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SUBSTITUTED PIPERAZINES

AS POTENTIAL SCHISTOSOMICIDES

by

Carmen Maria Mercado

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in
The University of Michigan
1970

Doctoral Committee:

Professor Joseph H. Burckhalter, Chairman
Associate Professor Daniel T. Longone
Professor Joseph E. Sinsheimer
Professor Henry H. Swain

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ABSTRACT

SUBSTITUTED PIPERAZINES
AS POTENTIAL SCHISTOSOMICIDES

by

Carmen Maria Mercado

Chairman: Joseph H. Burckhalter

The synthesis of analogs of 1-methyl-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine has been described. The purpose of the research for this dissertation was preparation of compounds which might possess antiparasitic effects, especially against schistosomiasis and malaria. The following compounds were prepared: 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)acetyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)phenyl]piperazine, 4-(7-chloro-4-quinolylamino)-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol, 1-(3-chloro-4-methylphenyl)-4-(7-chloro-4-quinolyl)piperazine, and 4-[5-(7-chloro-4-quinolylamino)-2-thenoyl]-1-methylpiperazine. N-(5-Nitrothiazol-2-yl)-α-(1-methyl-4-piperazino)-acetamide and N-(5-nitrothiazol-2-yl)-β-(1-methyl-4-piperazino)propionamide. Mannich bases of special interest were also prepared: 4-acetamido-α-(3-chloro-4-methylanilino)-o-cresol, α-(3-chloro-4-methylanilino)-2,4-dimethyl-o-cresol and α-anilino-2,4-dimethyl-o-cresol.

Attempts to prepare 1-(3-chloro-4-methylphenyl)-4-[3-(7-chloro-4-quinolylamino)propionyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)ethyl]piperazine, 4-[5-(7-chloro-4-quinolylamino)-2-furoyl]-1-methylpiperazine, 4-[6-(7-chloro-4-quinolylamino)-nicotinoyl]-1-methylpiperazine and 4-[3-(7-chloro-4-quinolylamino)-2-pyrazinoyl]-1-methylpiperazine were discussed.

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To my mother

CARMEN MARIA RIVERA

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ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to Professor Joseph H. Burckhalter for suggestion of the problem, and for his encouragement and helpful suggestions throughout this research.

I would like to thank Dr. Fortune Kohen and my fellow graduate students for their understanding and advice. Particular thanks go to the members of my committee and to Dr. Ljerka Polak.

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I. HISTORICAL INTRODUCTION

This section is intended only as a brief historical introduction to the disease schistosomiasis and the agents which have been used for its treatment. More detailed reviews have been made elsewhere.[1-5]

Schistosomiasis, also known as bilharziasis, continues to be endemic in a large part of the world. It affects from 180 to 200 million persons.[6] The infection is caused by a trematode of the genus Schistosoma of which mainly three species, Schistosoma mansoni, S. haematobium and S. japonicum are mainly responsible for the disease in man.

The severity and clinical picture presented by schistosomiasis depend on the species of schistosome. Although the parasites have similar life cycles, they differ in geographical distribution and in the organs which they affect. S. mansoni which is found both in Africa and in the Americas causes intestinal schistosomiasis. On the other hand, S. japonicum, the predominant species found in Asia, affects mainly the spleen and liver. The third species, S. haematobium, affects the organs of the urinary tract; it is found in Asia and Africa.

People become infected by exposure to water containing the infected snail. Then the cercariae penetrate man through the skin and eventually reach the liver where they remain until sexually mature. The male and female then pair up and migrate to the vessels of the intestines or the urinary tract. The eggs laid by the adult worm are excreted and upon contact with water hatch into miracidia which invade the intermediate host, a water snail. By asexual reproduction thousands of cercariae

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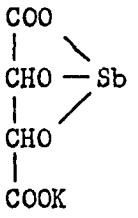
emerge from each miracidium. The cercariae are then shed by the snail, and the life cycle can start all over again.

Prevention of schistosomiasis has been attempted primarily in two ways. One way is by killing the snail with chemicals known as molluscicides.[7] Unfortunately, their use is subject to limitation because valuable water life and vegetation are also destroyed by the chemicals. The other way is by treatment of infected individuals. However, at present there is no ideal drug which is both curative and free from side effects.

The first useful drug for schistosomiasis was tartar emetic (1).



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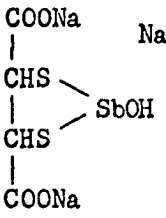

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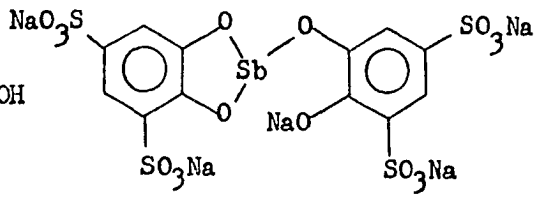

3

Two other organic antimonials customarily used in the treatment of schistosomiasis are Astiban (2) and Fuadin (3).[4] The tervalent antimony compounds, although toxic, are effective against all three species of schistosomes regardless of host. Their activity is due to inhibition of the enzyme, phosphofructokinase, which converts fructose-6-phosphate to fructose-1,6-diphosphate.[8] This results in a decrease in the formation of lactic acid, and thus, the reproduction and survival of the worm are impaired. Since both activity and toxicity of the organic antimonials depend on the amount of antimony, attempts to reduce their toxicity have failed.

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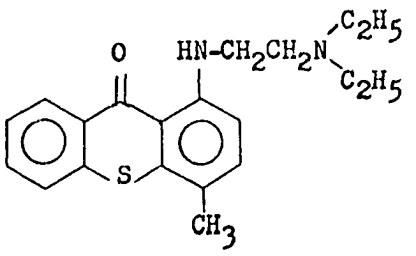
Non-metal containing drugs having oral activity against schistosomiasis have been developed. The first promising one was lucanthone (4). Lucan-



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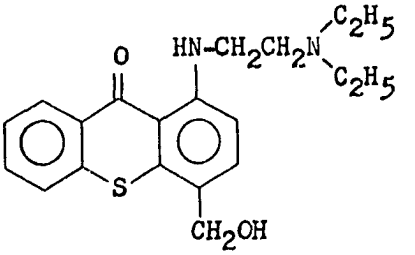
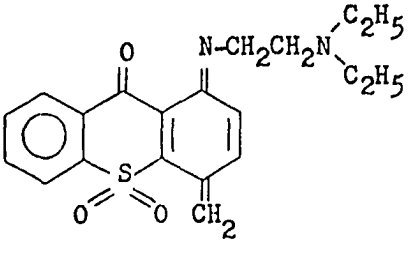


5

thone can be administered orally, but it is relatively toxic and is not effective in S. japonicum. A member of the miracil series, lucanthone, is thought to be hydroxylated in the host to the active metabolite, hycanthone (5).[9] Hycanthone besides being more active is less toxic than lucanthone.[10] Both compounds are currently used at least experimentally in the treatment of schistosomiasis.

Of further interest is the report that lucanthone is oxidized in the presence of a peroxidase enzyme to a p-quinoneazomethinemethene intermediate (6).[12] Thus, both 5 and 6 might play important roles in



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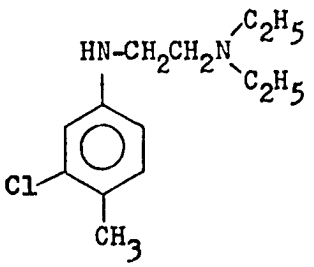
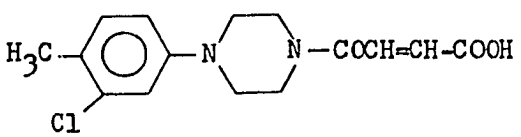
the mode of action of lucanthone.

Many analogs bearing the partial structure of lucanthone have been synthesized.[11] Of special interest is the mirasan series whose basic skeleton consits of the 3-chloro-p-toluidine moiety as exemplified by mirasan (7). It has been noted that a methyl group para to the dialkyl-



7

aminoalkylamino chain and a chloro or electron withdrawing group ortho to the methyl group are essential for activity. Replacement of the basic side chain of mirasan (7) by a piperazyl group led to compound S 688 (8) with prophylactic properties in mice.[11,13] Introduction of



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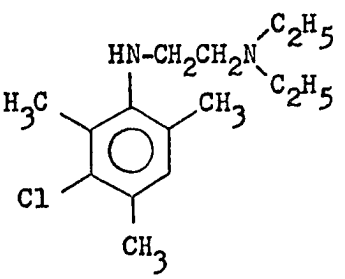

9

additional methyl groups at positions 2 and 6 of the benzene ring of

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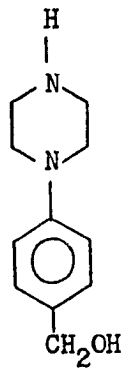
mirasan (e.g. 9), resulted in the same prophylactic effect.[11]

W. G. Duncan and D. W. Henry[14] synthesized analogs of 7 in which the chlorine atom was replaced by a phenyl ring or a substituted phenyl group. The resulting compounds were found to be inactive. Recently, Archer and coworkers[15] reported the schistosomal activity of xanthenones, 4-methyl-3-chloroanilines and their hydroxymethyl derivatives. In all cases, the hydroxymethyl derivative was more active than the methyl analog in Swiss mice and Syrian hamsters. Other compounds related to the mirasans have been synthesized and they exhibit antischistosomal activity. Compounds 10 to 12 are representative.[16,17,18] Unfortunately,



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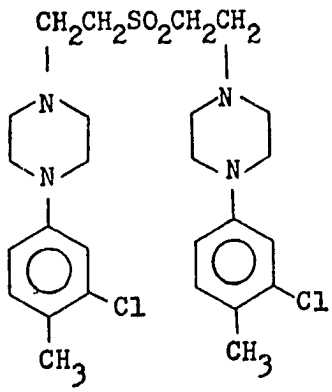

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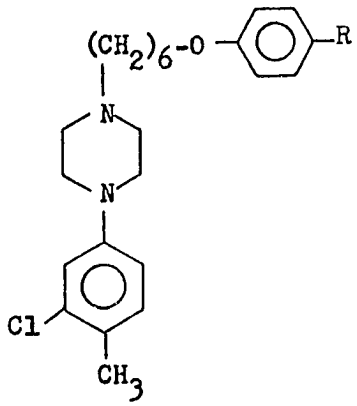

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the mirasans are not effective in human schistosomiasis.

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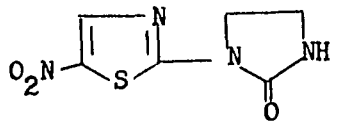
A promising new agent, niridazole (13), a 2-amino-5-nitrothiazole



13

derivative bearing no structural resemblance to lucanthone, has been recently introduced for treatment of schistosomiasis in humans.[4,19,20] Studies with niridazole have shown that the drug is taken up by the worm in the unchanged form and that metabolites representing the reduced drug accumulate in the parasite. Therefore, the presence of a nitro group is essential for activity.

Although niridazole is effective in impairing all three species of schistosome, it has the disadvantage of very serious central nervous system disturbances which include epileptiform seizures. This has prevented the use of niridazole on a wide basis.

