Harris and C. Hauser, J. Org. Chem., 29, 3249 (1964).

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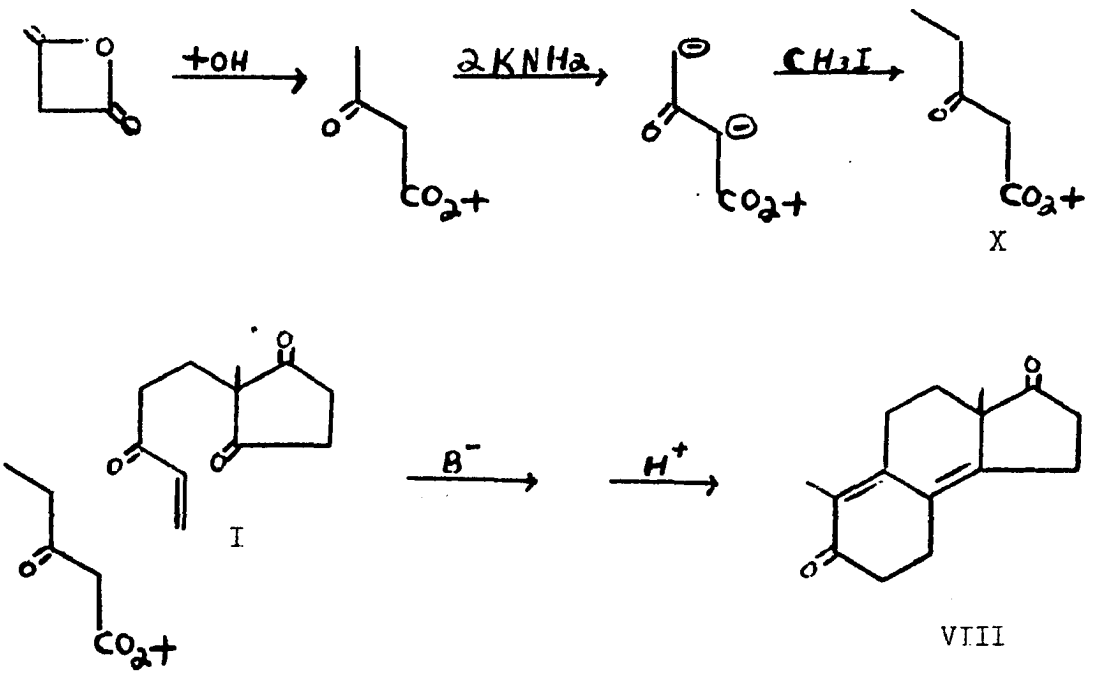
The mass spectrum confirmed the molecular weight (p = 172). Compound X was treated with I using the standard conditions employed by Migdalof[1] in the reaction of I with t-butyl acetoacetate; (i, KO+ in +OH; ii, TsOH/AcOH at 90° - 3 hr.). The resultant oil was shown to contain 75% of VIII by comparative glc with the pure compound. Crystalline VIII was isolated in 54% overall yield. It is significant that this was the only compound chromatographically detected in the crude oil, suggesting that little if any undesired aromatic by-product analogous to IX (page 12) or abnormal diene-dione corresponding to V (page 5) are produced.



[1] B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

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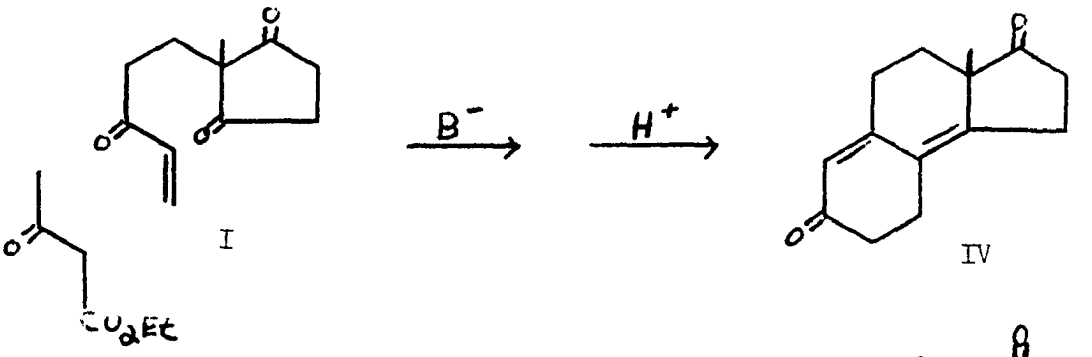
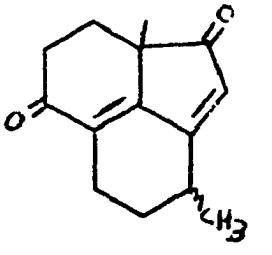
Ethyl acetoacetate was treated with I using the reaction conditions cited above. The crude oil was shown to contain 58% of IV and trace amounts of III and V by comparative glc.[1] Pure IV was isolated in 50% yield by column chromatography.[2] These results are embodied in the following scheme.



I

IV

III



V

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[1]These compounds were previously prepared: B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

[2]IR and NMR spectrum and glc retention time are identical to pure IV.

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Thus it is seen that in the acetoacetate series, the nature of the alkyl group of the ester has little effect on the distribution of products, whereas in the propionylacetate series the ester is quite crucial. This difference arises from the strikingly different results for ethyl acetoacetate relative to ethyl propionylacetate with respect to salicylate formation. Another difference is seen in the seeming absence of abnormal cyclization in the propionyl series.

These results may be understood in terms of the relative rates of aldolization (ra) and decarboalkoxylation (rd) of the respective bicyclic intermediates. Path A, which is the desired one for our purposes, requires that rd > ra; i.e. that the β-ketoester be discharged before formation of the dienone functionality. To the extent that this is not the case (i.e. ra > rd) an intermediate such as X will be produced. The latter would be expected to aromatize via its enolic tautomer.[1] The two paths of product formation and a table summarizing these results are shown below:

---

[1] J. J. Panouse and C. Sannie, Bull. Soc. Chim. France, 1435 (1956).

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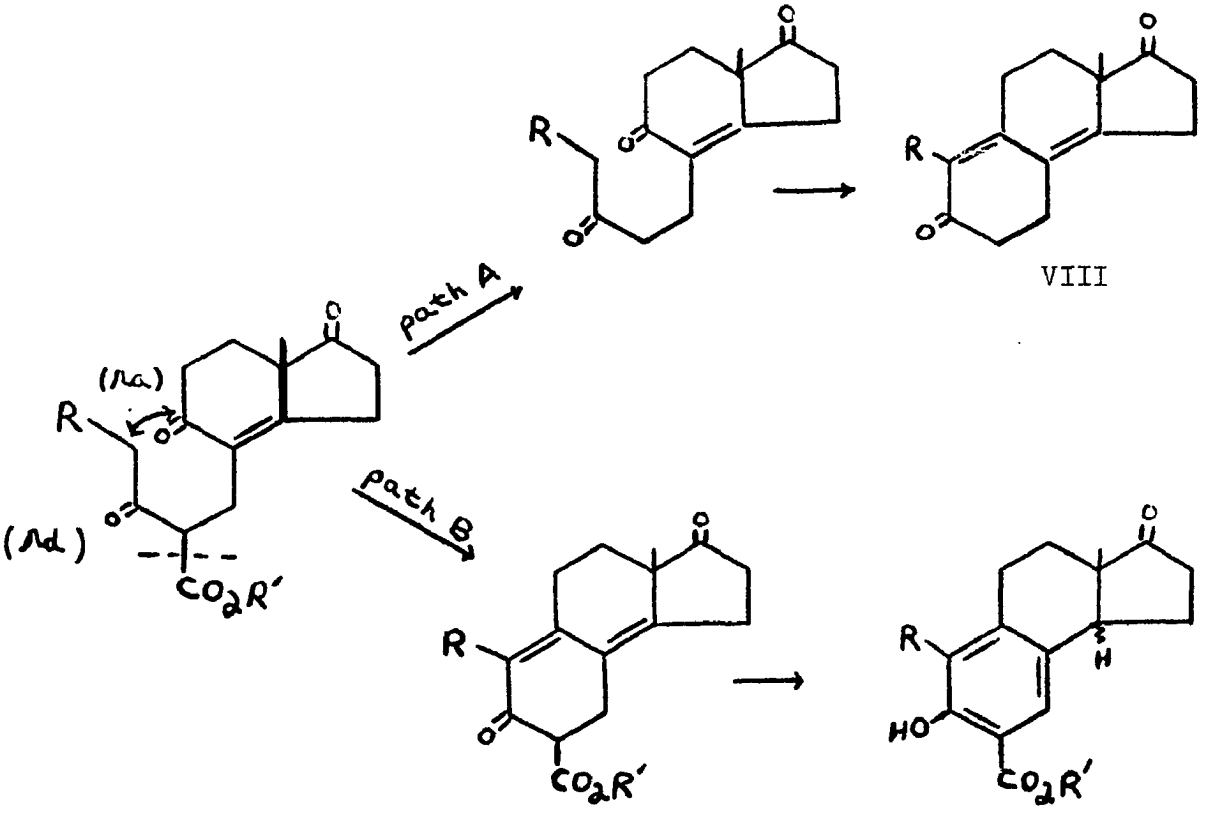

VIII

X

IX

	R	R'	Path	Compound VIII	Compound IX
1.	CH_3	t-butyl	A	75%	--
2.	H	t-butyl	A	52%	--
3.	CH_3	ethyl	A+B	29% (A)	42% (B)
4.	H	ethyl	A	58%	--

It is likely that (ra), involving enolization of the acyclic ketone, is faster when R is methyl. This increase in rate is enough to make (ra) faster than (rd) when R' is ethyl and explains the results obtained in case 3. The suppression of abnormal tricyclic products of the type V in the propionyl series may also be a consequence of the greater ability of an ethyl ketone to serve as the nucleophilic component in an acid catalyzed aldol condensation. If an approach

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to steroid synthesis were to be developed by the addition of more elaborate β-ketoesters to I, it would be desirable for the nucleophiles to contain the t-butyl ester grouping to insure that rd > ra.

The known 6-chloro-5-heptene-2-one, XI,[1] was prepared in the hope that a t-butyl ester could be appended to the methyl ketone by acylation with t-butyl azidoformate. This attempt was unsuccessful and our attention was directed toward the preparation of the corresponding methyl ester.

Methyl esters were as yet untested in this reaction sequence, but were expected to be intermediate in desirability relative to the t-butyl and ethyl cases.

Compound XI was treated with sodium hydride-dimethyl carbonate[2] in benzene to give in 52% yield a mixture of two isomeric compounds in a 9 to 1 ratio. The higher boiling isomer (bp 75-77°/0.2 mm) was isolated in 30% yield by careful fractionation and was assigned structure XIII on the basis of its elemental analysis and spectral properties. Its infrared spectrum contains maxima at 5.75μ (ester carbonyl), and 5.85μ (ketone carbonyl). The nmr spectrum exhibits a singlet (3H) at τ 6.30 (methyl ester), a broad singlet (3H) at τ 7.9 (allylic methyl), a singlet (1.2H) at τ 6.65 (methylene protons of β-dicarbonyl), along with the vinylic (.4H) and hydroxyl (.4H) proton of the enolic form at τ 5.05 and τ -2.10 respectively. The vinylic proton adjacent to the enol chloride appears as a broad complex signal at τ 4.3-4.7. The allylic and β-keto methylene protons were present as a complex signal (4H) at τ 7.2-7.8. The mass

---

[1] M. Schechter and F. LaForge, U. S. 2,754,500 (C.A. 46:9080e).

[2] W. S. Johnson, N. Jensen, J. Hooz and E. Leopold, J. Am. Chem. Soc., 90, 5870 (1968).

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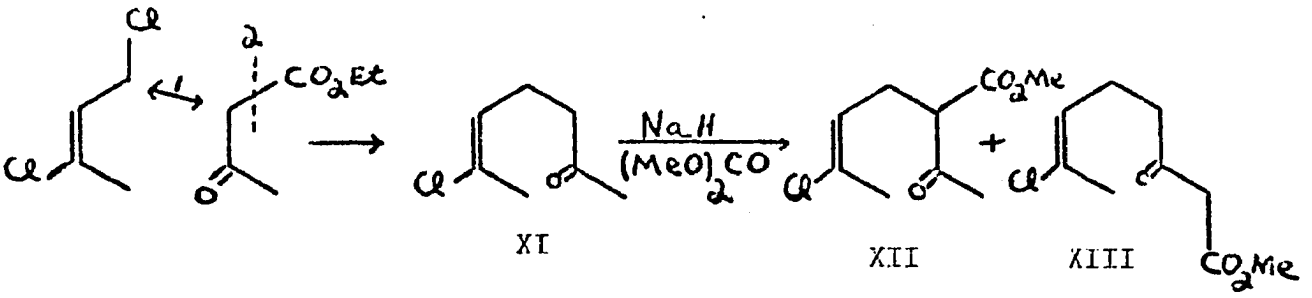
spectrum confirms the molecular weight (p = 204) and the presence of chlorine (p + 2 = 206).

The lower boiling compound (bp 69-72°/0.2 mm), despite repeated distillation, was always contaminated with its isomer. However, it was isolated in pure form by preparative glc and assigned structure XII. Its nmr spectrum was decisive in establishing its structure. It has the expected methyl resonance, τ 7.92 (allylic methyl), τ 7.85 (methyl ketone), and τ 6.30 (methyl ester). The methine proton (1H) appears as a complex signal τ 6.4-6.7. Complex multiplets at τ 7.2-7.7 (2H), and at τ 4.4-4.7 (1H) account for the methylene and vinylic protons. The mass spectrum indicated, as with compound XIII, the molecular weight (p = 204) and the presence of chlorine (p + 2 = 206).



XI XII XIII

The base catalyzed reaction of I with XIII afforded a viscous oil which was subjected, without purification, to acid conditions identical with those used in the preparation of VIII.

Two crystalline products were obtained from the reaction after column chromatographic separation. The structure of XIV (1%, mp 134-135°) was assigned on the basis of elemental analysis, and

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the following spectral data. The infrared spectrum contains absorption maxima at 5.78μ (cyclopentanone), 5.95μ (aromatic ester). The nmr spectrum includes a singlet (3H) at τ 8.91 (angular methyl), a broad singlet (3H) τ 7.90 (allylic methyl), a singlet (3H) at τ 6.05 (methyl ester), a complex signal (1H) at τ 4.3-4.7 (vinylic proton), a singlet (1H) at τ 2.30 (aromatic proton), and singlet (1H) at τ -0.82 (phenolic OH). Complex signals (2H) at τ 6.3-6.6 and (9H) at τ 6.6-8.8 account for the remaining protons. The mass spectrum indicates a molecular weight (p = 362), the presence of chlorine (p+2 = 364), and a base peak at (p - 31) attributed to the loss of $-OCH_3$ characteristic of aromatic methyl esters. The ultraviolet absorption spectrum is consistent with an aromatic ester[1] (217, 252 and 320 mμ).[2]

The second compound isolated (41%, mp 96.0-96.5°, ether-hexene) was shown to have the structure XV on the basis of its elemental analysis and spectral properties. The infrared spectrum exhibits maxima at 5.75μ (cyclopentanone), and at 6.05μ and 6.15μ (cyclohexanone in conjugation with 1,3-dione). The ultraviolet maximum (τ max = 308 mμ, ε = 18,200) is 28 mμ lower than would be predicted. This discrepancy need cause little alarm for there is an unexplained but well precedented deviation from the Woodward-Fieser

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[1] These data compare favorably with the published spectrum of methyl salicylate: E. D. Bergmann, Y. Husberz and S. Pinchos, J. Chem. Soc., 2351 (1950).

[2] While the nmr spectrum and sharp melting point point to this being a homogeneous substance, the stereochemistry of the C-D (steroid numbering) junction is not known.

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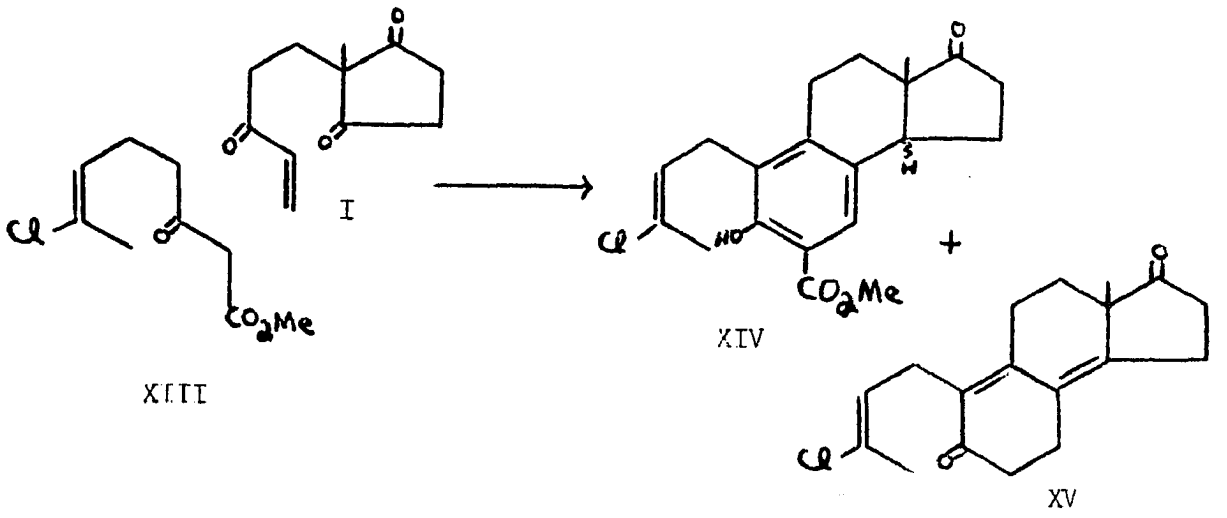
rules in dienones of this type.[1,2]



Its nmr spectrum exhibits methyl resonances at τ 8.79 (angular methyl) and τ 7.90 (allylic methyl), a multiplet (1H) at τ 4.2-4.8 (vinylic proton), a doublet (2H) at τ 6.7 (doubly allylic methylene). The remainder of the spectrum consists of a complex pattern (9H) at τ 6.9-7.7 and a complex pattern (3H) at τ 8.0-8.7.

The mass spectrum is similarly consistent in that it contains a parent peak at 304, p + 2 at 306, with a base peak at 269 (p - 35).

Additional support for the structure of XV was obtained via high resolution mass spectrometry. The exact mass of the base peak

---

[1] B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

[2] Such anomalous behavior has previously been reported for the chromophore.[3,4]

[3] A. Frey, Promotionsarbeit, ETH, Zurich (1954).

[4] C. Sannie and J. Panouse, Bull. Soc. Chim. France, 1435 (1956).

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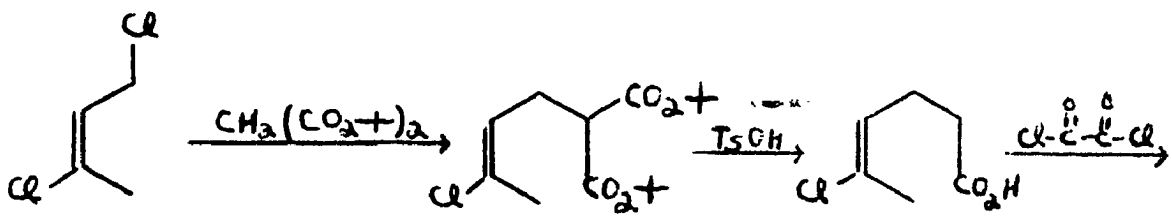
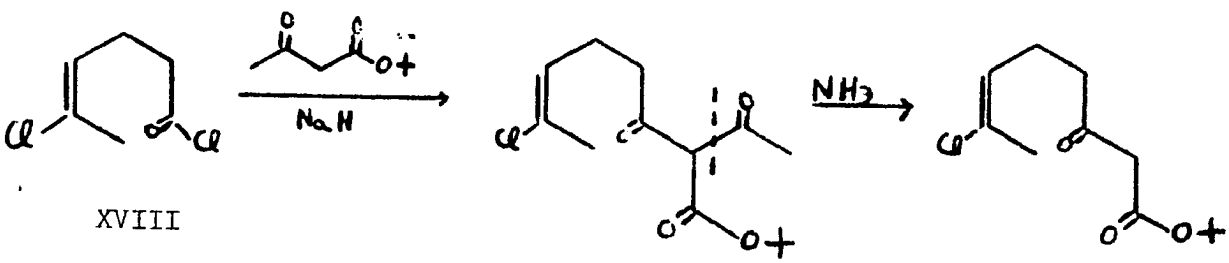
(269) was compared with the known mass of the (269) peak in perfluoro kerosene. The measured value compared favorably with the calculated value.

With the synthesis and rigorous structure proof of XV, a major objective of this investigation had been accomplished. It will be noted that XV contains the functionality required for construction of the A ring. However, two serious problems detracted from the practicality of this approach. The formation of salicylate and the lack of total specificity in the carbomethoxylation could hardly be tolerated. An obvious solution presented itself in the form of compound XX. We proceeded accordingly:



XVI XVII



XVIII XIX XX

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The potassium salt of di-t-butyl malonate reacted with 1,3-dichloro-2-butene to afford, after vacuum distillation (68%) of XVI (bp 91-93°/0.15 mm). Its infrared spectrum has the expected maximum 5.75μ (ester carbonyl). Its nmr spectrum contains a singlet (18H) at τ 8.10 (t-butyl esters), a singlet (3H) at τ 7.93 (allylic methyl), and a complex signal (2H) at τ 7.3-7.7 (methylene protons). A triplet (1H) at τ 6.93 (methine proton), and a complex signal (1H) at τ 4.4-4.7 are also present. Compound XVI was converted to the known acid[1] XVII in (56%) yield by heating it in toluene under reflux in the presence of p-toluenesulfonic acid. No spectral data were reported[1] for compound XVII, but the infrared and nmr spectra determined in these laboratories are consistent with the proposed structure.

The acid XVII was converted, with quantitative weight recovery, to its acid chloride XVIII by reaction with oxalyl chloride.[2] The infrared spectrum of the latter shows the expected absorption at 5.55μ. This compound was unstable and was treated immediately with the sodium salt of t-butyl acetoacetate to give XIX. Compound XIX was subjected to ammonolysis[3] without purification and the desired compound XX was isolated (17% yield) *via* vacuum distillation. The structure of this compound was assigned on the basis of its elemental

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[1] O. Wichterle, Coll. Czech. Chem. Communs., 12, 93 (1947).

[2] R. Adams and L. H. Ulich, J. Am. Chem. Soc., 42, 599 (1920).

[3] E. Wenkert, A. Afonso, J. B. Bredenburg, C. Kaneko and A. Tahara, J. Am. Chem. Soc., 86, 2038 (1964).

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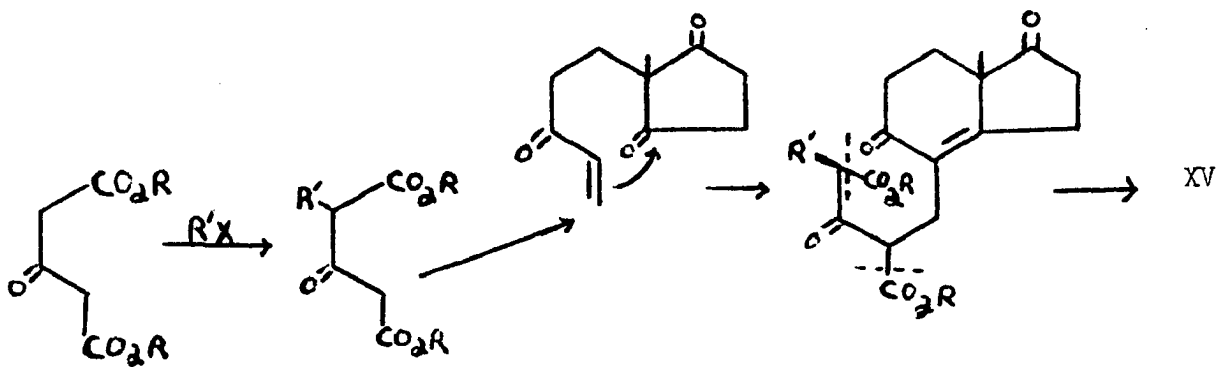
analysis and spectral properties. Its infrared spectrum exhibits maxima at 5.75μ (ester carbonyl), and at 5.85μ (ketone carbonyl). Its nmr spectrum contains a singlet (9H) at τ 8.58 (t-butyl ester), a broad singlet (3H) at τ 7.95 (allylic methyl), a complex signal (4H) at τ 7.3-7.2 (allylic and γ methylene adjacent to ketone), a singlet (2H) at τ 6.72 (methylene of β-dicarbonyl), and a complex signal (1H) at τ 4.3-4.7 (vinylic proton).

This compound underwent condensation with I under the standard condition [(i) KO+, +OH; (ii) TsOH/AcOH 78°] to give XV (51% yield) as the only product. It was satisfying that this reaction gave an increased yield without formation of aromatic side products. However, the numerous steps required and lower yield obtained in the synthesis of XX, made the use of this compound unattractive for the production of XV.

The purpose of the ester group in these nucleophiles (XIII and XX), is to facilitate carbanion formation at the methylene between the two carbonyl groups. Alkylation of this carbanion by I is followed by hydrolysis and decarboxylation with the formation of XV. If a properly monoalkylated derivative of acetonedicarboxylate (1,3-dichloro-2-butene) were to undergo Michael reaction at the methylene group, two fold hydrolysis and decarboxylation would also yield XV. This general scheme is depicted below.



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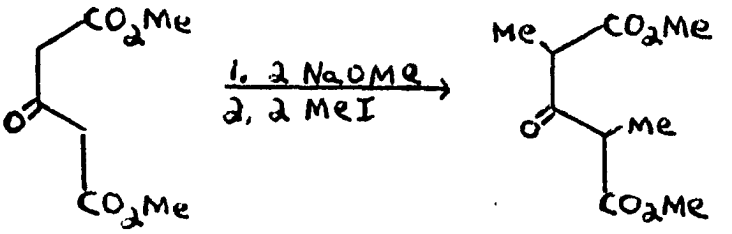
The crucial orienting step in this proposed reaction is the second alkylation. While various a priori arguments might be developed in analyzing this problem, some literature precedent favoring our proposal could be found:



Thus, Shroeter had long ago[1] claimed that double alkylation of dimethyl acetonedicarboxylate gave cleanly the 2,4-disubstituted products.[1] In one instance this claim was strongly supported by subsequent investigation.[2] Accordingly, dimethyl acetonedicarboxylate was converted [(i) sodium-methanol, (ii) 1,3-dichloro-2-butene)] to XXI. The structure of XXI was readily assigned on the basis of its elemental analysis and spectral properties. Its infrared spectrum exhibits maxima at 5.75μ (ester carbonyl), and at 5.85μ (ketone carbonyl). The nmr spectrum contains a broad singlet (3H) at τ 7.90 (allylic methyl), a complex signal (2H) at τ 7.2-7.6 (allylic methylene), a singlet (1.5H) at τ 6.45 (methylene of β-dicarbonyl), and the

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[1] G. Shroeter, Chem. Ber., 49, 2711 (1916).