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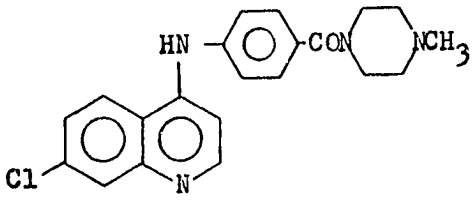
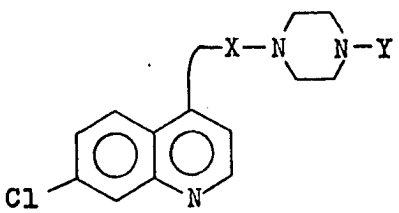
II. STATEMENT OF THE PROBLEM

1-Methyl-4-[4-(7-chloro-4-quinolylamino)-benzoyl]piperazine (14),



14

made in our laboratories,[21] was found to possess therapeutic activity in mice against both schistosomiasis and malaria. Therefore, the synthesis of analogs of 14 was undertaken; they possess the basic skeleton of 15 with modification of X or both X and Y. Since the mirasans, which



15

possess anti-schistosomal activity, all contain the 3-chloro-4-methylphenyl moiety, replacement of Y by this group was proposed. Thus, synthesis of compounds of type 16 to 22 was planned. These compounds are derivatives of the mirasans, especially of 8, with the additional presence of a 4-aminoquinoline group. In compounds 16, 17 and 18, the carbonyl group of 8 was kept, and in 19, 20 and 21, the carbonyl group was replaced by a methylene or benzene group as in 12 and 13. Compound 20 had precedence

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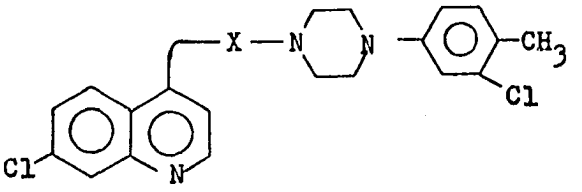
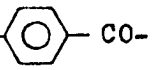
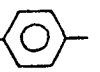


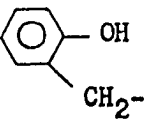
16 X = -HN-  -CO-

17 X = -HN-CH_2CO-

18 X = -HN-CH_2CH_2CO-

19 X = -HN-CH_2CH_2-

20 X = -HN- 

21 X = -HN- 

22 (X is a bond)

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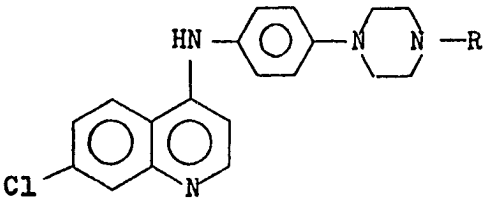
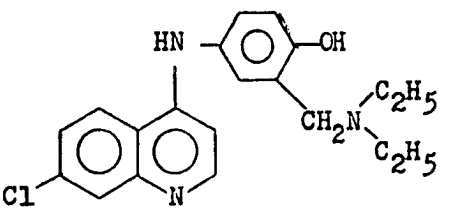
in the work of Loewe et al.[32] who synthesized 4-aminoquinoline derivatives of the following type. Their activity was shown to resemble that



of chloroquine, but the compounds were not active against chloroquine resistant strains of P. berghei in mice. The synthesis of compound 21 was undertaken where X is replaced by the 3-amino-6-hydroxybenzyl group, since amodiaquine (23), a potent antimalarial, possesses this group.



23

Further modifications of 14 were proposed in which the p-aminobenzamido moiety of 14 was to be replaced. It is known that p-amino-

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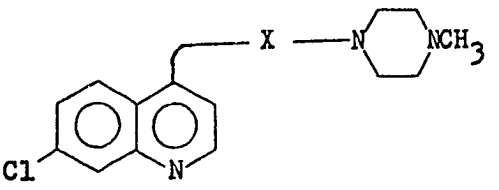
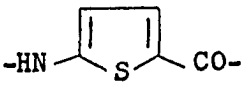
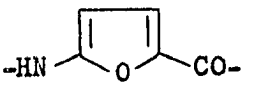
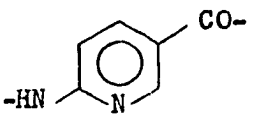
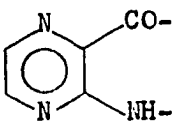
benzoic acid is necessary for the synthesis of folic acid by malarial parasites, and since the 2-amino-5-carboxylic acids of furan and thiophene are isoelectronic with p-aminobenzoic acid, the synthesis of compounds of type 24 and 25 was planned.



24 X = 

25 X = 

26 X = 

27 X = 

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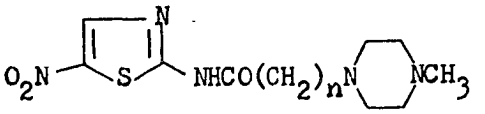
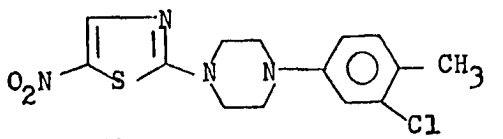
Such compounds might be expected to possess antiparasitic action because, with moieties which are isosteric with p-aminobenzoic acid, they may possess antimetabolic properties. Incorporation of other heterocycles such as pyridine and pyrazine in place of the benzene ring of the p-aminobenzamido group of 14 was also proposed, i.e. 26 and 27.

The broad spectrum of antiparasitic activity of the 2-amino-5-nitrothiazole nucleus, especially against schistosomiasis,[22,23] and the fact that niridazole (13) had potent activity against the three principal species of schistosome led to the study of a number of 5-nitrothiazole derivatives with different substituents at the 2-amino group. It seemed plausible that incorporation of the piperazine moiety would lead to active compounds, since piperazine derivatives are known for their effectiveness as anthelminthics in nematode infections; thus, the synthesis of compounds 28 to 30 was also undertaken.



28, n = 1
29, n = 2



30

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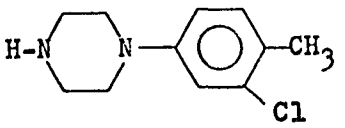
III. DISCUSSION AND RESULTS

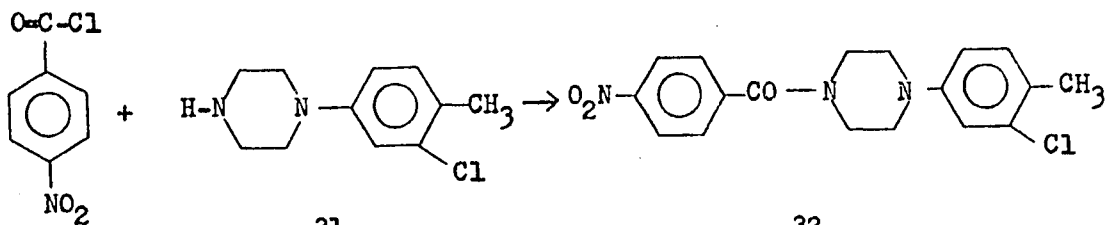
The desired 4-aminoquinolines were made by condensation of the appropriate amine with 4,7-dichloroquinoline (DCQ) according to the procedure of Surrey and Cutler.[24]

1-(3-Chloro-4-methylphenyl)piperazine (31), used throughout



31

this work, was obtained by heating diethanolamine with 3-chloro-4-methylaniline in 48% hydrobromic acid for 8 hr at 200°.[25] Synthesis of 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)benzoyl]-piperazine (16) was begun with the preparation of 1-(3-chloro-4-methylphenyl)-4-(4-nitrobenzoyl)piperazine (32) which was obtained in 78% yield



31 32

by treatment of 1-(3-chloro-4-methylphenyl)piperazine (31) with 4-nitrobenzoyl chloride in benzene solution at 0°. Subsequent reduction of 32 with

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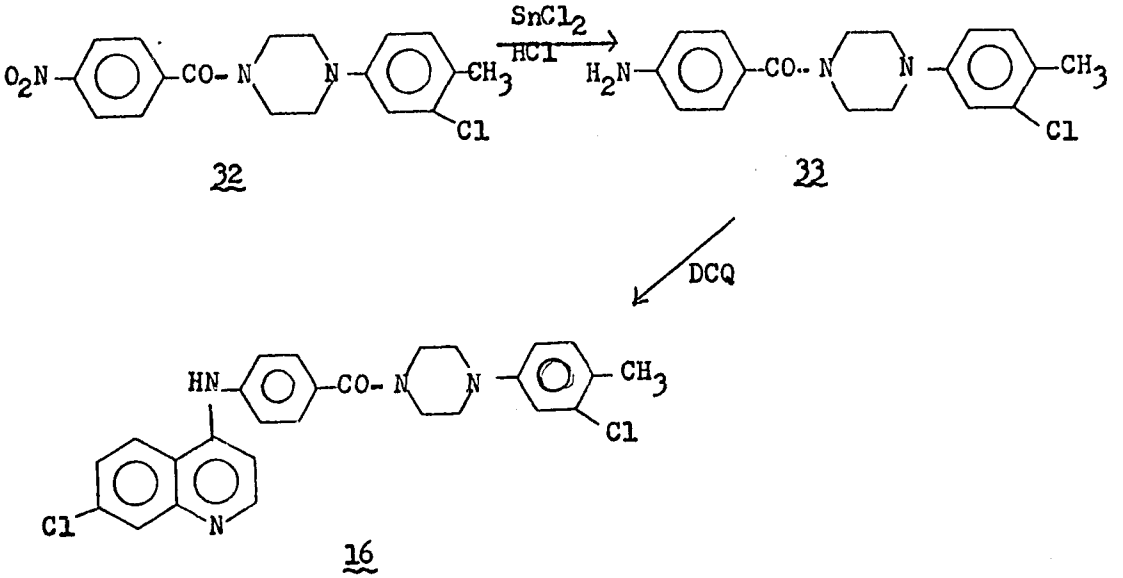
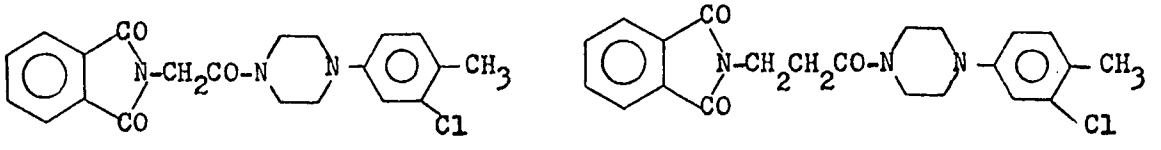
stannous chloride in concentrated hydrochloric acid[33] and condensation of 33 with DCQ at pH 4 gave the desired product 16 as the hydro-



32 33 16

chloride in almost quantitative yield. Neutralization with sodium bicarbonate afforded the free base. Reduction of 32 over platinum catalyst proved to be inadvisable because the aromatic chlorine atom was removed.

Compounds 34 and 35, serving as intermediates for the synthesis of



34 35

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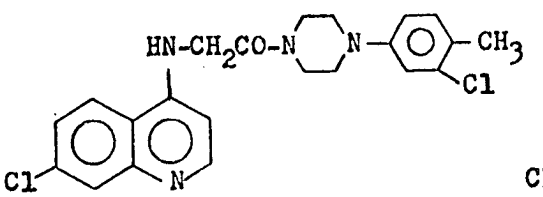
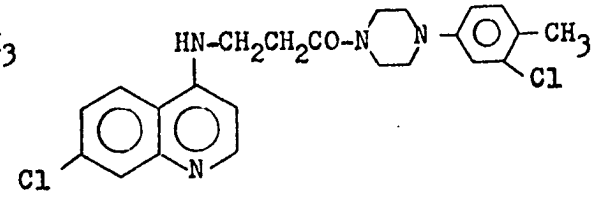
17 and 18, were prepared as follows. The amino function of the cor-

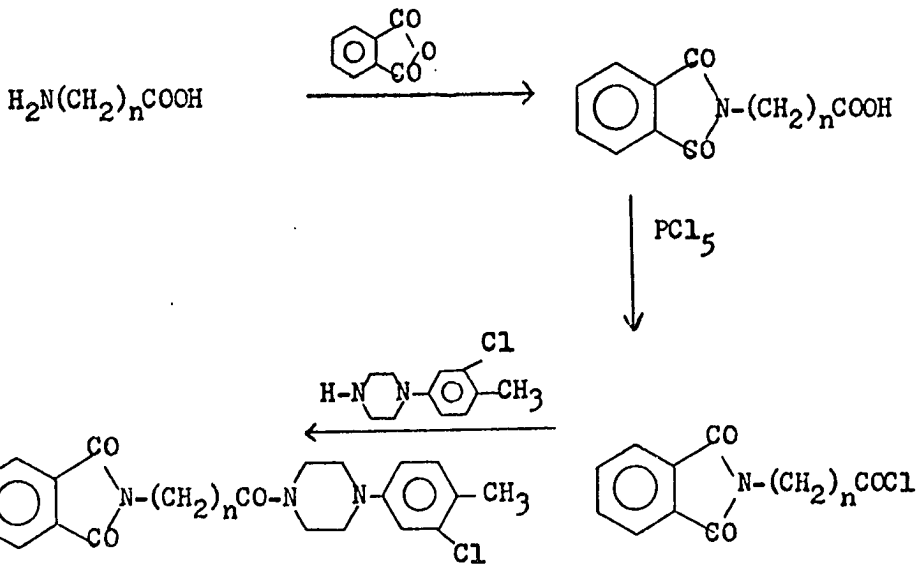


17



18

responding amino acids was protected by the phthaloyl group;[26] then



34, n = 1
35, n = 2

the acid chlorides[27,28] were prepared and reacted with 1-(3-chloro-4-methylphenyl)piperazine (31) to give 34 and 35 in 45% and 34% yields, respectively.

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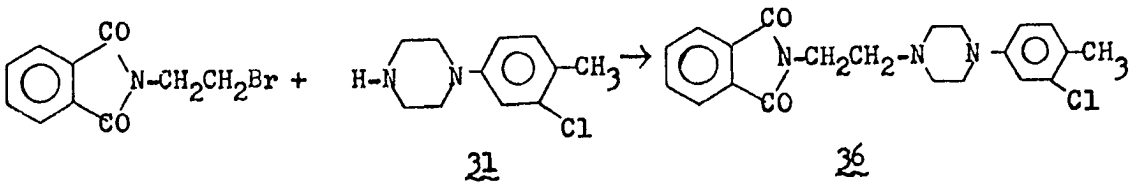
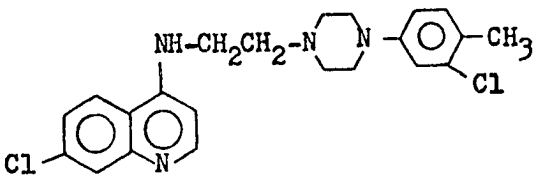
Compound 36, proposed as an intermediate leading to 19, was pre-



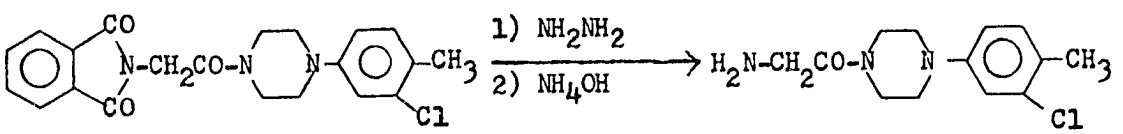
31 36



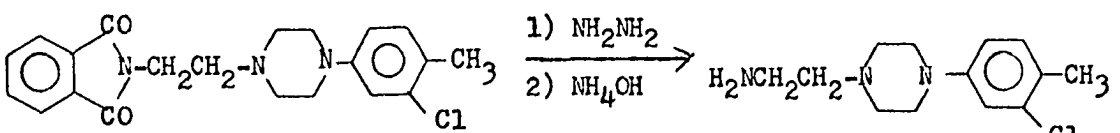
19

pared by refluxing β-bromoethylphthalimide with 31 in ethanol for sixteen hours. Addition of sodium bicarbonate and refluxing for four more hours gave 36 in 47% yield.

Removal of the phthaloyl group of 34 and 36 by means of hydrazine, followed by hydrolysis with ammonium hydroxide, led to the corresponding amines 37 and 38 in 94% and 44% yield, respectively. Compounds 37 and 38



34 37



36 38

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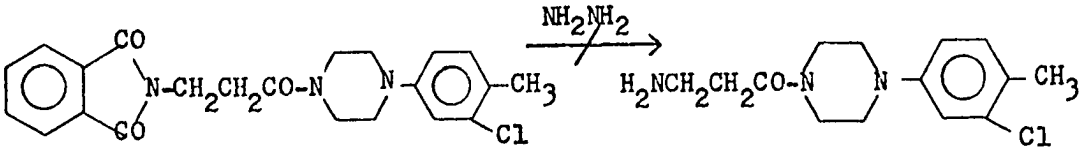
are low melting solids which could not be purified as the free bases due to their tendency to precipitate as oils. The trihydrochloride of 38 was then made, but 37 was used as such in the next reaction since the salt was hygroscopic.

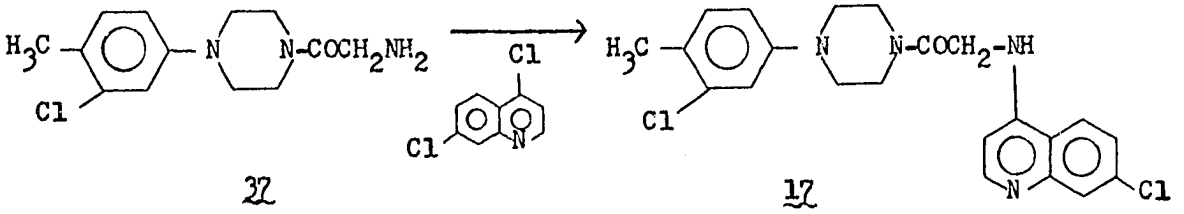
Attempts to hydrolyze compound 35 with hydrazine followed by



35

ammonium hydroxide were not effective because products of incomplete hydrolysis were obtained. Hydrolysis by means of hydrazine and hydrochloric acid[30] failed, since the piperazide bond was also broken. Therefore, synthesis of final compound 18 was not achieved.

Condensation of 37 with DCQ in phenol gave after neutralization



37 17

1-(3-chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)acetyl]piperazine (17) in 35% yield; however, under the same reaction conditions the

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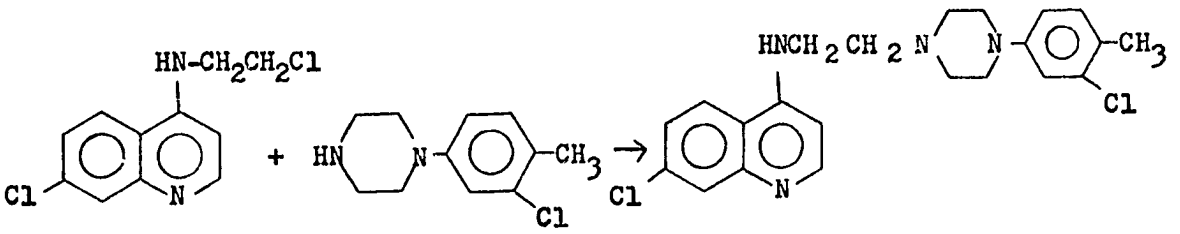
amine 38 failed to give the final product (19), and only starting material was recovered.

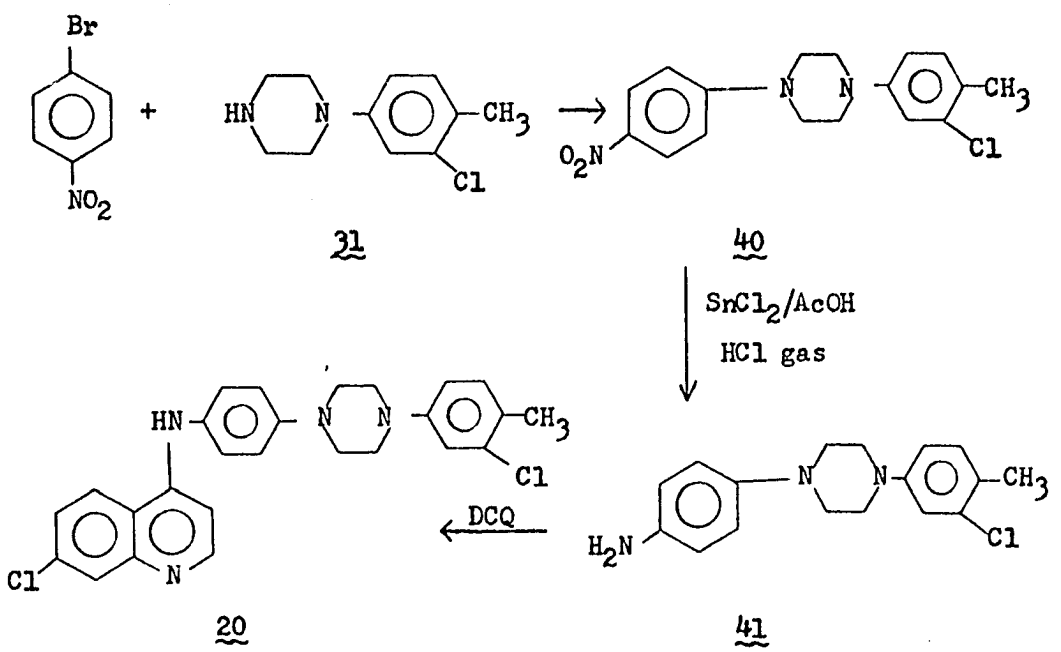
A different approach to 19 was then undertaken in which 39,



39 19

prepared according to Elderfield et al.,[31] was reacted with 1-(3-chloro-4-methylphenyl)piperazine (31) in an attempt to obtain 19. However, only the starting piperazine was recovered.

Synthesis of 20 was accomplished in the following way.



31 40 41 20

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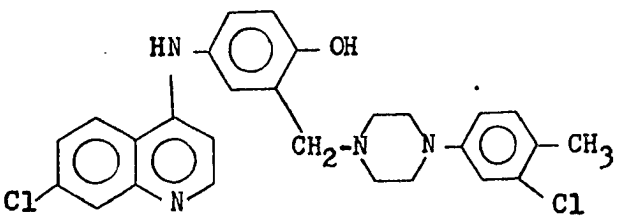
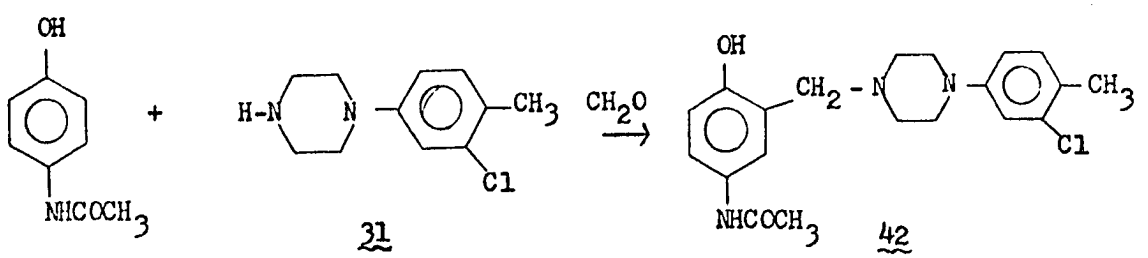
Condensation of 4-nitrobromobenzene with 1-(3-chloro-4-methylphenyl)-piperazine (31) by refluxing in pyridine gave 1-(3-chloro-4-methylphenyl)-4-(4-nitrophenyl)piperazine (40) in over 30% yield. When methanol was used as solvent in place of pyridine, starting material was recovered. Treatment of 40 with stannous chloride in acetic acid saturated with hydrogen chloride gas[32] gave 65% yield of 41; 41 was immediately condensed with DCQ to afford upon neutralization 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)phenyl]piperazine (20) in 65% yield. Reduction of 40 with stannous chloride in concentrated hydrochloric acid[33] gave only starting material.