[2] E. A. Coulson and J. B. Ditcham, J. Chem. Soc., 356 (1957).

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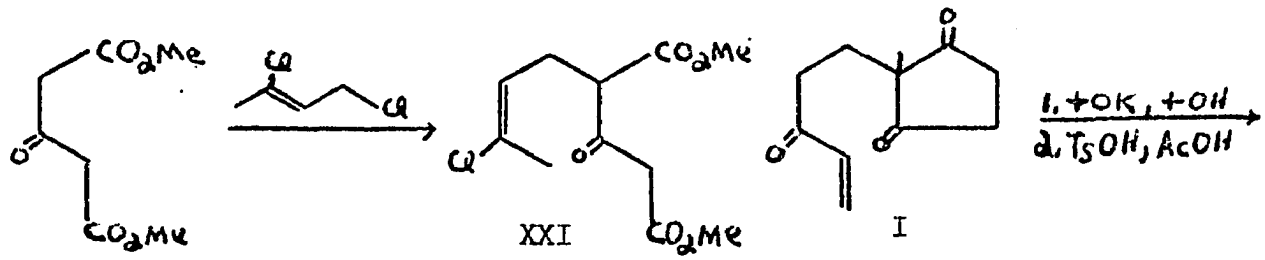
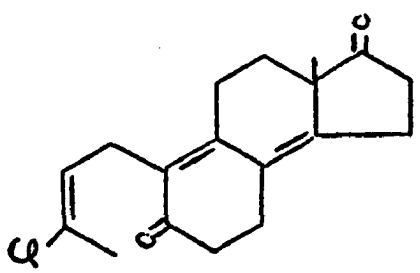
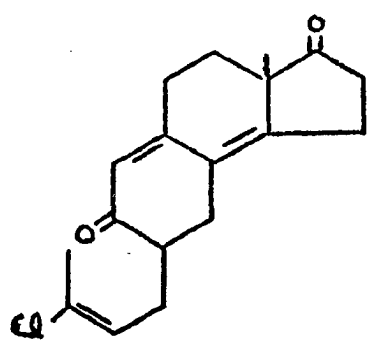
corresponding singlets at τ 4.90 (0.25H) and τ -2.10(0.25H) for the vinylic and hydroxyl protons of the enolic form. A multiplet (7H) at τ 6.2-6.4 accounts for the two methyl esters and the methine proton. The vinylic hydrogen (1H) appears as a multiplet at τ 4.9-4.7.

Condensation of XXI with I under the standard conditions gave an 18% yield of the desired XV. Compound XV-a which would have arisen from Michael addition to the methine position, was not detected in the reaction mixture. However, the modest yield indicated caution in assessing the full implications of this experiment. These reactions are shown below:





XV



XV-a (none detected)

Our previous experience with t-butyl esters suggested a possibility for improving the yield of XV and with it obtaining a fuller comprehension of the orientation of the Michael reaction. Accordingly, acetonedicarboxylic acid[1] was treated with isobutylene

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[1] R. Adams, H. M. Chiles and C. F. Rassweiler, Org. Syn., Coll. Vol., 1, 10 (1941).

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and a catalytic amount of sulfuric acid to yield di-t-butyl acetone-dicarboxylate XXII[1] as a crystalline solid (90%, mp 58-59° hexane). Its nmr spectrum consists of two singlets. The first (18H) at τ 8.55 (t-butyl esters), and the second (4H) at τ 6.52 (methylene protons). The infrared spectrum shows the expected maxima at 5.75μ (ester carbonyl) and at 5.85μ (ketone carbonyl). The elemental analysis was within 0.15% of the calculated value.

Alkylation of XXII with 1,3-dichloro-2-butene gave a crude reaction mixture containing di-t-butyl acetonedicarboxylate, the desired compound XXIII and dialkylated material. Purification attempts *via* distillation were unsuccessful due to decomposition, but pure XXIII (39%) was obtained by careful chromatographic separation.[2] Condensation of XXIII with I under standard conditions gave XV in 65% yield. No evidence for the presence of XV-a could be detected. The problem of a simple high yield synthesis of XV has thus been solved.[3,4] These reactions are illustrated below.

---

[1]Quite recently compound XXII was prepared by a more difficult route: H. Paul and P. Polczynski, J. für prak. Chem., 312, 240 (1970).

[2]Purification of this compound was conducted by Phillippa Heggs of these laboratories.

[3]Subsequent to this work, Miss Phillippa Heggs in our laboratory has achieved a high yield conversion of XXII → XXIII using a dianion approach.[4]

[4]L. Weiler, J. Am. Chem. Soc., 92, 6702 (1970).

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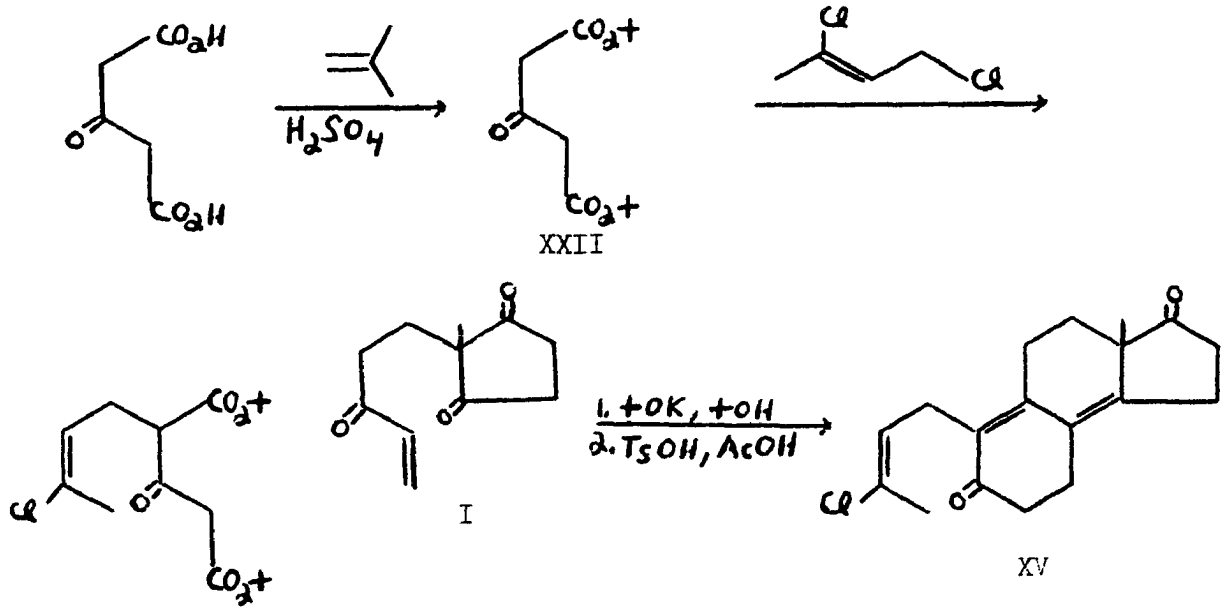

It was important to know if compound XV would survive the rather severe conditions required to hydrolyze an enol chloride (concentrated sulfuric acid), a synthetic step that had to eventually be realized if it were to be convered to steroidal compounds.

Therefore, XV was treated with concentrated sulfuric (0° for 0.5 hours) giving crystalline XXIV (61% yield) as the only product (mp 146-147° ether hexane). When this reaction was run under identical conditions, but using methylene chloride as a diluent, the yield rose to a pleasing 95%.

Structure XXIV could safely be assigned on the basis of elemental analysis and spectral data. The infrared spectrum exhibited

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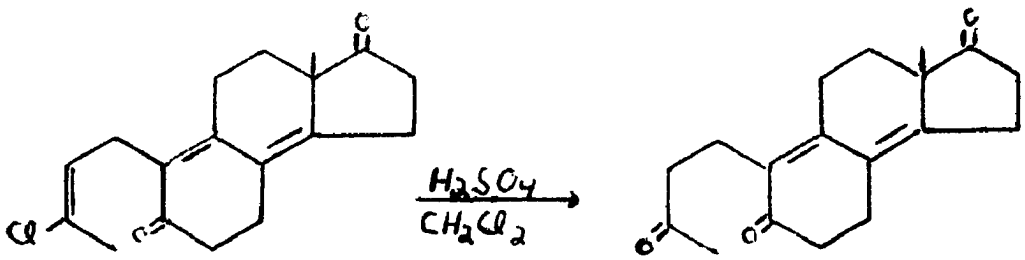
maxima at 5.75μ (cyclopentanone), at 5.85μ (acyclic ketone), at 6.05μ and 6.12μ (dienone). The nmr contained a singlet (3H) at τ 8.80 (angular methyl), a singlet (3H) at τ 7.90 (methyl ketone), and a complex singal (16H) at τ 6.9-8.8. The ultraviolet spectrum exhibited a maximum at 308 mμ. This value is, as expected, identical to the starting material. The mass spectrum verified the molecular weight (p = 286 parent and base), and the absence of chlorine. The high resolution mass spectrum gave a measure m/e 286.1564, which compared well with the calculated m/e = 286.1569 for $C_{18}C_{22}O_3$.



XV XXIV

The synthesis of compound XXV constitutes a formal synthesis of $8^{(14)}$-dehydroestrone. Thus, Solomon[1] has achieved the transformation of XXIV → XXV, the Merck tetracyclic triene-dione in 68% yield.[2,3] The latter had already been converted to $8^{(14)}$-dehydroestrone.[4]

---

[1] S. Danishefsky, L. S. Crawley, D. M. Solomon and P. Heggs, manuscript submitted to J. Am. Chem. Soc.

[2] T. B. Windholz, J. H. Fried, H. Schwam and A. A. Patchett, J. Am. Chem. Soc., 85, 1707 (1963).

[3] This constitutes, by far, the best synthesis of this compound. Ethynyl derivatives have been reported to have gonadotrophin inhibiting activity.[2]

[4] D. B. R. Johnston, D. Taub and T. B. Windholz, Steroids, 8, 365 (1966).

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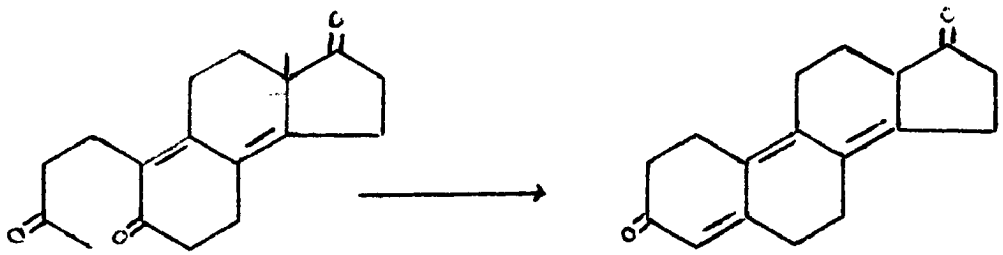

XXIV XXV

We turn to some preliminary results of experiments directed toward the introduction of the 19-methyl group of steroids. It will be noted that a priori one can consider the production of 4 enolates (a-d) upon treatment of XV with strong base. Neglecting stereochemistry, for the moment, a and b can each give one mono-alkylated product. Enolate c could, in principle, give two products c_1 and c_2. Enolate d could similarly give three products, d_1 - d_3. In addition to this multitude of mono-carbon alkylated products, one might consider dehydrohalogenation, and o-alkylation as viable possibilities. The product we want is clearly d_3.

The basis for attempting to produce this product, d_3, from the multitude of possibilities was as follows. Our hope was that the more stable anion would be the fully extended one, d. Precedent was available for the possibility of alkylation of an enone in the presence of a saturated ketone.[1] Compound d_3 would in fact be expected to

[1] G. Stork and J. E. McMurry, J. Am. Chem. Soc., 89, 5464 (1967).

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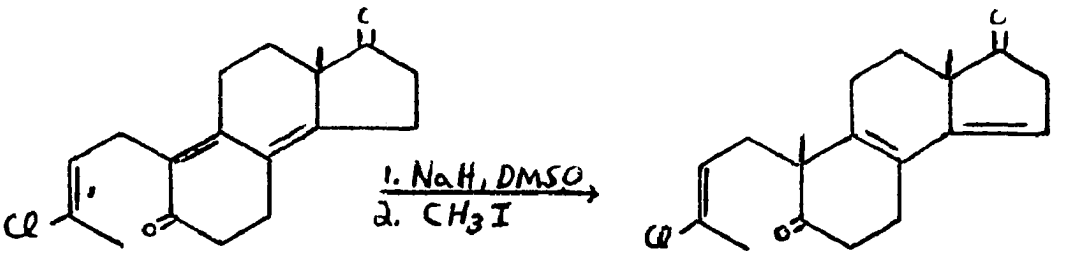
arise from anion d since all known carbon-alkylation of extended enolates occur at the α-position.[1] While base induced alkylation of dienones had never been reported, the possibility of such an α-alkylation seemed reasonable.