Synthesis of 21 was attempted via a Mannich reaction as described by Burckhalter et al.[34] Reaction of 4-acetamido-



21

phenol with 1-(3-chloro-4-methylphenyl)piperazine (31)



31 42

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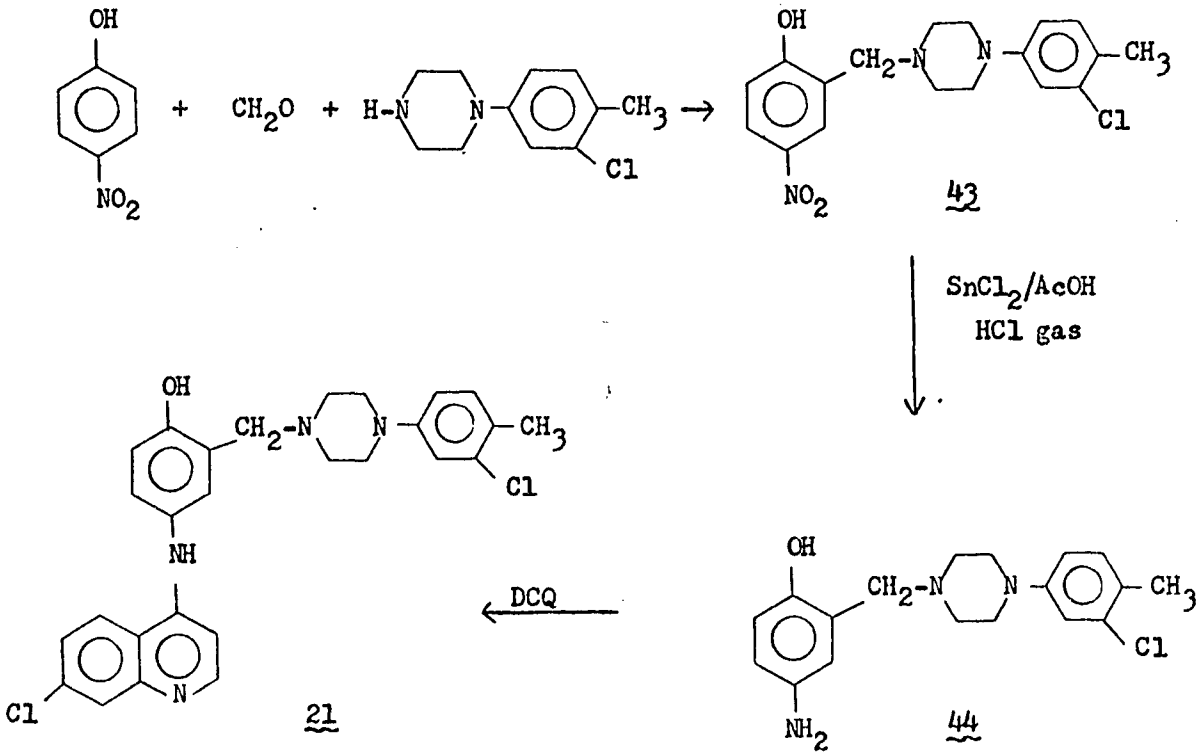
and paraformaldehyde gave intermediate 42. The crude product 42 was obtained in 50% yield. Hydrolysis of 42 with 20% hydrochloric acid[34] afforded a salt which was too hygroscopic, and the free base was too unstable to be isolated. Nevertheless, the hydrolysis mixture was treated with DCQ, the pH was adjusted to 4, and the mixture was heated, but neither the free base nor the salt of 21 could be obtained in pure form.

A different approach by means of 4-nitrophenol proved to be successful. Condensation of 4-nitrophenol, paraformaldehyde and 1-(3-chloro-4-methylphenyl)piperazine (31) in ethanol gave a product in 43% yield (crude) whose nmr spectrum is consistent with structure 43. Treatment of 43



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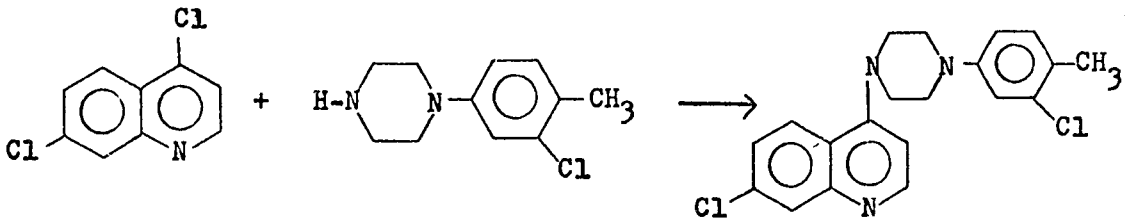
with stannous chloride in acetic acid saturated with hydrogen chloride gas[32] resulted in a 60% yield of 44. Condensation of 44 with DCQ at pH 4 in ethanol gave after basification with ammonium hydroxide the desired 4-(7-chloro-4-quinolylamino)-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol (21) in 56% yield. The amine 44 was difficult to identify since it appeared to be partially hydrated and the amine absorption was obscured in the nmr spectrum under the piperazine protons. D_2O exchange proved that the structure of 44 was correct and also the fact that condensation with DCQ gave 21 which analyzed correctly.

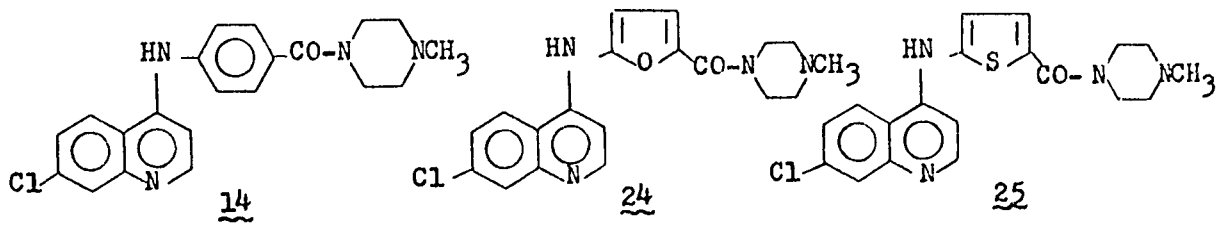
Synthesis of 1-(3-chloro-4-methylphenyl)-4-(7-chloro-4-quinolyl)-piperazine (22) was accomplished by coupling 1-(3-chloro-4-methylphenyl)-



31 22

piperazine (31) with DCQ in phenol. Neutralization with ammonium hydroxide gave 22 in 65% yield.

Furan and thiophene carboxylic acid analogs (24 and 25) of 14 were



14 24 25

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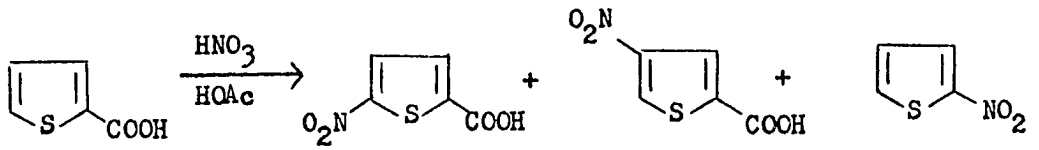
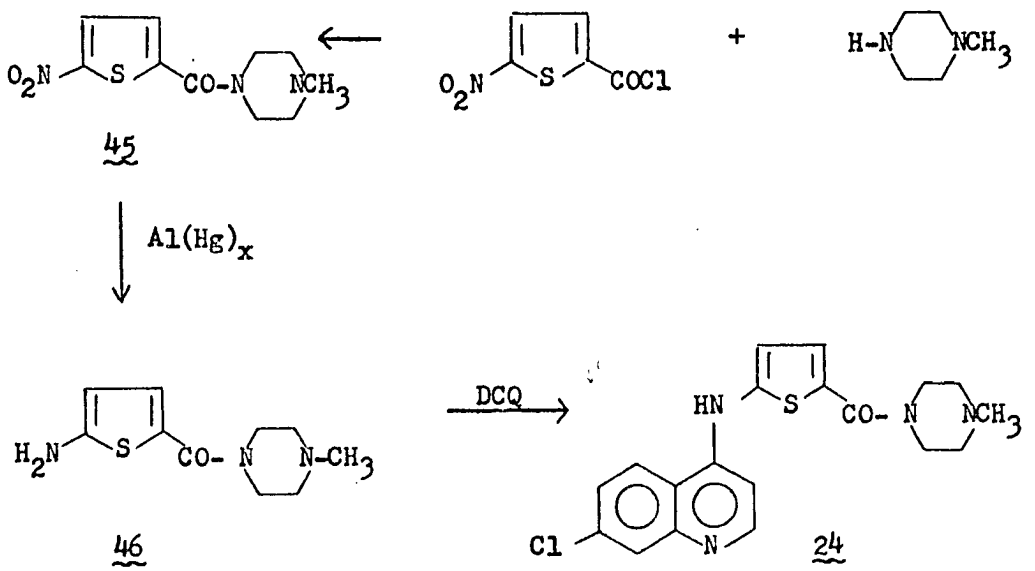
made from the corresponding 5-nitro-2-heterocyclic carboxylic acids.

Nitration of 2-thiophenecarboxylic acid, according to the method of Rinkes,[35] gave a mixture of 5-nitro and 4-nitrothiophene-2-carboxylic acids and 2-nitrothiophene. The mixture as such was treated with



thionyl chloride to give the acid chlorides, which were separated by distillation.[36] Condensation of 5-nitro-2-thenoyl chloride with 1-methylpiperazine gave 45 in 51% yield. Reduction with aluminum



amalgam in ether in a N_2 atmosphere, followed by condensation with DCQ at pH 4, gave the desired product 24 in 20% yield.

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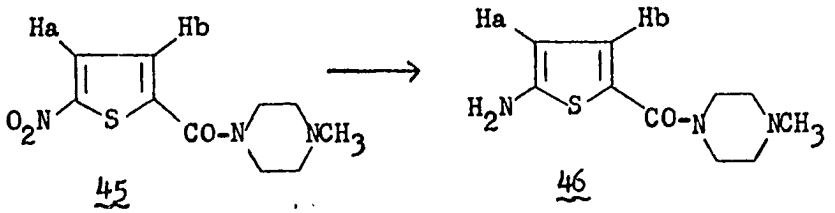
The reduction of the nitrothiophene 45 was followed by the upfield

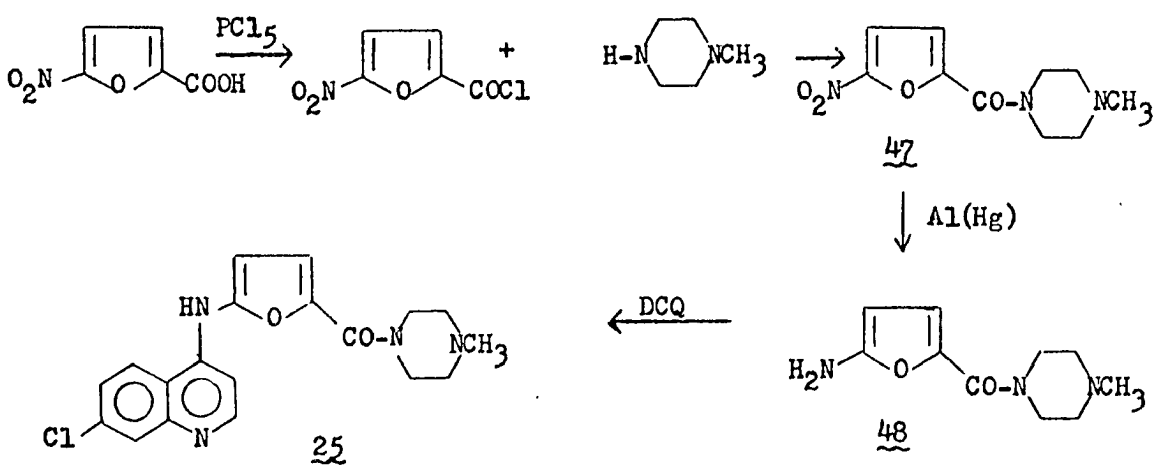


Ha δ 7.82
Hb δ 7.18

Ha δ 5.95
Hb δ 6.88

shift in the nmr spectrum of the pair of doublets at δ 7.82 and δ 7.18 (J=4 cps) to δ 6.88 and 5.95 (J=4 cps). As soon as the reaction was over, the catalyst was removed by filtration, since further reduction of the amine 46 gave products which had no aromatic protons, and were not identified any further. Optimum yield of 46 was obtained when the temperature was kept between 10 and 20°.