Compound XV was treated with one equivalent of dimsyl sodium in DMSO, followed by two equivalents of methyl iodide. Chromatography gave a crude oil (A) (51%) and starting material XV (39%). Crystallization of (A) gave XXVI (12%, mp 134°, ether-hexane). The structure of XXVI was assigned on the basis of its elemental analysis and spectral properties. The infrared spectrum exhibited maxima at 5.75μ (cyclopentanone), and at 5.85μ (cyclohexanone). The ultraviolet spectrum (λ_{max}^{EtOH} 244 mμ, ε = 14,900) is consistent with the desired structure.[2] The nmr spectrum exhibits a methyl resonance at τ 8.90 and at τ 8.63, a singlet (3H) at τ 7.90 (allylic methyl). The two vinylic protons are shown as complex signals at τ 4.1-4.3 (1H), and τ 4.7-5.1 (1H). The remainder of the spectrum is a complex multiplet (12H) at τ 8.3-8.6. The mass spectrum shows the correct molecular weight (p = 318) and the presence of chlorine (p + 2 = 320).



XV XXVI

[1] J. Conia, Record of Chemical Progress, 24, 43 (1963).

[2] Woodward-Fieser rules predict λ_{max} 244 mμ.

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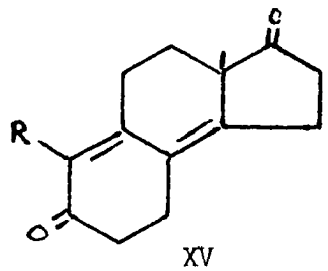
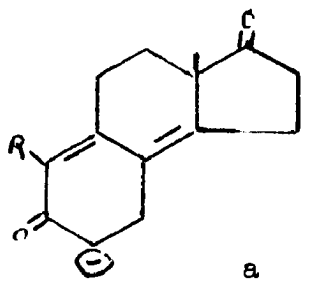
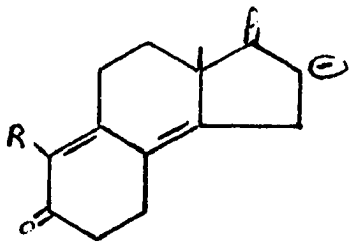


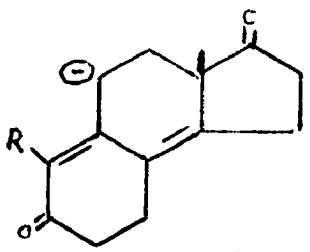
XV



a



b



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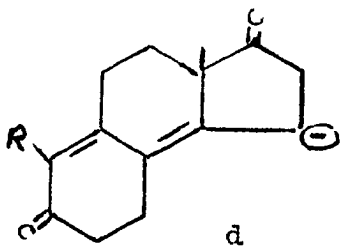
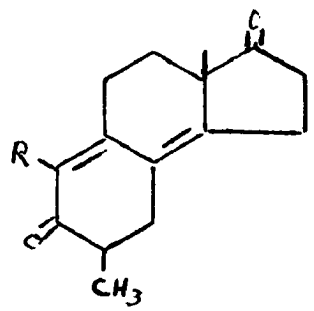
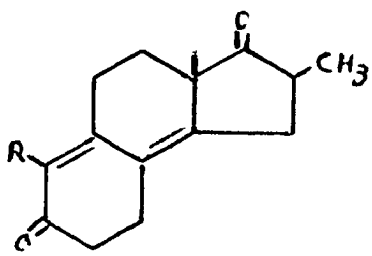


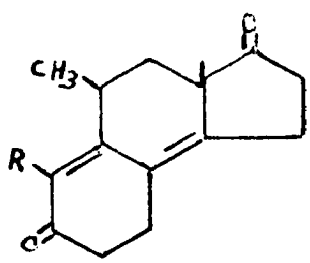
d



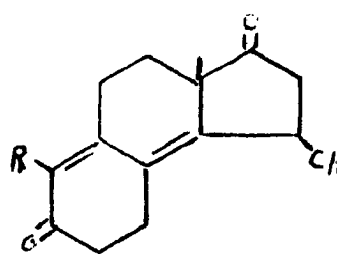
a_1



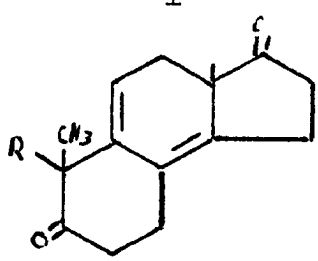
b_1



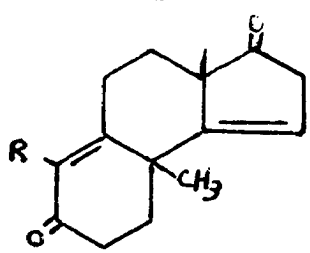
c_1



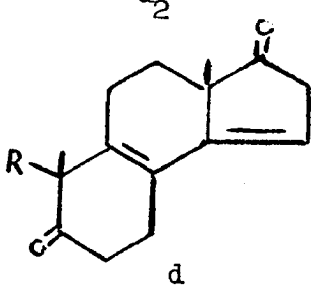
d_1



c_2



d_2



d_3

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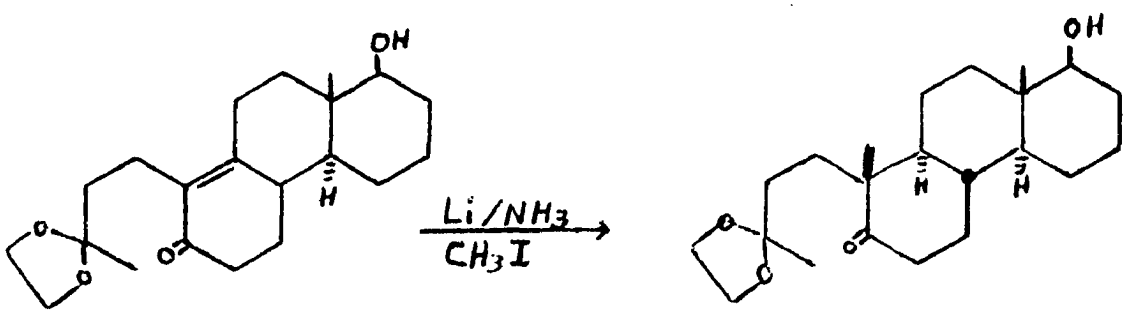
The mother liquor of (A), as seen by the glc trace (page 35) contained no less than 7 compounds. Peak f (p = 318) corresponds to XXVI while the major peak, e, (p = 318) is assumed to be the C_{10} epimer of XXVI. Both e and f are contaminated with dialkylated product due to incomplete separation from g (p = 332).

Other workers in this area have reported a mixture of epimeric products in similar methylation attempts.[1,2] It is encouraging that in the above case, the desired epimer was the one to crystallize.

A solution to this problem might be found in the work of Stork,[3] who obtained only the desired epimer on reductive alkylation of the system illustrated below.



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[1] L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, J. Am. Chem. Soc., 78, 4111 (1956).

[2] G. Stork, H. J. E. Loewenthal and P. C. Mukharji, J. Am. Chem. Soc., 78, 501 (1956).

[3] G. Stork and J. E. McMurry, J. Am. Chem. Soc., 89, 5464 (1967).

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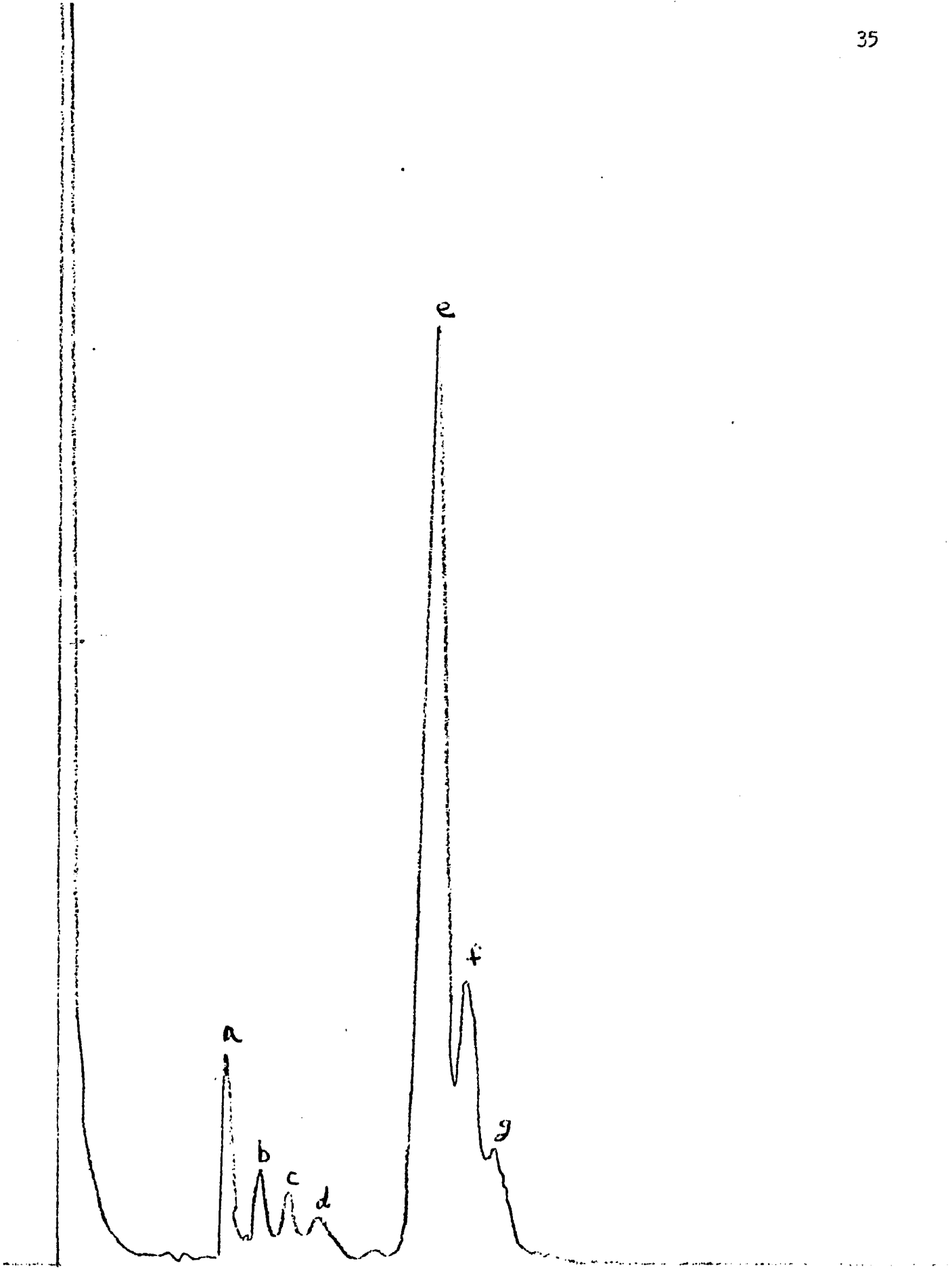

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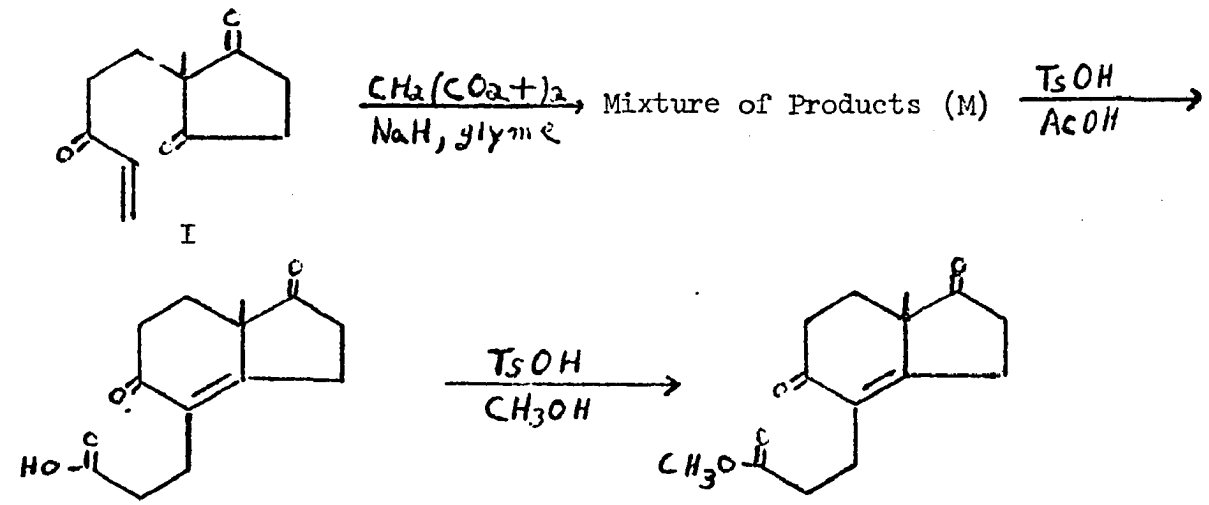
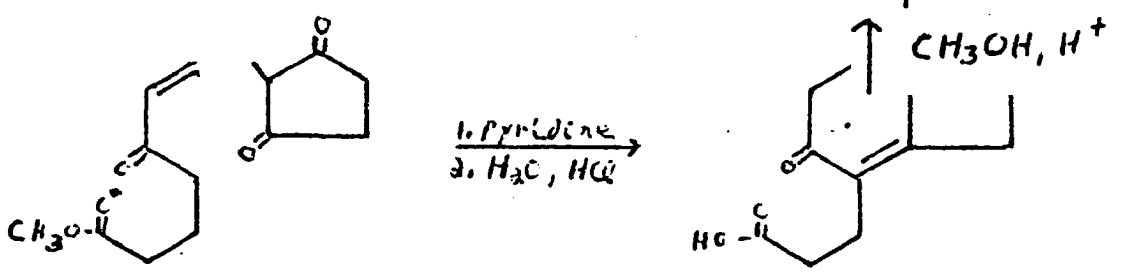
The versatility of compound I in steroid synthesis was further demonstrated by its application to a simple synthesis of XXVIII, the intermediate in the Roussel-Uclaf synthesis of steroids[1,2] (see page 9).

Treatment of I with the sodium salt of di-t-butyl malonate in monoglyme followed by heating the crude reaction mixture in acid (TsOH/AcOH, 37 hr. at reflux) gave a crude acidic product. Esterification of the presumed XXVII gave crystalline XXVIII in 40% yield after isolation by column chromatography. Our synthetic scheme and the approach used by Rousel are illustrated below:



Rousel Method



[1] G. Nomine, G. Amiard and V. Torelli, Bull. Soc. Chim. France, 3664 (1968).

[2] A sample of XXVII and XXVIII was generously provided by Dr. L. Velluz.

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IV. EXPERIMENTAL

A. Source of Reagents

Unless otherwise specified, reagents were obtained from Fisher Scientific Co. and were used without further purification. The 1,3-dichloro-2-butene was purchased from Aldrich Chemical Co., and was distilled prior to use. Dimethyl carbonate was obtained from Eastman Organic Chemicals and was used without purification.

Sodium hydride was obtained commercially as a 1:1 dispersion in mineral oil (Metal Hydrides, Inc., Callery Chemical Co., or Ventron). Mineral oil was removed prior to use by repeated washing with n-pentane until no further weight reduction was found.

Solvents were dried by distillation from metal hydrides as indicated; t-butyl alcohol, benzene and toluene (calcium hydride), monoglyme (sodium hydride).

The 2-methyl-1,3-dyclopentanedione was provided without charge by Dr. E. P. Oliveto (Hoffmann-La Roche, Inc.), and was recrystallized from methanol.

The p-toluenesulfonic acid (Matheson, Coleman and Bell) was used as obtained.

B. Experimental Techniques

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 137 Infrared Spectrophotometer in chloroform or carbon tetrachloride solution using sodium chloride optics. Only selected

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high intensity absorptions were reported. The polystyrene absorption at 6.238μ was used as a reference. The nmr spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are reported in τ units. Spectra were recorded using TMS as internal reference. Ultraviolet spectra were recorded on a Perkin Elmer 124 double beam spectrophotometer. Mass spectra were obtained on an LKB Type 9000A Gas Chromatograph-Mass Spectrometer by either direct probe or by the use of analytical glc columns. Elementary analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tennessee.

All glc yield data were obtained employing a Varian-Aerograph Series 1200 glc apparatus using a flame ionization detector and a Varian Model 20 recorder equipped with a disc integrator. General glc studies were conducted either on this instrument or on a Varian-Aerograph Model A-90P3 instrument using a thermal conductivity detector.

C. Procedures

1. Preparation of t-Butyl Propionylacetate [X]

The Hauser[1] method for terminal alkylation of ethyl acetoacetate was employed. Tert-butyl acetoacetate, 15.8 g (0.1 m) in 30 ml of anhydrous ether, was added dropwise over a 20 min period to 0.2 m of potassium amide[2] in 300 ml of commercial anhydrous ammonia.

---

[1] J. Wolfe, T. Harris and C. Hauser, J. Org. Chem., 29, 3249 (1964).

[2] C. R. Hauser and W. R. Dunnavant, Org. Syn., Coll. Vol., 4, 962 (1963).

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To this stirred suspension was added 17.04 g (0.12 m) of methyl iodide in 30 ml of anhydrous ether. After stirring 20 min, the reaction was neutralized by the addition of excess ammonium chloride and the ammonia was replaced by ether. The reaction mixture was poured into 200 ml of cold water, and cold dilute hydrochloric acid was added with stirring until the pH of the solution was approximately 8. The ethereal layer was separated and washed with water until the washings were neutral. The ether layer was dried (Na_2SO_4) and the solvent was removed by distillation through a 6-inch Vigereaux column at atmospheric pressure. The residue, 12.64 g, was distilled at 18 mm, affording 4.84 g of t-butyl acetoacetate from 69-76° and 5.2043 g of impure product from 76-78°C. Compound X was obtained by passage through a 6' 20% Apiezon-L column and was collected in approximately 5% yield.

Data for Compound X

glc 6' 20% Apiezon-L column

T = 100°C retention time = 14 min flow rate = 25 ml/min

IR: (5.75, 5.85μ)

NMR:

Description	Chemical Shift, $\tau^{CCl_4}_{ppm}$	Approximate Area
triplet (J=7Hz)	8.95	3H
singlet	8.53	9H
quartet (J=7Hz)	7.45	2H
singlet	6.71	2H

Mass Spectrum: Calc'd for $C_9H_{16}O_3$

p = 172

Base peak = 57

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2. Preparation of VIII

A solution of 0.0047 g (1.2 mmoles) of freshly cut potassium in 2 ml of t-butyl alcohol was treated with 0.0704 g (0.409 mmoles) of t-butyl propionylacetate in 2 ml of t-butyl alcohol. To the stirred solution was added, dropwise, over a 45-min period, a solution prepared from 0.0783 g (0.409 mmoles) of pure I in 3 ml of t-butyl alcohol. The reaction mixture was stirred at room temperature for 46 hr.

The solution was treated with 2 drops of concentrated hydrochloric acid, and solvent removed in vacuo leaving 0.1578 g of a yellow-white semi-solid. A solution of the residue in 2 ml of glacial acetic acid was heated to 90°, 0.1580 g of p-toluenesulfonic acid was added and the temperature maintained at 90° for 3 hr. The solution was concentrated under reduced pressure, 15 ml of chloroform added, and the organic layer washed several times with water. The chloroform layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 230 mg of crude VIII as a dark oil. Quantitative yield data were obtained by glc analysis using crystalline VIII as standard. This indicated the oil contained VIII (76%).

glc data: 3% QF1 5' x 1/8" steel column
T = 200° flow rate = 25 ml/min

chloroform solution	conc.	retention time (min)	relative peak area
recrystallized VIII	8.2 mg/1.0 ml	9.8	81.0, 80.0, 79.9, 80.2, 80.0
crude VIII	7.4 mg/1.0 ml	9.8	25.5, 25.9, 25.0, 25.4, 25.7

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Column chromatography of the crude oil (220 mg) on 4.6 g of silicic acid using 1:1 benzene-chloroform solution was eluting solvent afforded, on recrystallization from ether-pentane, 51 mg of crystalline VIII in 54% overall yield.

Data for Compound VIII

IR: $\lambda_{max}^{CHCl_3}$ 5.74, 6.03, 6.09μ

Melting point: 88-89°

3. Preparation of IV

A solution of 0.0782 g (.002 m) of freshly cut potassium in 20 ml of t-butyl alcohol was treated with 1.30 g (.01 m) of ethyl acetoacetate. To the stirred solution was added, dropwise over a 45-min period, a solution prepared from 1.94 g (.01 m) of distilled I in 10 ml of t-butyl alcohol. The reaction mixture was stirred at room temperature for 41 hr.

The solution was treated with 0.4 ml of concentrated hydrochloric acid and then filtered to remove 0.268 g of potassium chloride. The solvent was removed under reduced pressure leaving 3.098 g of a viscous orange oil. A solution of the oil in 25 ml of glacial acetic acid was heated to 90°, 3.1 g of p-toluenesulfonic acid was added and the temperature maintained at 90° for 3 hr. The solution was concentrated under reduced pressure, 50 ml of chloroform was added and the organic layer was washed several times with water. The chloroform layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 2.1442 g of a viscous orange oil. Quantitative yield data were obtained gas chromatographically using crystalline IV as standard.[1]

[1]Recrystallized sample previously prepared by B. Migdalof, Ph. D. Thesis, University of Pittsburgh, 1969.

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glc data: 3% QF1, 5' x 1/8" steel column

T = 200° flow rate = 25 ml/min

chloroform solution	conc.	retention time (min)	relative peak area
recrystallized IV	12.6 mg/ml	10.5	60.0, 61.0, 59.5, 60.0
crude IV	16.7 mg/ml	10.5	45.0, 45.0, 45.0, 45.0

Yield of IV - 50%

Column chromatography of the crude oil on 80 g of silicic acid using 1:1 benzene-chloroform solution as eluting solvent afforded, as an oil, 1.0897 g of the desired product in 50% yield.

Data for Compound IV

IR: $\lambda_{max}^{HCCl_3}$ 5.75, 6.01, 6.10, 6.30μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
broad singlet	4.21	1
complex	6.9-8.7	12
singlet	8.80	3

4. Preparation of 6-Chloro-5-heptene-2-one [XI]

The method of Schechter and LaForge[1] was used with minor modifications. To a solution of 23 g (1 m) of sodium in 500 ml of absolute ethanol was added 130 g (1 m) of ethyl acetoacetate. The solution was heated to reflux and 125 g (1 m) of 1,3-dichloro-2-butene was added dropwise over a two-hr period. After 16 hr of

[1] M. Schechter and F. LaForge, U. S. 2,574,500 (C. A., 46, 5080c).

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heating under reflux, the reaction was allowed to cool and the salt was removed by filtration. Removal of the ethanol by distillation at atmospheric pressure left 183 g of a crude dark liquid. This crude material was added to 1 liter of 5% sodium hydroxide solution and allowed to stir at room temperature for 14 hr. The solution was made acidic by slow addition of 1:1 H_2SO_4-H_2O and then heated at reflux until evolution of carbon dioxide had ceased. The reaction mixture was extracted with two 200-ml portions of ether and the combined ether extracts were washed first with saturated sodium bicarbonate solution and then with a saturated salt solution. The ether layer was dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was distilled at 22 mm, giving a residue from 93-103°, 58 g or 40% yield.

Data for Compound XI

IR: $\lambda_{max}^{CCl_4}$ 5.85, 6.01 (small)μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet (broad)	7.9-8.0	6
complex	7.3-7.8	4
complex	4.3-4.7	1

5. Reaction of XI with Dimethyl Carbonate. Preparation of XII and XIII

The method of W. S. Johnson[1] for the preparation of ethyl isobutyroacetate was used with minor modifications.

---

[1] W. S. Johnson, N. Jensen, J. Hooz and E. Leopold, J. Am. Chem. Soc., 90, 5877 (1968).

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Sodium hydride, 16.56 g (.69 m), was placed in a flame dried 1 l. 3-neck flask under a nitrogen atmosphere. To this was added 300 ml of anhydrous benzene and 54 g (.6 m) of dimethyl carbonate. The mixture was stirred and heated under reflux while a solution of 43.95 g (.3 m) of XI in 30 ml of anhydrous benzene was added dropwise over a period of 3 hr. The mixture was heated under reflux for an additional hour and then cooled in an ice bath. Glacial acetic acid, 54 ml, was added followed by 180 ml of water. The aqueous phase was extracted with benzene, and the combined organic layers were washed with water, saturated brine, and then dried (Na_2SO_4). The solvent was removed at the rotary evaporator leaving a crude yellow oil. Distillation at 0.2 mm gave two fractions: (A) from 69-72°, 13.69 g (22.4%) and (B) from 75-77°, 18.16 g (30%). (A) was a mixture of XII and XIII and (B) was pure XIII. Compound XII was isolated in pure form by preparative glc.

glc data: 20% Apiezon-L 6' x 1/4" steel column

T = 170° flow rate = 25 ml/min

	retention time (min)
XII	9
XIII	12

Data for Compound XII

IR: $\lambda_{max}^{CHCl_3}$ 5.75, 5.85μ

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NMR: Description	Chemical Shift, $\tau^{CDCl_3}_{ppm}$	Approximate Area
complex	7.92	3
singlet	7.85	3
complex	7.2-7.7	2
complex	6.4-6.7	1
singlet	6.30	3
complex	4.4-4.7	1

Mass Spectrum: Calc'd for $C_9H_{13}ClO_3$

p = 204

p + 2 = 206

Base Peak = 43

Data for Compound XIII

IR: $\lambda^{CHCl_3}_{max}$ 5.75, 5.85μ

NMR: Description	Chemical Shift, $\tau^{CDCl_3}_{ppm}$	Approximate Area
complex	7.90	3
complex	7.2-7.8	4
singlet	6.65	1.2
singlet	6.30	3
singlet	5.05	0.4
complex	4.3-4.7	1
singlet	-2.10	0.4

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Analysis: Calc'd for $C_9H_{13}ClO_3$: C, 52.82; H, 6.40

Found: C, 53.05; H, 6.59

Mass Spectrum: Calc'd for $C_9H_{13}ClO$

p = 204

p + 2 = 206

Base Peak = 102

6. Reaction of I with XIII. Preparation of XIV and XV

A solution of 0.5865 g (.015 m) of freshly cut potassium in 80 ml of anhydrous t-butyl alcohol was treated with 15.33 g (.075 m) of XIII. To the stirred solution was added, dropwise over a 45-min period, a solution prepared from 14.55 g (.075 m) of undistilled I in 40 ml of anhydrous t-butyl alcohol. The reaction mixture was stirred at room temperature for 30 hr.