The furoic acid analog (25) of 15 was similarly made from 5-nitro-2-furoic acid. Formation of the acid chloride[37] followed by condensation with 1-methylpiperazine gave 47 in 50% yield. Reduction of the nitro-



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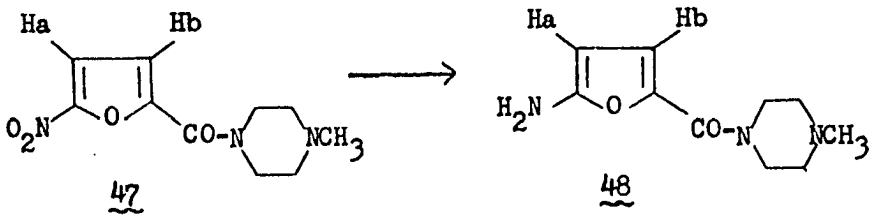
furamide 47 in ether with aluminum amalgam at room temperature in a N_2 atmosphere, according to the procedure of Dann,[36] gave 48. However, efforts to condense 48 with DCQ to give 25 were unsuccessful owing to the instability of 48 to acid and to heat.

The reduction of 47 to 48 was also followed by nmr. An upfield



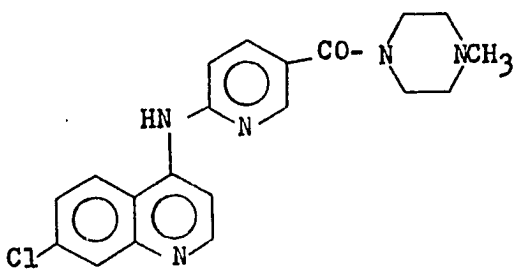
47 48

Ha δ 7.42
Hb δ 7.21
J = 3.6 cps

Ha δ 5.34
Hb δ 7.02
J = 3.8 cps

shift of the aromatic protons was observed as indicated.

The starting material for 26 was 6-aminonicotinic acid, which was



26

prepared by the method of Ferrari.[39] The corresponding acid chloride was made by treating the acid with PCl_5 in acetyl chloride.[40] Conden-

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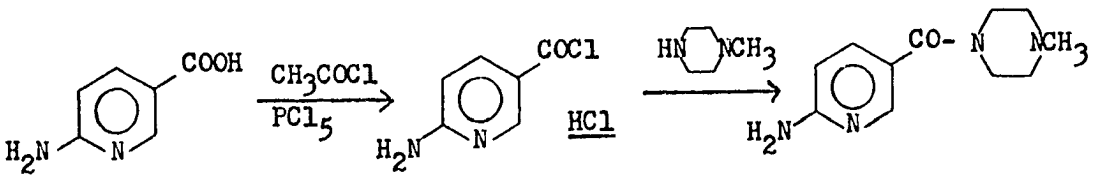
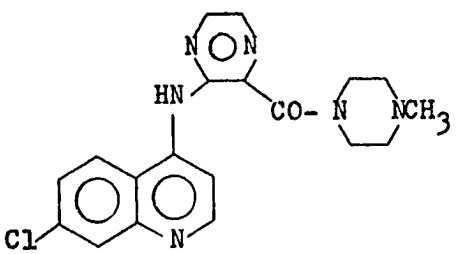
sation of the resulting acid chloride with 1-methylpiperazine gave 49.



49

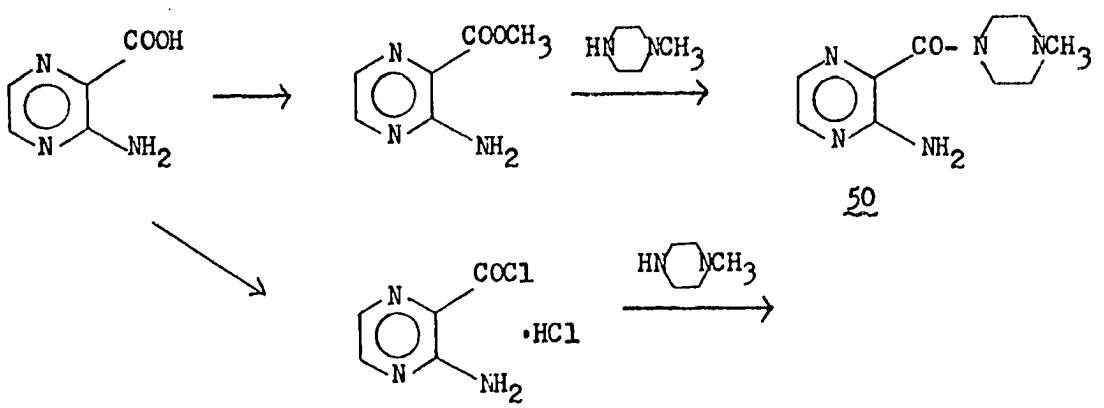
However, all attempts to condense 49 with DCQ proved to be unsuccessful. Failure was not surprising owing to the decreased nucleophilicity of the amino moiety of 2-aminopyridines compared with aniline.

For the preparation of 27, the methyl ester of 3-aminopyrazine-



27

2-carboxylic acid was made by the procedure of Ellingson et al.[41]

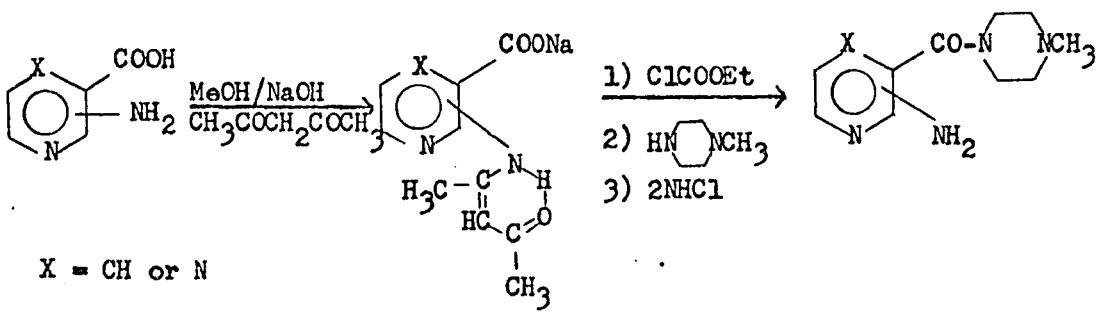


50

Condensation of the ester with the 1-methylpiperazine gave poor yields of 50. However, better yields of 50 were obtained by treatment of 3-aminopyrazine-2-carboxylic acid with PCl_5 in acetyl chloride and reacting the resulting acid chloride with 1-methylpiperazine.

Since 50 contained also an amidine moiety, condensation with DCQ was again unsuccessful.

Attempts to prepare 49 and 50 by protecting the amino group of 3-aminopyrazine-2-carboxylic acid with acetylacetone[42] followed by



condensation at 0° with ethyl chloroformate[43] and 1-methylpiperazine failed. From the reaction of the salt of the amino acid with acetylacetone, the starting material was obtained since the amino group was not a strong enough nucleophile to attack the carbonyl function in acetylacetone.

Synthesis of the nitrothiazole derivatives (28 and 29) was accomplished via the following route. Acylation of 2-aminothiazole with either α-chloroacetyl chloride or β-chloropropionyl chloride gave 51 and 52, respectively.[44,45] Condensation of 51 and 52 with 1-methyl-

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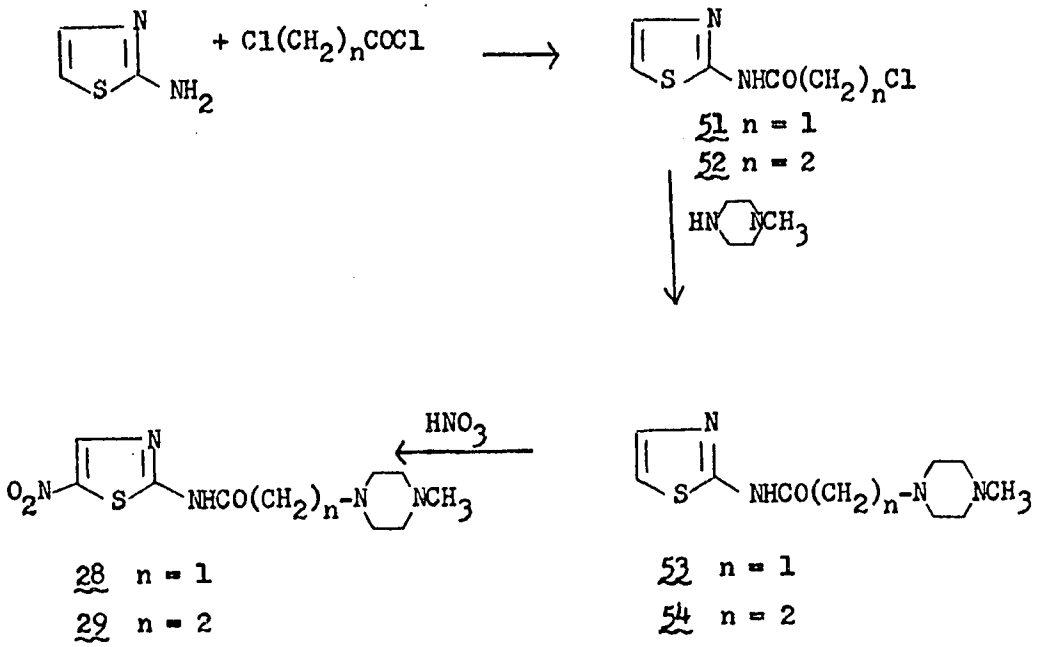
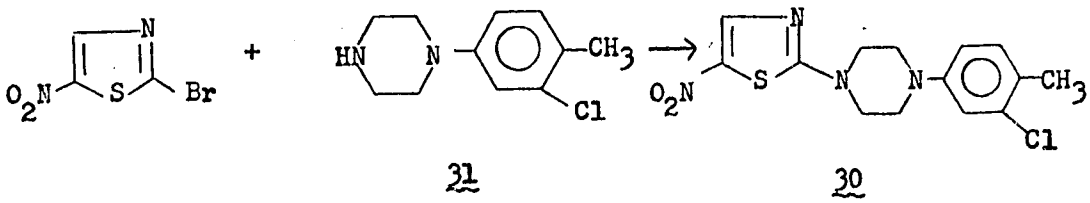


piperazine gave 53 and 54 as the hydrochlorides which were then nitrated as the salt to afford 28 and 29, respectively.

The nitrothiazole 30 was prepared by a nucleophilic displacement



31 30

of the bromo atom of 2-bromo-5-nitrothiazole by 1-(3-chloro-4-methylphenyl)piperazine (31). Synthesis of 30 by the same route has been recently reported by Werbel et al.[46]

During the course of this work, an unusual Mannich reaction of

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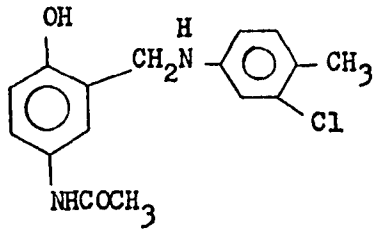
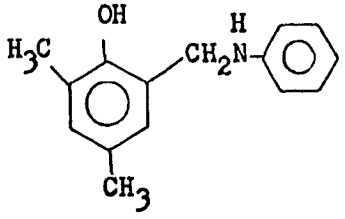
primary aromatic amines in place of the customary aliphatic amines was observed. Thus, 3-chloro-4-methylaniline, 4-acetamidophenol and paraformaldehyde under Mannich conditions gave 55 in 20% yield.



55



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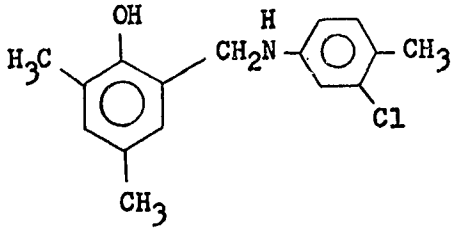

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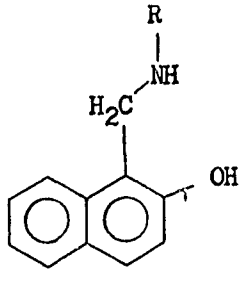
Similarly, 2,4-dimethylphenol reacted with aniline and paraformaldehyde to give 13% yield of 56 and with 3-chloro-4-methylaniline to give 20% yield of 57. This study was not pursued further owing to a report of a similar use of aromatic amines by Burke and coworkers[47] who obtained type 58 compounds.