Concentrated hydrochloric acid was added dropwise with stirring until the solution had a pH = 2. The solvent was removed at the rotor evaporator leaving 30.68 g of viscous oil. A solution of the oil in 600 ml of glacial acetic acid was heated to 90°, 30 g of p-toluene sulfonic acid added and the temperature was maintained at 90° for 4 hr. The solution was concentrated under reduced pressure; 300 ml of chloroform was added and the organic layer was washed several times with water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 26.821 g of a viscous orange oil. Column chromatography of the crude oil on 850 g of silica gel using chloroform as eluting solvent afforded 3.92 g (14%) of XIV (mp = 134-135° ether-hexane) and as a semi-solid 9.35 g (41%) of XV.

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Recrystallization gave 6.62 g (29%) of XV (mp 96.0-96.5° ether-hexane).

Data for Compound XIV

IR: $\lambda_{max}^{CHCl_3}$ 5.78, 5.95μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	8.91	3
complex	6.7-8.8	12
[singlet]	[7.90]	[3]
complex	6.3-6.6	5
[singlet]	[6.05]	[3]
complex	4.3-4.7	1
singlet	2.30	1
singlet	-0.82	1

Mass Spectrum: Calc'd for $C_{20}H_{33}O_4Cl$

Molecular ion: 362

p + 2 peak: 364

Base peak: 362

Analysis: Calc'd for $C_{20}H_{33}O_4Cl$: C, 66.20; H, 6.38

Found: C, 66.01; H, 6.57

Melting Point: 134-135°

UV: λ_{max}^{EtOH} 217 mμ (ε = 39,800)

252 mμ (ε = 10,200)

320 mμ (ε = 4,850)

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Data for Compound XV

IR: $\lambda_{max}^{CHCl_3}$ 5.75, 6.05, 6.15μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	8.79	3
complex	8.0-8.7	3
singlet	7.90	3
complex	6.9-7.7	9
doublet	6.7	2
complex	4.7-4.8	1

Analysis: Calc'd for $C_{18}H_{21}ClO_2$: C, 70.92; H, 6.94

Found: C, 71.16; H, 7.05

Mass Spectrum: Calc'd for $C_{18}H_{21}ClO_2$

p = 304

p + 2 = 306

Base peak = 269

High Resolution Mass Spectrum[1]

Standard PFK: 269

measured m/e	Identity	calculated m/e
269.1543	$C_{18}H_{21}O_2$	269.1542

UV: λ_{max}^{EtOH} 308 mμ (ε = 18,200)

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[1]Sample run by Jim Boal of Mellon Institute.

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7. Reaction of Di-t-Butyl Malonate with 1,3-Dichloro-2-butene.

Preparation of XVI

A solution of 7.82 g (0.2 m) of freshly cut potassium in 500 ml of t-butyl alcohol was treated with 43.2 g (0.2 m) of di-t-butyl malonate.[1] To the refluxing solution was added, dropwise over a 2-hr period, a solution prepared from 25.0 g (0.2 m) of 1,3-dichloro-2-butene in 60 ml of t-butyl alcohol. The reaction was allowed to heat at reflux for 2 hr. The t-butyl alcohol was removed under reduced pressure and the residue was vacuum distilled through a seven-inch Vigereaux column.

After a forerun of 7.88 g (18%) of di-t-butyl malonate, bp 42°/.15 mm, the product distilled, giving 41.63 g (68%) of clear liquid, bp 91-93°/0.15 mm.

Data for Compound XVI

IR: $\lambda_{max}^{CCl_4}$ 5.75μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	8.10	18
singlet (broad)	7.95	3
complex	7.3-7.7	2
triplet	6.93	1
complex	4.4-4.7	1

[1] C. Ratta, Org. Syn., 30, 20 (1950).

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8. Reaction of XVI with p-Toluenesulfonic Acid. Preparation of XVII

A solution prepared from 600 ml of toluene, 41.63 g (0.203 m) of XVI and 0.4 g of p-toluenesulfonic acid was heated (10 hr) at reflux until evolution of gas ceased. The solvent was removed under reduced pressure and the brown solid residue was subjected to vacuum distillation through a 7-inch Vigereaux column. The product distilled as a clear oil, bp 120-124°/10 mm, giving 16.84 g (56%) of XVII.[1]

Data for Compound XVII

IR: $\lambda_{max}^{CCl_4}$ 3.03-4.00, 5.85μ

NMR:

Description	Chemical Shift, τ_{ppm}^{neat}	Approximate Area
singlet (broad)	7.90	3
complex	7.4-7.8	4
complex	4.3-4.7	1
singlet	-2.16	1

9. Reaction of XVII with Oxalyl Chloride. Preparation of XVIII

The method of Adams and Ulrich[2] for the preparation of acid chlorides was used with modification.

A solution prepared from 5.3783 g (0.0362 m) of XVII in 15 ml of anhydrous benzene, was treated with 12.60 g (0.0901 m) of oxalyl

---

[1] O. Wichterle, Coll. Czech. Chem. Communs., 12, 93 (1947).

[2] R. Adams and L. Ulrich, J. Am. Chem. Soc., 42, 599 (1920).

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chloride. The reaction was allowed to stir at room temperature for five hr. The solvent and excess oxalyl chloride were removed at reduced pressure leaving 6.08 g (≈ 100%) of a clear brown liquid. Anhydrous ether, 50 ml, was added and the solution was used immediately in the subsequent step.

Data for Compound XVIII

IR: $\lambda_{max}^{CCl_4}$ 5.55μ

10. Reaction of XVIII with t-Butyl Acetoacetate. Preparation of XIX and XX

The sodium salt of t-butyl acetoacetate was prepared by dropwise addition of 6.8846 g (0.0435 m) of t-butyl acetoacetate in 10 ml of ether to 1.0440 g (0.0435 m) of sodium hydride in 200 ml of ether. This salt was treated with 7.2645 g (0.0435 m) of freshly prepared XVIII in 50 ml of ether. The reaction was allowed to stir at room temperature for 18 hr. The salt was removed by filtration and the ether was evaporated under reduced pressure leaving 11.4212 g of viscous oil, XX. This oil was dissolved in 50 ml of ether, cooled to 5° in an ice-water bath, and anhydrous ammonia was bubbled through the reaction for 0.5 hr.[1] The ether layer was washed with water and then dried (calcium chloride). Removal of the solvent under reduced pressure gave 6.2848 g of a crude liquid.

Vacuum distillation gave 2.490 g (36%) of t-butyl acetoacetate (bp 65-70°/1.25 mm) and 1.890 g (17%) of XX.

---

[1] E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko and A. Tahara, J. Am. Chem. Soc., 86, 2038 (1964).

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Data for Compound XX

IR: $\lambda_{max}^{CHCl_3}$ 5.75, 5.85μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	8.56	9
complex	7.9-8.0	3
complex	7.2-7.8	4
singlet	6.75	2
complex	4.3-4.6	1

Analysis: Calc'd for $C_{12}H_{19}Cl$: C, 58.41; H, 7.76

Found: C, 58.34; H, 7.67

Mass Spectrum: Calc'd for $C_{12}H_{19}Cl$ m/e = 246

Parent peak = absent

Major peaks = 146, 89, 57

Base peak = 43

11. Reaction of XX with I. Preparation of XV

A solution of 0.044 g (1.17 mmoles) of freshly cut potassium in 12 ml of anhydrous t-butyl alcohol was treated with 1.450 g (5.88 mmoles) of XX. To the stirred solution was added dropwise over a 45-min period a solution prepared from 1.141 g (5.88 mmoles) of distilled I in 8 ml of anhydrous t-butyl alcohol. The reaction mixture was stirred at room temperature for 18 hr.

Concentrated hydrochloric acid was added dropwise with stirring until the solution had a pH = 2. The solvent was removed

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on the rotary evaporator leaving 2.59 g of a viscous oil. A solution of the oil in 14 ml of glacial acetic acid was heated to 78°, 2.60 g of p-toluenesulfonic acid added and the temperature was maintained at 78° for 2 hr. The solution was concentrated under reduced pressure; 30 ml of chloroform was added and the organic layer was washed several times with water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 1.85 g of a viscous orange oil. Column chromatography of the crude oil on 60 g of silica gel using chloroform as eluting solvent afforded, as an oil 0.91 g of XV in 51% yield.

12. Reaction of Dimethyl Acetonedicarboxylate with 1,3-Dichloro-2-butene. Preparation of XXI

A solution of 1.104 g (.0481 m) of freshly cut sodium in 50 ml of absolute methanol was treated with 8.3770 g (.0481 m) of dimethyl acetonedicarboxylate. To the refluxing solution was added dropwise over 2 hr, a solution prepared from 6.0125 g (.0481 m) of 1,3-dichloro-2-butene in 10 ml of absolute methanol. The reaction mixture was allowed to reflux overnight.

Filtration to remove sodium chloride and evaporation of the solvent under reduced pressure left 11.29 g of a crude yellow oil. Fractional distillation of the oil gave 2.0766 g (24%) of starting material, bp 67-72°/.05 mm; 3.12 g (24%) of product, bp 104-113°/.05 mm; and 2.8258 g of dialkylated material, bp 120-140°/.05 mm.

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Data for Compound XXI

IR: $\lambda_{max}^{HCCl_3}$ 5.75; 5.85 (shoulder); (6.05, 6.15) weak

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet (borad)	7.90	3
complex	7.2-7.6	2
singlet	6.45	1.5
overlapping singlets	6.2-6.4	7
singlet	4.90	0.25
complex	4.4-4.7	1
singlet	-2.10	0.25

Analysis: Calc'd for $C_{11}H_{15}ClO_5$: C, 50.29; H, 5.75

Found: C, 50.47; H, 5.76

13. Reaction of XXI with I. Preparation of XV

A solution of 0.0345 g (0.73 mmoles) of freshly cut potassium in 8 ml of anhydrous t-butyl alcohol was treated with 0.9813 g (3.67 mmoles) of XXI. To the stirred solution was added dropwise over a 45-min period a solution prepared from 0.7119 g (3.67 mmoles) of distilled I in 4 ml of anhydrous t-butyl alcohol. The reaction mixture was stirred at room temperature for 40 hr.

Concentrated hydrochloric acid was added dropwise with stirring until the solution had a pH = 2. The solvent was removed on the rotary evaporator leaving 1.6774 g of a viscous oil. A solution of the oil in 20 ml of glacial acetic acid was heated to 90°;

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1.7 g of p-toluenesulfonic acid was added and the temperature was maintained at 90° for 9 hr. The solution was concentrated under reduced pressure; 50 ml of chloroform was added and the organic layer was washed several times with water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 1.2297 g of a viscous orange oil. Column chromatography of the crude oil on 30 g of silica gel using chloroform as eluting solvent afforded, as an oil, 0.2005 g of the desired product in 18% yield.

14. Preparation of Di-t-butyl Acetonedicarboxylate [XXII]

A 150 ml stainless steel bomb was cooled in a dry ice-acetone bath, care being taken to prevent the condensation of moisture in the bomb. Ten grams (.06849 m) of freshly prepared acetonedicarboxylic acid[1,2] was placed in the bottom of the bomb and covered with 120 ml of isobutylene. One ml of concentrated sulfuric acid was added slowly and the bomb was quickly sealed. The bomb was mechanically shaken at room temperature for 26 hr. The bomb was cooled in a dry ice-acetone bath, opened, and the contents poured into 150 ml of anhydrous ether. The ether layer was washed twice with water, once with sodium bicarbonate, and then twice with water. Removal of the ether on the rotary evaporator gave 15.95 g (90%) of a white solid. The solid was recrystallized from hexane, mp 58-59°.

Data for Compound XXII

IR: $\lambda_{max}^{CCl_4}$ 5.75, 5.85μ

---

[1] R. Adams, H. M. Chiles and C. F. Rassweiler, Org. Syn., Coll. Vol., 1, 10 (1941).

[2] Lower yields were obtained if this compound was not used immediately.

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NMR: Description	Chemical Shift, $\tau^{CCl_4}_{ppm}$	Approximate Area
singlet	8.55	18
singlet	6.52	4

Mass Spectrum: Calc'd for $C_{13}H_{22}O_5$ m/e = 258

Molecular ion: absence

Major peaks: 175, 111, 57, 43

Base peak: 57

Analysis: Calc'd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58

Found: C, 60.30; H, 8.69

15. Reaction of Di-t-butyl Acetonedicarboxylate with 1,3-Dichloro-2-butene. Preparation of XXIII

A solution of 1.564 g (.04 m) of freshly cut potassium in 100 ml of t-butyl alcohol was treated with 10.320 g (.04 m) of di-t-butyl acetonedicarboxylate. To the refluxing solution was added over a two-hr period a solution prepared from 5.000 g (.04 m) of 1,3-dichloro-2-butene in 20 ml of t-butyl alcohol. The reaction was allowed to reflux overnight. The reaction was allowed to cool and was then filtered removing 2.614 g of potassium chloride. Removal of the solvent under reduced pressure gave 13.165 g of an orange oil in 82% crude yield. A thin-layer chromatogram (Brinckman - silica gel) of the crude oil showed the presence of three compounds; RF - benzene; 0.15, 0.35, 0.60. These were shown to be starting material, mono-alkylated and dialkylated material, respectively. Attempts to purify

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the crude oil by vacuum distillation were unsuccessful due to decomposition. Column chromatography[1] on silica gel gave XXIII in 39% yield.