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IV. PHARMACOLOGICAL RESULTS*

The compounds synthesized for this dissertation are currently being screened for antischistosomal activity in mice and for antimalarial activity in mice and chicks as well as in mosquitoes.

In the mosquito screening test, chemicals are examined for their ability to suppress the development of malarial oocysts in the midgut, or to cause suppression in the number of sporozoites in the salivary gland of the mosquito. The drug test is performed using a standard strain of Aedes aegypti infected with Plasmodium gallinaceum. If one or more mosquitoes are negative for sporozoites, partial sporozoite suppression is indicated. If all mosquitoes are negative for sporozoites, complete sporozoite suppression is indicated. Abnormal oocysts are also indicated since they are probably the result of drug activity. Table I shows the results of testing of some of the compounds. 1-(3-Chloro-4-methylphenyl)-4-(2-aminoethyl)piperazine (38) trihydrochloride showed complete or partial suppression in the tests made.

In the rodent test, mice infected with P. berghei are treated with the chemical at three different dose levels. Of the compounds tested, none were found to be curative, and 38 and 33 were toxic. Table II shows the changes in survival time and toxic deaths for the compounds tested.

Testing of compounds synthesized against schistosomiasis in mice and against malaria in birds is currently in progress.

* We are indebted to the U. S. Army Medical Research and Development Command for pharmacological testing.

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TABLE I

RESULTS OF ANTIMALARIAL TESTS IN MOSQUITOES

Compound No.	MAR No.	Toxic Deaths %	Abnormal Oocysts %	Oocysts Suppression %	Sporozoites Suppression %	
54	1169	60	25	0	0	
43	1153	-	0	0	0	
42	1154	29	0	0	0	
38	1116	100	0	0	25	partial suppression
		71	0	100/30	100	complete suppression
		100	0	0	0	
16	1114	0	0	0	0	
22	1115	11	0	0	0	
40	1117	4	0	25/13	0	
33	1095	9	0	0	0	
34	1093	3	0	0	0	
32	1094	6	0	0	0	

TABLE II

RESULTS OF ANTIMALARIAL TESTS IN MICE

Compound No.	MAR No.	Dose	T-C	Toxic
16	1114	40	0.3	00
		160,640	0.7	00
20	1148	20,80	0.5	00
		320	0.7	00
22	1115	40,160,640	0.1	00
32	1094	160	0.2	00
		320,640	0.4	00
33	1095	160	0.4	00
		320	0.8	01 Toxic
		640	1.3	03 Toxic
34	1093	160	0.0	00
		320,640	0.2	00
35	1096	160,320	0.0	00
		640	0.2	00
36	1091	160,320	0.2	00
		640	0.4	00
38	1116	40	0.1	0
		160	0.3	0
		640	-	05 Toxic
40	1117	40,160	0.7	00
		640	0.9	00
42	1154	40,160	0.3	00
		640	0.7	00
43	1153	40	0.3	00
		160	0.5	00
		640	0.9	00
54	1169	20,40,80,160	0.1	00
		320,640	0.3	00

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V. EXPERIMENTAL

Melting points were determined in a Mel-Temp electric block. They are uncorrected. Infrared spectra were obtained with either a Perkin-Elmer Model 137 or Model 337 spectrophotometer. The nmr spectra were determined by means of a Varian Associates Model A-60-A spectrometer. Chemical shifts were measured with tetramethylsilane as an internal standard. Microanalyses were done by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

1-(3-Chloro-4-methylphenyl)-4-(4-nitrobenzoyl)piperazine (32).- A suspension of 10.5 g (0.1 mole) of 4-nitrobenzoyl chloride in 50 ml of benzene was added to a solution of 21.1 g (0.1 mole) of 1-(3-chloro-4-methylphenyl)piperazine (31)[25] in 50 ml of benzene while the temperature was kept below 5°. The mixture was allowed to sit in ice bath for ½ hr and at room temperature for 2 hr. A $NaHCO_3$ solution was added slowly with stirring until neutrality was reached. Then it was extracted with benzene to give 28 g (78% yield) of 32. Recrystallization from t-butyl alcohol gave crystals of mp 140-142°; ν_{max}^{KBr} 1615 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_3$: C, 60.05; H, 5.04; N, 11.67. Found: C, 60.19; H, 5.15; N, 11.56.

1-(3-Chloro-4-methylphenyl)-4-(4-aminobenzoyl)piperazine (33).- A solution of 53 g (0.23 mole) of stannous chloride in 55 ml of concentrated HCl was added to a solution of 28 g (0.077 mole) of 32 in 230 ml of ethanol.[33] Stirring was continued for 2 hr at 45° after addition was completed. A white solid mass precipitated. The suspen-

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sion was neutralized with Na_2CO_3 solution and extracted with chloroform. The chloroform was removed by evaporation, and the product was precipitated with petroleum ether. Recrystallization from tetrahydrofuran-petroleum ether gave 18 g (70% yield) of product (33). An analytical sample was obtained by recrystallization from benzene, mp 137-138.5°; $\nu_{max}^{CHCl_3}$ 3340, 3440 (NH_2), and 1605 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{20}ClN_3O$: C, 65.54; H, 6.11; N, 12.74. Found: C, 65.77; H, 6.24; N, 12.64.

1-(3-Chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)-benzoyl]piperazine (16).- A mixture of 16.5 g (0.05 mole) of 33 and 9.9 g (0.05 mole) of DCQ in 50 ml of ethanol at pH 4 was refluxed on a steam bath for 3 hr. It was allowed to stand overnight, whereupon 28 g (99% yield) of product was obtained, mp 244-255°. In order to obtain the free base, it was triturated with Na_2CO_3 solution. The resulting light yellow solid (16) was collected and was recrystallized from tetrahydrofuran, mp 240-242°; ν_{max}^{KBr} 3280 (NH), and 1580 cm^{-1} (C=O).

Anal. Calcd. for $C_{27}H_{24}Cl_2N_4O$: C, 65.99; H, 4.93; N, 11.40. Found: C, 66.08; H, 5.28; N, 11.48.

1-(3-Chloro-4-methylphenyl)-4-(3-phthalimidopropionyl)piperazine (35).- The acid chloride obtained from 33 g (0.15 mole) of 3-phthalimidopropionic acid[28] was dissolved in 50 ml of benzene and was added with stirring to a solution of 21 g (0.1 mole) of 1-(3-chloro-4-methylphenyl)-piperazine (31)[25] kept at a temperature below 5°. The solution stood for 3 hr at room temperature. The product was collected and then triturated with $NaHCO_3$ solution. The resulting material was collected and

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recrystallized from tetrahydrofuran and then from 95% alcohol to give 14 g (34% yield) of product (35), mp 165-166°C; $\nu_{max}^{CHCl_3}$ 1750, 1690 (C=O, phthaloyl group) and 1620 cm^{-1} (C=O, amide). Nmr resonances in $CDCl_3$ at δ 2.35 (singlet, 3H); 2.75 (triplet, 2H); 3.08 (triplet, 2H); 3.62 (broad, 2H); 4.02 (triplet, 2H); aromatic protons 6.55-7.14 and 7.70 (7H).

Anal. Calcd. for $C_{22}H_{22}ClN_3O_3$: C, 64.13; H, 5.38; N, 10.20. Found: C, 64.14; H, 5.41; N, 10.21.

1-(3-Chloro-4-methylphenyl)-4-(2-phthalimidoacetyl)piperazine (34).- The foregoing procedure was followed for the acid chloride obtained from 28 g (0.14 mole) of phthaloylglycine.[27] It was recrystallized from dimethylformamide giving 18 g (45% yield) of 34, mp 202-204°; $\nu_{max}^{CHCl_3}$ 1755, 1700 (C=O, phthaloyl group), 1650 cm^{-1} (C=O, amide).

Anal. Calcd. for $C_{21}H_{20}ClN_3O_3$: C, 63.37; H, 5.07; N, 10.56. Found: C, 63.18; H, 5.12.

1-(3-Chloro-4-methylphenyl)-4-(2-aminoacetyl)piperazine (37).- A mixture of 13.3 g (0.033 mole) of 34, 100 ml of ethanol and 2 ml of 64% hydrazine hydrate was refluxed for 3 hr. The alcohol was removed under reduced pressure and the residue was shaken with 20 ml of 6N NH_4OH.[29] The mixture was diluted with 40 ml of water and heated for 5 min on the steam bath. The amine was extracted with chloroform, and the solvent was removed under reduced pressure. Cyclohexane was then added to the residue with stirring. The precipitated gummy solid 37 was collected; 8.4 g (94% yield), mp 70-86°, ν_{max}^{Nujol} 1650 cm^{-1}. It was used without further purification for the next reaction.

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1-(3-Chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)-acetyl]piperazine (17).- A mixture of 2.7 g (0.01 mole) of 37 and 1.9 g (0.01 mole) of DCQ in 2 g of phenol was refluxed for 2 hr.[24] The reaction mixture was added to 10 ml of acetic acid and the resulting solution was neutralized with NH_4OH. The product was extracted with chloroform, the solvent was removed by evaporation, methanol was added and the solution was placed in the refrigerator overnight. The precipitated crystals were collected, and recrystallization from methanol gave 1.5 g (35% yield) of pure crystalline 17, mp 191-193°. ν_{max}^{KBr} 1630 cm^{-1} (C=O, amide). Nmr^{CDCl_3} peaks at δ 2.28 (singlet, 3H); 3.0-3.2 (multiplet, 4H); 3.5-3.7 (broad, 2H); 3.7-3.95 (multiplet, 4H); and several lines in aromatic region 6.1-8.4 (9H).

Anal. Calcd. for $C_{22}H_{22}Cl_2N_4O$: C, 61.54; H, 5.17; N, 13.05. Found: C, 61.57; H, 5.19; N, 12.94.

1-(3-Chloro-4-methylphenyl)-4-(2-phthalimidoethyl)piperazine (36).- A mixture of 21 g (0.1 mole) of 1-(3-chloro-4-methylphenyl)piperazine (31)[25] and 25.5 g (0.1 mole) of β-bromoethylphthalimide in ethanol was refluxed for 16 hr. $NaHCO_3$ was added, and refluxing was continued for 4 hr. After standing overnight, the solution was concentrated. Cooling caused the separation of 18 g (47% yield) of yellow product (36), mp 135-138°. Recrystallization from tetrahydrofuran only slightly elevated the mp to 136-138°; $\nu_{max}^{CHCl_3}$ 1750, 1685 cm^{-1} (C=O, phthaloyl group). Nmr^{CHCl_3} peaks at δ 2.23 (singlet, 3H); 2.65 (multiplet, 4H); 3.02 (triplet, 2H); 3.80 (triplet, 2H); 6.50-7.05 (multiplet, 3H) and 7.68 (multiplet, 4H).

Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$: C, 65.68; H, 5.78; N, 10.94. Found: C, 65.58; H, 5.79; N, 10.91.

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1-(3-Chloro-4-methylphenyl)-4-(2-aminoethyl)piperazine (38) hydrochloride.- A mixture of 11.5 g (0.03 mole) of phthalimide 36 and 1.5 ml of 50% aq. hydrazine hydrate was refluxed for 3 hr in 60 ml of abs. ethanol. The ethanol was removed under pressure and the mixture was shaken with 18 ml of 2N NH_4OH and then was diluted with 35 ml of H_2O.[29] The solution was extracted with chloroform, the chloroform extract was dried and hydrogen chloride was passed into the solution. The salt was collected; crude 17 g (44% yield), mp 188-192°. Several recrystallizations from methanol gave 8 g (21% yield) of white solid 38 hydrochloride, mp 205-207°. Nmr D_2O peaks at δ 2.25 (singlet, 3H); 2.65-3.35 (multiplet, 12H); 4.73 (singlet, 5H) and 6.65-7.18 (multiplet, 3H).

Anal. Calcd. for $C_{13}H_{23}Cl_4N_3$: C, 42.99; H, 6.39; N, 11.58. Found: C, 43.08; H, 6.39; N, 11.57.