Data for Compound XXIII

IR: $\lambda_{max}^{CCl_4}$ 5.75; 5.85μ(shoulder); (6.05, 6.15μ) weak

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	8.57	18
singlet (broad)	7.90	3
complex	7.2-7.6	2
complex	6.4-6.6	3
complex	4.4-4.7	1

16. Reaction of XXIII with I. Preparation of XV

A solution of .0790 g (.002 m) of freshly cut potassium in 25 ml of anhydrous t-butyl alcohol was treated with 3.465 g (.01 m) of crude XXIII.[2] To the stirred solution was added dropwise over a 45-min period, a solution prepared from 1.94 g (.01 m) of undistilled I in 10 ml of anhydrous t-butyl alcohol. The reaction mixture was stirred at room temperature for 18 hr.

Concentrated hydrochloric acid was added dropwise with stirring until the solution had a pH = 2. The solvent was removed

---

[1] This chromatographic separation was performed by Phillippa Heggs of these laboratories.

[2] Studies of this reaction using pure XXIII (see page 28) were conducted by Dr. Daniel Solomon of these laboratories.

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on the rotary evaporator leaving 5.47 g of a viscous oil. A solution of the oil in 25 ml of glacial acetic acid was heated to 90°, 5.4 g of p-toluene sulfonic acid added and the temperature was maintained at 90° for 3 hr. The solution was concentrated under reduced pressure; 60 ml of chloroform was added and the organic layer was washed several times with water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo leaving 2.530 g of a viscous orange oil. Column chromatography of the crude oil on 50 g of silica gel using chloroform as eluting solvent afforded 1.365 g of the desired product (not crystallized) in 44% yield.

17. Reaction of XV with Sulfuric Acid. Preparation of XXIV

The procedure of J. A. Marshall[1] for the hydrolysis of enol chlorides was used with minor modifications. Concentrated sulfuric acid, 3 ml, was cooled to 0°C in an ice-water bath and then added directly to 0.2262 g (7.425 mmoles) of XV. The reaction was kept at 0° while a rapid stream of nitrogen was bubbled through the solution for 0.5 hr. The reaction was poured with stirring into 20 ml of crushed ice and water and the product was rapidly extracted with four 20 ml portions of ether. The combined ether extracts were washed with water until the washings were neutral to litmus and then dried over calcium chloride. Removal of the solvent under reduced pressure gave 0.130 g (61%) of a light yellow solid. The compound was recrystallized from ether-hexane, mp 146-147°.

---

[1] J. Marshall and D. Schaeffer, J. Org. Chem., 30, 3642 (1965).

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Data for Compound XXIV

IR: $\lambda_{max}^{CHCl_3}$ 5.75, 5.85, 6.05, 6.12μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	8.80	3
complex	7.9-8.8	4
singlet	7.9	3
complex	6.9-7.6	12

Mass Spectrum: Calc'd for $C_{18}H_{22}O_3$

Molecular ion: 286

Base peak: 286

UV: $\lambda_{max}^{ethanol}$ 308 mμ (ε = 17,200)

High Resolution Mass Spectrum:[1]

Standard PFK 281

measured m/e	Identity	calculated m/e
286.1564	$C_{18}H_{22}O_3$	286.1569

Analysis: Calc'd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74

Found: C, 75.76; H, 7.74

[1]Sample run by Jim Boal of Mellon Institute.

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18. Reaction of XV with Sulfuric Acid. Preparation of XXIV.

Method B

A solution prepared from 0.3045 g (1 mmole) of XV, dissolved in 15 ml of methylene chloride, was cooled to 0° in an ice-water bath. Ice cold sulfuric acid (3 ml) was added directly and the reaction was stirred at 0° for 0.5 hr. The reaction mixture was poured onto 30 g of crushed ice and the product was extracted with methylene chloride. The organic layer was washed with water until the washings were neutral and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 0.2700 g (94%) of XXIV (mp 146-147°, ether-hexane).

19. Reaction of XV with Methyl Iodide. Preparation of XXVI

Sodium hydride, 0.1200 g (2.58 mmoles)-(57% oil dispersion) was heated at 80° for one hour in 50 ml of anhydrous DMSO. The reaction was cooled to 35° and 0.8678 g (2.85 mmoles) of XV in 10 ml of DMSO was added directly. This reaction was allowed to stir for 10 minutes and a 2 molar excess of methyl iodide was added directly. The reaction was allowed to continue stirring at 35° for an additional 45 minutes. After being cooled to room temperature, the mixture was poured into 100 ml of 1:1 ether-hexane. The organic layer was washed three times with H_2O and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 1.0132 g of a crude oil. Column chromatography on 45 g of silica gel gave 0.4685 g (51%) of an oil (A) and 0.2941 g (39%) of starting material. Crystallization of oil (A) gave 0.1101 g (12%) of XXVI (mp 134° ether-hexane).

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Data for Compound XXVI

IR: $\lambda_{max}^{CHCl_3}$ 5.75, 5.85μ

NMR:

Description	Chemical Shift, τ ^{CDCl_3} ppm	Approximate Area
singlet	8.90	3
singlet	8.63	3
complex	8.3-8.6	} 15
singlet (borad)	[7.90]	[3] }
complex	4.1-4.3	1
complex	4.7-5.1	1

UV: λ_{max}^{EtOH} 244mμ (ε = 14,900)

Analysis: Calc'd for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27

Found: C, 71.76; H, 7.15

Mass Spectrum: Calc'd for $C_{19}H_{23}ClO_2$

Molecular ion	318
p + 2	320
Base peak	201

For discussion of the mother liquor of A, see page 34.

20. Preparation of XXVII

A solution of .06 g (2.5 mmole) of sodium hydride in 15 ml of dry monoglyme was treated with 4.32 g (.02 m) of di-t-butyl malonate. The reaction was heated under reflux for 1 hr. After this time 1.78 g (9.17 mmole) of I was added directly. Refluxing was continued for

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3.5 hr. After cooling, the reaction was made acidic by addition of several drops of concentrated hydrochloric acid. The solvent was removed under reduced pressure. To the residue was added 25 ml of glacial acetic acid and 4 g of p-toluenesulfonic acid. The mixture was heated under reflux for 37 hr. The acetic acid was removed under reduced pressure and 75 ml of anhydrous methanol was added to the residue. The reaction was heated under reflux for .5 hr and ca. 50 ml of methanol was removed by distillation. Fresh anhydrous methanol (50 ml) was added and refluxing was continued for 4.5 hr. After cooling, the methanol was removed under reduced pressure and the residue was dissolved in 100 ml of chloroform. The organic layer was washed with water until the washings were neutral to litmus. The solvent was removed leaving 2.465 g of a dark oil. Chromatography of this oil on 100 g of silicic acid gave 0.9190 g (40%) of the desired product as a clear oil which crystallized after being seeded[1] and cooled. Recrystallization from isopropyl ether gave 0.827 g of XXVII or 36% overall yield for the three steps.

Data for Compound XXVII

IR: $\lambda_{max}^{CHCl_3}$ 5.75 and 6.03μ

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[1] A sample of XXVII was generously provided by Dr. L. Velluz.

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NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	8.65	3
complex	6.7-8.4	12
singlet	6.3	3

Melting Point: 74-75° Reported 76°[1]

Mass Spectrum: Calc'd for $C_{14}H_{18}O_4$

Molecular ion 250

Base peak 250

---

[1] G. Nomine, G. Amiord and V. Torelli, Bull. Soc. Chim. France, 3664 (1968).

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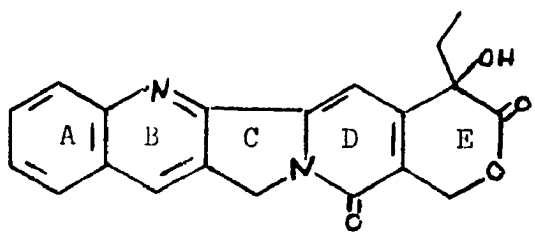
V. APPENDIX - A NEW SYNTHESIS OF UNSYMMETRICAL PHTHALIMIDINES

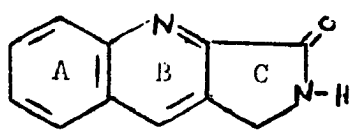
In 1966, Wall and co-workers[1] reported the structure elucidation of the novel alkaloid Camptothecin (1).



1

The antitumor and antileukemic properties exhibited by 1 on test animals aroused considerable medical interest. The lack of availability placed a high premium on its synthesis.

We thought that a reasonable approach to the synthesis of 1 might be to first construct the A, B, C ring system and then to add the remaining rings as one unit or in a multistep sequence. The quinoline-lactam, 2, seemed a likely choice for the A, B and C ring system.



2

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[1] M. Wall, M. Wani, C. Cook, K. Palmer, A. McPhail and G. Sim, J. Am. Chem. Soc., 88, 3888 (1966).

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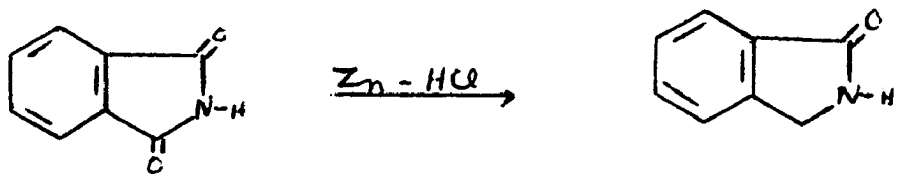
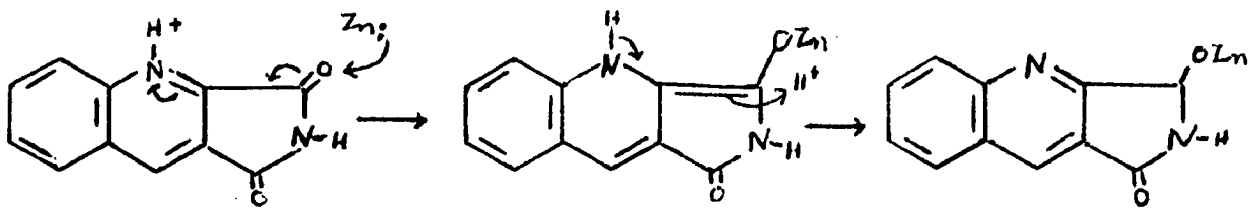
The common synthesis of phthalimidine involves the selective reduction of one of the carbonyl groups of phthalimide.[1]

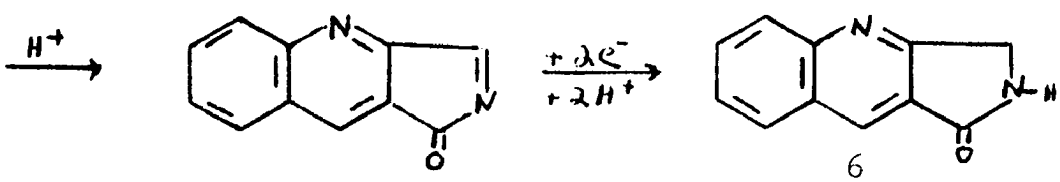


3 4

This method would hardly be satisfactory for our purposes. It would be reasonable to suppose that N-protonation would labelize the 2- rather than the 3-oxo group towards reduction.



5



6

If 2 was to be used in the synthesis of camptothecin, we needed a new method for the construction of the C ring. So in the hope that our results could be applied to the quinoline system, we attempted a new synthesis of phthalimidine. Our approach and a discussion of its successful execution are given below.

---

[1] K. Packendorff, Ber., 67, 907 (1934).

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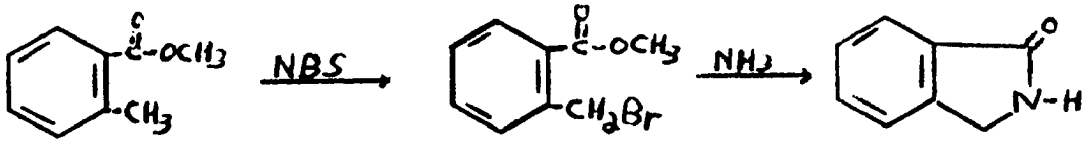
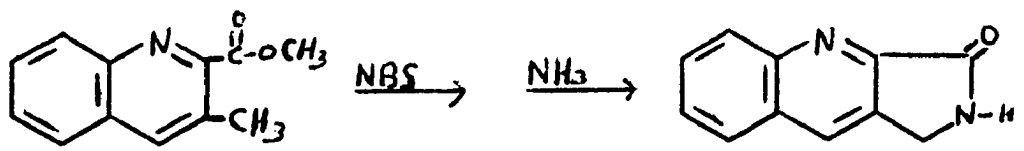


8 9 4

The methyl ester of o-toluic acid (8) was mono-brominated[1] to give a 6 to 1 mixture of the known methyl α-bromo-o-toluate[2] (9) and the starting material. This crude reaction mixture was dissolved in methanol and treated with anhydrous ammonia to give crystalline phthalimidine[3] (4) (mp 149-150°, H_2O) in 56% overall yield. Bryson[4] applied this method in the synthesis of 2.



2

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[1] L. Velluz, Substances naturelles de synthese, 7, 31 (1953).

[2] E. Eliel and D. Rivand, J. Org. Chem., 17, 1252 (1952).

[3] K. Packendorff, Ber., 67, 907 (1934).

[4] T. Bryson, Ph. D. Thesis, University of Pittsburgh, 1970.