1-[(3-Chloro-4-methylphenyl)-4-(4-nitrophenyl)piperazine] (40).- A mixture of 21 g (0.1 mole) of 1-(3-chloro-4-methylphenyl)piperazine (31)[25] and 20.2 g (0.1 mole) of p-nitrobromobenzene in 120 ml of pyridine was refluxed with stirring for 12 hr. The solvent was removed under reduced pressure. Methanol was added to give 33 g of crystalline crude product, mp 80-90°. One recrystallization from methanol gave a first crop of crystals, 10 g (30% yield) of 40, mp 126-128°. Nmr^{CDCl_3} absorption at δ 2.25 (singlet, 3H); 3.15-4.65 (multiplet, 8H); 6.6-7.2 (multiplet, 5H) and 7.95-8.15 (doublet, 2H).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12.67. Found: C, 61.56; H, 5.46; N, 12.59.

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1-(3-Chloro-4-methylphenyl)-4-(4-aminophenyl)piperazine (41).- A mixture of 11 g (0.033 mole) of 40 and 50 ml of reducing solution (prepared by mixing 180 g of $SnCl_2$ with 200 ml of glacial acetic acid and by passing hydrogen chloride gas through the mixture until the $SnCl_2$ dissolved. The final volume was made up to 400 ml with acetic acid)[32] was stirred for 1 day. It was collected by filtration, washed with acetic acid and with ether. Concd. NaOH solution was then added, and the product was extracted with chloroform. The chloroform layer was dried and concentrated. The product was recrystallized from methanol-chloroform to give 6.5 g (65% yield) of a light brown solid (41), mp 166-170°. Analytical sample, mp 171-174°, nmr δ 2.25 (singlet, 3H); 3.20 (singlet, 10H); and 6.5-7.2 (multiplet, 7H), nmr taken in $CDCl_3$.

Anal. Calcd. for $C_{17}H_{20}ClN_3$: C, 67.65; H, 6.68; N, 13.93. Found: C, 65.36; H, 6.43; N, 13.41.

Calculations based upon C=65.36 suggest a molecular weight of 312.38 (0.587 mole of water). Calcd. for $C_{17}H_{20}ClN_3$ 0.587 H_2O: C, 65.36; H, 6.64; N, 13.46.

1-(3-Chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolyl amino)phenyl]-piperazine (20).- A mixture of 3.02 g (0.01 mole) of 41 and 1.98 g (0.01 mole) of DCQ was refluxed in 30 ml of ethanol for 1 hr at a pH of 4. $NaHCO_3$ was added and refluxing was continued $\frac{1}{2}$ hr more. The precipitate was collected and recrystallization from pyridine-tetrahydrofuran gave 3 g (65% yield) of crystalline (20), mp 269-273°. The nmr spectrum showed resonances at δ 2.50 (singlet, 3H); 4.6 (singlet, 9H) and 6.8-9.2 (multiplet, 712H) taken in CF_3COOH.

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Anal. Calcd. for $C_{26}H_{24}Cl_2N_4$: C, 67.38; H, 5.22; N, 12.09. Found: C, 67.15; H, 5.13; N, 12.04.

4-Acetamido-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol (42).- A mixture of 24 g (0.15 mole) of 4-acetamidophenol, 5 g (0.15 mole) of paraformaldehyde, and 31.6 g (0.15 mole) of 1-(3-chloro-4-methylphenylpiperazine (31)[25] in 40 ml of absolute ethanol was heated on a steam bath for 2 hr.[34] The solvent was removed under reduced pressure. The residue was dried overnight under high vacuum. It was recrystallized from tetrahydrofuran petroleum ether to give a 50% yield of crude product, mp 189-200°. Two recrystallizations from pyridine gave product 42, mp 241-244°.

Anal. Calcd. for $C_{20}H_{24}N_3ClO_2$: C, 64.24; H, 6.47; N, 11.24. Found: C, 64.27; H, 6.38; N, 11.28.

4-Nitro-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol (43).- A mixture of 6.5 g (0.05 mole) of p-nitrophenol, 1.5 g (0.05 mole) of paraformaldehyde and 10.5 g (0.05 mole) of 1-(3-chloro-4-methylphenyl)-piperazine (31)[25] was refluxed in 50 ml of ethanol for 3 hr. The solvent was removed under reduced pressure and the resulting oil was shaken thoroughly in 95% ethanol. A yellow solid, 43, separated, 7.8 g (43% yield) of 43, mp 175-187°. Recrystallization from dimethylformamide-water, three times gave pure crystals which melted at 193-195°. Nmr in $CDCl_3$ gave resonances at δ 2.28 (singlet, 3H); 2.65-3.25 (multiplet, 8H); 1.92 (singlet, 2H); and aromatics 6.6-7.2 and 7.9-8.2 (several, 6H).

Anal. Calcd. for $C_{18}H_{20}N_3ClO_3$: C, 59.75; H, 5.57; N, 11.62. Found: C, 59.59; H, 5.61; N, 11.65.

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4-Amino-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol (44).- Reduction of 3.6 g (0.01 mole) of 43 in 15 ml of reducing solution, as described for compound 41, gave 2 g (60% yield) of 44, mp 144-150°.

4-(7-Chloro-4-quinolylamino)-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol (21).- A mixture of 6.6 g (0.02 mole) of 44 and 4 g (0.02 mole) of DCQ in 200 ml of ethanol was refluxed for 3 hr at a pH of 4. The ethanol was removed under reduced pressure, water was added and the mixture was neutralized with dilute NH_4OH. The product was extracted with ether, the ether solution was dried, and the ether was removed. The crude product was recrystallized from a water-isopropanol mixture to give 5.5 g (56% yield) of pure 21, mp 194-196°. Nmr^{CF_3COOH} peaks at δ 2.47 (singlet, 3H); 4.22 (broad, 8H); 4.73 (singlet, 2H) and 7.45 (multiplet, 8H).

Anal. Calcd. for $C_{17}H_{16}N_4OCl_2$: C, 65.72; H, 5.32; N, 11.36. Found: C, 65.08; H, 5.26; N, 11.19. (A trace of ash.)

1-(3-Chloro-4-methylphenyl)-4-(7-chloro-4-quinolyl)piperazine (22).- A mixture of 10.5 g (0.05 mole) of 1-(3-chloro-4-methylphenyl)piperazine (31)[25], 10 g of phenol and 9.9 g (0.05 mole) of DCQ was heated at 125° for 2 hr. The reaction mixture was added to 10 ml of acetic acid and made basic with dil. NH_4OH. The product was extracted with chloroform, and methanol was added upon removal of the chloroform by evaporation. From the solution, overnight 15.1 g of crude product precipitated, mp 169-175°. Recrystallization from tetrahydrofuran gave 12.1 g (65% yield) of 22, mp 174-176°. Nmr^{CDCl_3} absorption at δ 2.3 (singlet, 3H); 3.4 (singlet, 8H); 6.7-7.5 (multiplet); 7.9 (singlet); 8.0 (doublet) and 8.7 (doublet) all 8H.

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Anal. Calcd. for $C_{20}H_{19}Cl_2N_3$: C, 64.52; H, 5.14; N, 11.29. Found: C, 64.57; H, 5.08; N, 11.23.

4-(5-Nitro-2-thenoyl)-1-methylpiperazine (45).- To 45 g of the solid mixture obtained from the nitration of 2-thiophene carboxylic acid,[35] 200 g of thionyl chloride was added, and the solution was refluxed for 3 hr. Thionyl chloride was removed and the residue was distilled to yield 35 g of 5-nitro-2-thiophenecarbonyl chloride (bp 127-130°/3.0-3.2 mm). A solution of the acid chloride in 100 ml of benzene was then added dropwise to a solution of 20 g (0.2 mole) of 1-methylpiperazine in 200 ml of benzene with stirring at 0-10°. After addition was complete, the mixture was stirred overnight at room temperature. The salt was collected, was placed in water, was basified with $NaHCO_3$, was extracted in chloroform and was dried over anhyd. Na_2SO_4. The chloroform was removed at reduced pressure and the residue was allowed to cool in the refrigerator. The crystals were collected to afford 42 g (82% yield) of crude 45. Recrystallization of 5 g of the crude material from water yielded 3.5 g (51%) of pure compound 45, mp 75-76°. ν_{max}^{Nujol} 1620 cm^{-1} (C=O, amide). Nmr ^{CDCl_3} peaks at δ 2.33 (singlet, 3H); 2.47 (triplet, 4H); 3.75 (triplet, 4H); 7.18 (doublet, 1H) and 7.82 (doublet, 1H).

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.04; H, 5.13; N, 16.45. Found: C, 46.82; H, 4.99; N, 16.14.

4-(5-Amino-2-thenoyl)-1-methylpiperazine (46).- To 5 g (0.02 mole) of 45 in 500 ml of ether, 10 ml of water and 5 g of aluminum amalgam[36] (prepared by procedure given in Reagents for Organic Synthesis)[38] was added while the mixture was cooled and a stream of nitrogen was passed

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into it. The reaction mixture was stirred for about an hour, until the reaction was over. Then the unreacted aluminum was removed by filtration, the ether was removed under reduced pressure and the residue was cooled in the refrigerator. The crystals which formed were collected on a filter to give 1.5 g (33% yield) of 46, mp 163-165°. ν_{max}^{Nujol} 1640 cm^{-1} (C=O, amide). Nmr^{CHCl_3} δ 2.33 (singlet, 3H); 2.43 (triplet, 4H); 3.75 (triplet, 4H); 4.30 (broad, 2H); 5.95 (doublet, 1H) and 6.88 (doublet, 1H).

Anal. Calcd. for $C_{10}H_{15}N_3OS$: C, 53.35; H, 6.71; N, 18.66. Found: C, 53.39; H, 6.64; N, 18.60.

4-[5-(7-Chloro-4-quinolylamino)-2-thenoyl]-1-methylpiperazine (24) dihydrochloride dihydrate.- A mixture of 2.2 g (0.01 mole) of 46, 2 g (0.01 mole) of DCQ and 100 ml of ethanol was refluxed for 3 hr. A solid was formed, which was collected and recrystallized from ethanol to give 1 g (20% yield) of product, mp 273-275°. ν_{max}^{Nujol} 1615 cm^{-1} (C=O, amide).

Anal. Calcd. for $C_{19}H_{19}ClN_4OS \cdot 2HCl \cdot 2H_2O$: C, 46.02; H, 4.68; N, 11.30. Found: C, 45.97; H, 4.29; N, 11.28.

4-(5-Nitro-2-furoyl)-1-methylpiperazine (47).- A solution of 32 g (0.2 mole) of 5-nitro-2-furoyl chloride in 100 ml of ether was added dropwise with cooling to a solution of 20 g (0.2 mole) of 1-methylpiperazine in 200 ml of ether. The reaction mixture was stirred overnight. The salt was collected, placed in water and neutralized with 6N NH_4OH. The product was extracted with chloroform, the chloroform extract was dried over Na_2SO_4, and the solvent was removed to yield

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42 g (87%) of crude product, mp 83-90°. Recrystallization from 95% ethanol followed by recrystallization from cyclohexane gave pure crystals, mp 95-96°. ν_{max}^{Nujol} 1625 cm^{-1} (C=O, amide). Nmr^{CDCl_3} peaks at δ 2.37 (singlet, 3H); 2.52 (triplet, 4H); 3.87 (triplet, 4H); 7.21 (doublet, 1H) and 7.42 (doublet, 1H).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.50; N, 17.70. Found: C, 50.27; H, 5.48; N, 17.64.

4-(5-Amino-2-furoyl)-1-methylpiperazine (48).- To 5 g (0.02 mole) of 47 in 500 ml of ether, 10 ml of water was added followed by addition of 5 g of aluminum amalgam while a stream of nitrogen was passed into the mixture. After the mixture was stirred at room temperature for one hour, a solid material was removed by filtration, and the ether was removed under reduced pressure. The nmr of the residual yellow oil suggested the presence of a compound of structure 48. However, nothing further was done with this amine because of its instability. ν_{max} 1630 (C=O, amide). Nmr^{CDCl_3} peaks at δ 2.34 (singlet, 3H); 2.45 (triplet, 4H); 3.85 (triplet, 4H); 4.71 (broad, 2H); 5.34 (doublet, 1H) and 7.02 (doublet, 1H).