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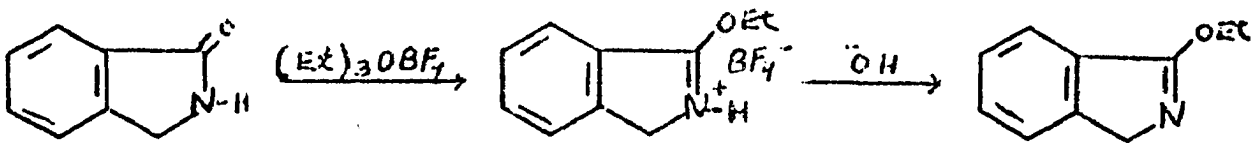
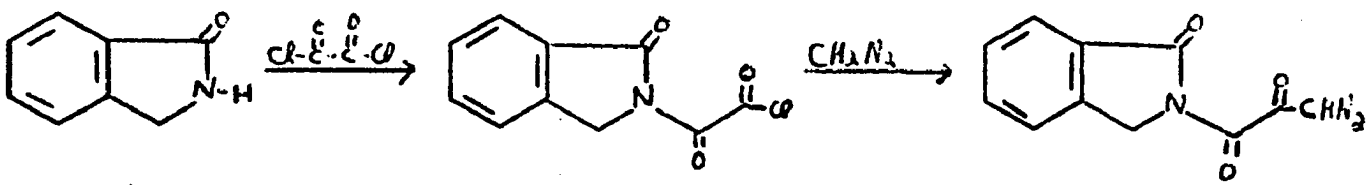
With a large supply of phthalimidine in hand, we felt that some preliminary model probes into the further elaboration of the Camptothecin nucleus might be profitably conducted. The results were to be applied to the problem of total synthesis of Camptothecin. The known imino ether of phthalimidine[1] (11) was prepared in 36% yield by reaction of 4 with triethyoxonium fluoroborate,[2] followed by neutralization of the resultant salt, 10.



4 10 11

Attempts to effect reaction of 11 with a variety of reagents (diethyl acetonedicarboxylate, ethyl acetoacetate, diethyl malonate, methyl magnesium chloride and methyl lithium) were in our hands unsuccessful, and this approach was discontinued.

A second approach, involving reaction at the nitrogen of phthalimidine, is illustrated below:



4 12 13

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[1] S. Petersen and E. Trietze, Ann., 623, 166 (1959).

[2] H. Meerwein, Org. Syn., 46, 113 (1966).

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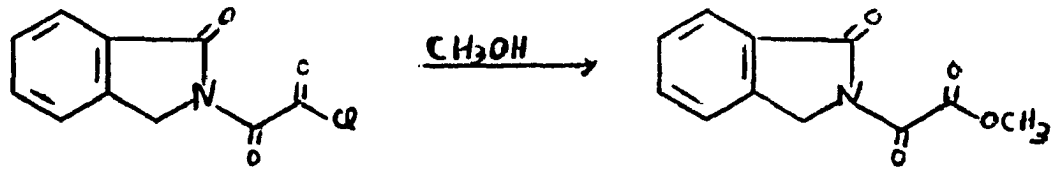

12 14

The crystalline acid chloride 12 (mp 116-118°) was prepared in 93% yield by reaction of phthalimidine with an excess of oxalyl chloride. The infrared spectrum shows maxima at 5.55, 5.70 and 5.85μ. The nmr consists of a singlet (2H) at τ 5.1 (methylene protons) and a complex signal (4H) at τ 1.5-2.7 (aromatic protons). Compound 12 was unstable and was treated directly with diazomethane[1] to give 13 (70%), as a white crystalline solid (mp 159-161° d). Structure was assigned on the basis of its elemental analysis and spectral properties. Its infrared spectrum exhibits maxima at 4.65, 5.70, 5.90 and 6.05μ. The nmr spectrum consists of a singlet (1H) at τ 6.4 (methine proton), a singlet (2H) at 5.1 (methylene protons), and a complex signal (4H) at τ 2.0-2.6.

Reaction of 12 with methanol gave crystalline 14 (69%) (mp 136-137°, benzene). The infrared spectrum contained maxima at 5.72 and 5.89μ. The nmr consist of a singlet (3H) at τ 6.03 (methyl ester), a singlet (2H) at τ 5.20 (methylene protons), and a complex signal (4H) at τ 1.9-2.1.

[1] J. A. Moore and O. E. Reed, Org. Syn., 41, 16 (1961).

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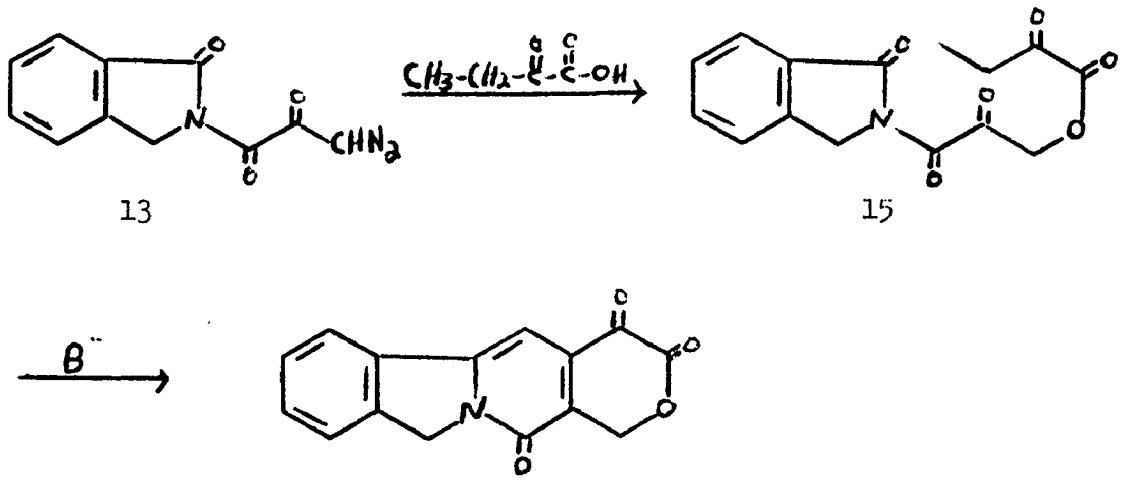
The envisioned use of compound 13 for the further construction of the Camptothecin nucleus is shown below.



13 15

Reaction of 13 with 2-oxobutyric gave a complex mixture of questionable identity which did not lend itself to purification in our hands. Treatment of the crude mixture with acid gave no recognizable products except for phthalimidine.

1. Preparation of Methyl-o-toluate

To a solution prepared from 500 g (3.4 m) of o-toluic acid and 1500 ml of absolute methanol was added 15 ml of concentrated sulfuric acid. The solution was heated under reflux for 2 hr and then allowed to cool. The solution was decanted into a separatory funnel containing 1 liter of methylene chloride. One liter of water was added, the mixture shaken and the organic layer separated. The organic layer was washed once with water, twice with a 5% solution of sodium carbonate, and then once with water. The organic layer

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was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Distillation of the residue at atmospheric pressure gave 419 g (82%) of 8 from 210-212°.

Data for Compound 8

IR: $\lambda_{max}^{CCl_4}$ 5.99μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	7.45	3
singlet	6.25	3
complex	2.6-3.1	3
complex	2.0-2.2	1

2. Reaction of 8 with N-Bromosuccinimide.[1] Preparation of Methyl α-Bromo-O-toluate [9]

A solution prepared from 45 g (0.3 m) of 8, 57 g (0.32 m) of N-bromosuccinimide, 0.6 g of dibenzoyl peroxide and 180 ml of CCl_4 was heated under reflux for 4 hr. The reaction mixture was cooled and then filtered to remove the succinimide. Removal of the solvent gave 62.0 g (93%) of an orange oil. This oil was shown to consist of 6:1 of phthalimidine: starting material by nmr and was used in the subsequent step without purification.[2]

---

[1] L. Velluz, Substances naturelles de synthèse, 7, 31 (1953).

[2] Pure 9 was previously prepared by E. Elicl and D. Rivand, J. Org. Chem., 17, 1252 (1952).

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Data for crude 9

IR: $\lambda_{max}^{CCl_4}$ 5.99μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CCl_4}$	Approximate Area
singlet	7.45	0.5
singlet	6.20	2.0
singlet	5.10	3.5
complex	2.6-2.9	2.3
complex	2.0-2.2	1.2

3. Reaction of 9 with Ammonia. Preparation of Phthalimidine [4]

A solution prepared from 62 g (0.2 m of 9 based on nmr of the residue from the previous experiment) in 250 ml of methanol and 75 ml of concentrated ammonium hydroxide was heated under reflux for 2 hr. During this time anhydrous ammonia was bubbled into the medium. The reaction was allowed to cool and the solvent was removed under pressure. The white crystalline residue was washed with H_2O and then ether and allowed to air dry, giving 20.2 g (56%) of phthalimidine (mp 149-150° recrystallized from H_2O).[1]

Data for Compound 4

IR: $\lambda_{max}^{CHCl_3}$ 5.89μ

---

[1]The melting point of phthalimidine was reported as 150° by K. Packendorff, Ber., 67, 907 (1934).

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NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	5.52	2
complex	2.3-2.7	3
complex	2.0-2.3	1

4. Reaction of Phthalimidine with Oxalyl Chloride. Preparation of 12

A solution prepared from 7.98 g (.06 m) of phthalimidine in 400 ml of benzene was added dropwise over a .5 hr period to 15.3 g (.12 m) of oxalyl chloride in 410 ml of benzene. The reaction was allowed to stir for 14 hr at room temperature. The solvent was removed under reduced pressure and the yellow crystalline residue was washed with CCl_4 and collected by suction filtration. Yield of crude 12, 12.42 g (93%) (mp 116-118°).[1]

Data for Compound 12

IR: $\lambda_{max}^{CH_2Cl_2}$ 5.55, 5.70, 5.85μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	5.1	2
complex	1.5-2.7	4

[1] Compound 12 decomposes on standing.

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5. Reaction of 12 with Diazomethane. Preparation of 13

A solution prepared from 3.99 g (.030 m) of 12 in 200 ml of ether was added dropwise over a 1 hr period to diazomethane (.046 m) in 250 ml of ether.[1] Addition was made at 0° and the reaction was stirred for 10 minutes after addition was complete. A few drops of acetic acid were added to neutralize the excess diazomethane, and the crystalline product was removed by filtration giving 4.80 g (70%) of 13, mp 159-161 ($CHCl_3$-CCl_4).

Data for Compound 13

IR: $\lambda_{max}^{CH_2Cl_2}$ 4.65, 5.70, 5.90, 6.05μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	6.4	1
singlet	5.1	2
complex	2.0-2.6	4

Analysis: Calc'd for $C_{11}H_7N_3O_3$: C, 57.65; H, 3.08; N, 18.33

Found: C, 57.81; H, 3.20; N, 18.10

6. Reaction of 12 with Methanol. Preparation of 14

Compound 12, 0.2235 g (1 mmole), was shaken with 10 ml of anhydrous methanol. The resulting crystals were removed by filtration giving 0.150 g (69%) of 14 (mp 136-137°, benzene).

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[1] J. A. Moore and D. E. Reed, Org. Syn., 41, 16 (1961).

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Data for Compound 14

IR: $\lambda_{max}^{CHCl_3}$ 5.72, 5.89μ

NMR:

Description	Chemical Shift, $\tau_{ppm}^{CDCl_3}$	Approximate Area
singlet	6.03	3
singlet	5.20	2
complex	1.9-2.1	4

Analysis: Calc'd for $C_{11}H_9NO_4$: C, 60.28; H, 4.14

Found: C, 60.13; H, 4.25

Melting Point: 136-137°.

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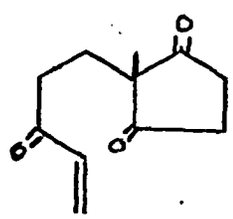
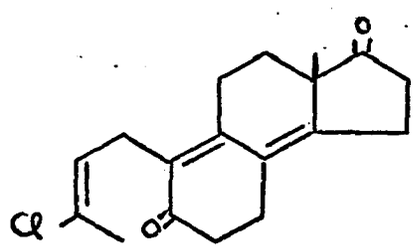
SUMMARY

A study of the reaction of compound I with a variety of nucleophiles has resulted in several closely related syntheses of XV, a compound of relevance to steroid synthesis. The synthetic utility of XV was illustrated by its conversion to XXV, which constitutes a formal synthesis of $8^{(14)}$-dehydroestrone. Compound XV was methylated to give XXVI, opening a possible route to other steroid compounds. A new synthesis of XXVIII, an important intermediate in the Rousel-Uclaf synthesis of steroids, was developed via compound I.

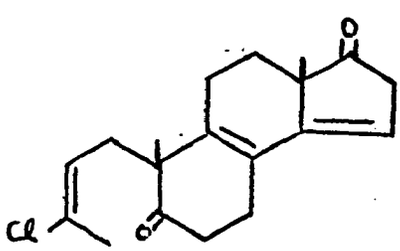
A method for the synthesis of unsymmetrical phthalimidines was developed.



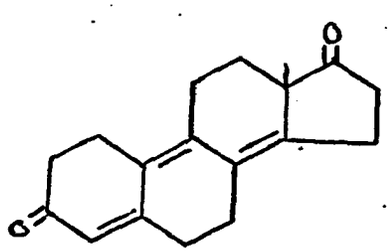
I



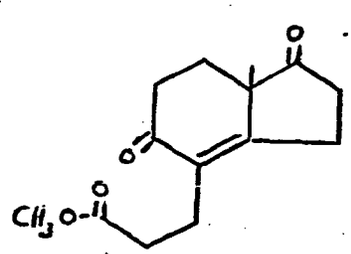
XV



XXVI



XXV



XXVIII

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