4-(6-Aminonicotinoyl)-1-methylpiperazine (49).- A mixture of 5 g (0.035 mole) of 6-aminonicotinic acid, 10 g of acetyl chloride and 10 g of PCl_5 was stirred at room temperature for 24 hr. The yellow acid chloride salt was collected and washed with dichloroethane. Then, it was placed in 25 ml of ether and while cooling 6 g (0.06 mole) of 1-methylpiperazine in 25 ml of ether was added and the mixture was stirred overnight at room temperature. The mixture was neutralized with a saturated solution of $NaHCO_3$, extracted with chloroform and the chloro-

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form extract dried over Na_2SO_4. Removal of chloroform and addition of petroleum ether precipitated an oil which solidified upon stirring. Recrystallization from benzene gave 4 g (52% yield) of 49, mp 139-140.5°. ν_{max}^{Nujol} 1630 cm^{-1} (C=O, amide). Nmr^{CDCl_3} peaks at δ 2.17 (singlet, 3H); 2.25 (triplet, 4H); 3.45 (triplet, 4H); 6.20 (doublet, 1H); 6.76 (quartet, 1H) and 7.37 (doublet, 1H).

Anal. Calcd. for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.92; H, 7.23; N, 25.27.

4-(3-Amino-2-pyrazinoyl)-1-methylpiperazine (50). - (Method A) - A mixture of 5 g (0.035 mole) of 3-amino-2-pyrazinecarboxylic acid, 1 g of acetyl chloride and 10 g of PCl_5 was stirred for 4 hours. The yellow salt was collected, washed with dichloroethane and placed in 25 ml of ether. Five g (0.05 mole) of 1-methylpiperazine in 25 ml of ether was then added while cooling, and the mixture was stirred overnight at room temperature. The mixture was neutralized with a saturated solution of $NaHCO_3$, extracted with chloroform and the chloroform extracted was dried over Na_2SO_4. Removal of chloroform under reduced pressure left an oil which was then recrystallized from cyclohexane to give 2.5 g (45% yield) of crystalline 50, mp 116-119°. Sublimation at reduced pressure (0.05 mm, oil bath 100°C) gave pure crystals, mp 118-119°. ν_{max}^{Nujol} 1610 cm^{-1} (C=O, amide). Nmr^{CDCl_3} peaks at δ 2.28 (singlet, 3H); 2.60 (quartet, 4H); 3.21 (quartet, 4H); 7.66 (doublet, 1H) and 7.90 (doublet, 1H).

Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.84; N, 31.65. Found: C, 54.06; H, 6.70; N, 31.47.

(Method B) - A mixture of 3.1 g (0.02 mole) of methyl 3-amino-pyrazine-2-carboxylate and 4 g (0.04 mole) of 1-methylpiperazine was heated in an oil bath at 195° for 8 hr. The mixture was cooled to

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room temperature, was was added and the product was extracted with chloroform. The chloroform layer was dried over Na_2SO_4 and was evaporated to leave an oil which was recrystallized from cyclohexane to give 0.5 g (11% yield) of 50. Nmr spectra were identical with those of the product obtained by Method A.

N-(Thiazol-2-yl)-α-(1-methyl-4-piperazino)acetamide (53) hydrochloride.- A mixture of 10.5 g (0.06 mole) of N-(thiazol-2-yl)-α-chloroacetamide and 6 g (0.06 mole) of 1-methylpiperazine was refluxed in 150 ml of ethanol for 24 hr. The ethanol was evaporated and ether was added during cooling in ice and with stirring. The crude material was filtered to give 9 g (54% yield) of product, mp 245-257°. Recrystallization from methanol-ether gave crystals which melted at 254-257°. ν_{max}^{Nujol} 1670 cm^{-1} (C=O, amide). Nmr peaks in d_6-DMSO at δ 2.56 (singlet, 3H); 2.80 (broad, 4H); 3.12 (broad, 4H); 3.32 (singlet, 2H); 7.02 (doublet, 1H) and 7.26 (doublet, 1H).

Anal. Calcd. for $C_{10}H_{16}N_4OS \cdot HCl$: C, 43.41; H, 6.20; N, 20.25. Found: C, 43.31; H, 6.07; N, 20.32.

N-(5-Nitrothiazol-2-yl)-α-(1-methyl-4-piperazino)acetamide (28).- To 10 g (0.037 mole) of 53 at 0-5°, 30 ml of sulfuric acid and 18 ml of fuming nitric acid was added dropwise with stirring. The mixture was stirred at room temperature for 4 hr, thrown into ice water and neutralized with a saturated solution of $NaHCO_3$. The solid which precipitated was filtered to give 6 g of 28. The filtrate was then extracted with chloroform, the chloroform extract was dried over Na_2SO_4, the solution was concentrated to 10 ml and petroleum ether was added to the residue to give a total of 8.5 g of 28 (81% yield), mp 155-170° dec. Recrystallization from acetone gave pure crystals, mp 185-187° dec.

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ν_{max}^{Nujol} 1600 cm^{-1} (C=O, amide).

Anal. Calcd. for $C_{10}H_{15}N_5O_3S$: C, 42.10; H, 5.30; N, 24.55.

N-(Thiazol-2-yl)-β-(1-methyl-4-piperazino)propionamide (54) hydrochloride.- A mixture of 8.5 g (0.05 mole) of N-(thiazol-2-yl)-β-chloropropionamide[21] and 5 g (0.05 mole) of 1-methylpiperazine in 150 ml of ethanol was refluxed for 18 hr. The solvent was evaporated and ether was added during cooling in ice and stirring. The crude material was filtered to give 13.2 g (90% yield), of 54 hydrochloride, mp 192-196°. An analytical sample was obtained by recrystallization from isopropyl alcohol, mp 199-201°. ν_{max}^{KBr} 1685 cm^{-1} (C=O, amide).

Anal. Calcd. for $C_{11}H_{19}ClN_4OS$: C, 45.43; H, 6.59; N, 19.27. Found: C, 45.41; H, 6.58; N, 19.12.

N-(5-Nitrothiazol-2-yl)-β-(1-methyl-4-piperazino)propionamide (29).- To 10 g (0.034 mole) of 54 at 0-5°, 30 ml of sulfuric acid and 18 ml of fuming nitric acid was added dropwise while stirring. The mixture was stirred at room temperature for 4 hr and thrown into ice water. The mixture was neutralized with a saturated solution of $NaHCO_3$, extracted with chloroform and the chloroform extract dried over Na_2SO_4. The solution was concentrated to 10 ml and petroleum ether was added to the residue. The solid which precipitated was collected to give 7 g (67% yield) of crude 29, mp 162-176°. Recrystallization from acetone (3x) followed by recrystallization from benzene gave pure

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crystals of 29, mp 172-176° dec. ν_{max}^{Nujol} 1665 cm^{-1} (C=O, amide).

Anal. Calcd. for $C_{11}H_{17}H_5O_3S$: C, 44.14; H, 5.73; N, 23.40. Found: C, 44.14; H, 5.69; N, 23.41.

4-Acetamido-α-(3-chloro-4-methylanilino)-o-cresol (55).- A mixture of 15.1 g (0.1 mole) of 4-acetamidophenol, 3 g (0.1 mole) of paraformaldehyde and 14.1 g (0.1 mole) of 3-chloro-4-methylaniline in 30 ml of ethanol was refluxed for 3½ hr. Solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran. The product was precipitated by the addition of petroleum ether. This procedure was repeated until a constant melting point was recorded, mp 171-173°. The yield was about 20%; ν_{max}^{KBr} 1680 cm^{-1} (C=O). Nmr peaks in d_6-DMSO at δ 1.98 (singlet, 3H); 2.17 (singlet, 3H); 3.27 (singlet, 2H); 5.33 (singlet, 2H); 6.55-7.42 (multiplet, 6H) and 9.61 (singlet, 1H)

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.00; H, 5.62; N, 9.19; Cl, 11.63. Found: C, 63.19; H, 5.51; N, 9.20; Cl, 11.72.

α-Anilino-2,4-dimethyl-o-cresol (56).- A mixture of 6.1 g (0.05 mole) of 2,4-dimethylphenol, 1.5 g (0.05 mole) of paraformaldehyde, and 4.65 g (0.05 mole) of aniline in 50 ml of ethanol was refluxed for 3 hr and allowed to stand overnight. The solvent was removed and the residue was allowed to stand. When crystals began to form, n-hexane was added with stirring. Crystals which formed were collected to give 1.5 g (13% yield) of 56, mp 71-73°. Analytical sample, mp 75-76°, was obtained after recrystallization from methanol. Nmr peaks at δ 2.18

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(singlet, 6H); 3.48 (singlet, 2H); 4.20 (broad, 1H); 6.40-7.08 (multiplet, 7H) and 8.20 (singlet, 1H).

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.75; H, 7.57. Found: C, 79.32; H, 7.59.

α-(3-Chloro-4-methylanilino)-2,4-dimethyl-o-cresol (57).- A mixture of 6.1 g (0.05 mole) of 2,4-dimethylphenol, 1.5 g (0.05 mole) of paraformaldehyde and 7.2 g (0.05 mole) of 3-chloro-4-methylaniline in 50 ml of ethanol was refluxed for 3 hr. The solution was allowed to stand for one day. The solvent was removed and the oily residue was allowed to stand. When crystals began to form, 2-propanol was added. The solution stood in the cold for about one month whereupon crystals which separated were collected to give 2.7 g (20% yield) of 57, mp 93-95°. Pure crystals, mp 104-105°, were obtained by recrystallization from acetone. Nmr peaks at δ 2.16 and 2.20 (singlets, 6H); 2.35 (singlet, 3H); 4.48 (singlet, 2H) in pyridine. In d_6-DMSO peaks were observed at δ 2.15 (singlet, 9H); 8.15 (singlet, 1H); 4.15-4.25 (broad, 2H) plus aromatic protons 6.4-7.05 (multiplet, 5H).

Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 69.65; H, 6.58; N, 5.08. Found: C, 69.72; H, 6.55; N, 4.98.

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VI. SUMMARY

The synthesis of analogs of 1-methyl-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine has been described. The purpose of the research for this dissertation was preparation of compounds which might possess antiparasitic effects, especially against schistosomiasis and malaria. The following compounds were prepared: 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)acetyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[4-(7-chloro-4-quinolylamino)phenyl]piperazine, 4-(7-chloro-4-quinolylamino)-α-[1-(3-chloro-4-methylphenyl)-4-piperazino]-o-cresol, 1-(3-chloro-4-methylphenyl)-4-(7-chloro-4-quinolyl)piperazine, and 4-[5-(7-chloro-4-quinolylamino)-2-thenoyl]-1-methylpiperazine. N-(5-Nitrothiazol-2-yl)-α-(1-methyl-4-piperazino)-acetamide and N-(5-nitrothiazol-2-yl)-β-(1-methyl-4-piperazino)propionamide. Mannich bases of special interest were also prepared: 4-acetamido-α-(3-chloro-4-methylanilino)-o-cresol, α-(3-chloro-4-methylanilino)-2,4-dimethyl-o-cresol and α-anilino-2,4-dimethyl-o-cresol.

Attempts to prepare 1-(3-chloro-4-methylphenyl)-4-[3-(7-chloro-4-quinolylamino)propionyl]piperazine, 1-(3-chloro-4-methylphenyl)-4-[2-(7-chloro-4-quinolylamino)ethyl]piperazine, 4-[5-(7-chloro-4-quinolylamino)-2-furoyl]-1-methylpiperazine, 4-[6-(7-chloro-4-quinolylamino)-nicotinoyl]-1-methylpiperazine and 4-[3-(7-chloro-4-quinolylamino)-2-pyrazinoyl]-1-methylpiperazine were discussed.

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