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A STUDY OF AMINO DERIVATIVES OF THIOPHENE ISOSTERS OF INDANONE AND TETRALONE

BY

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B.Sc.(Hons.), M.S. University of Baroda, 1954

M.Sc., University of Bombay, 1958

A Thesis
Submitted to the Faculty of
The University of Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Master of Science
in the Department of Pharmaceutical Chemistry

The University of Mississippi

August, 1964

A STUDY OF AMINO DERIVATIVES

OF THIOPHENE ISOSTERS

OF INDANONE AND TETRALONE

BY

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ACKNOWLEDGEMENTS

The writer wishes to express his gratitude to Dr. Joseph Sam for his patience, guidance and kind understanding during the course of this investigation and whom he holds in the highest esteem not only as a person but as a scientist of high calibre.

Acknowledgement is made to Bristol Laboratories, Syracuse, New York, for the financial support which made this investigation possible.

Thanks is also extended to Dr. Wilbert G. Walter for his helpful suggestions.

G. G. A.

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INTRODUCTION

A remarkable fact that certain physical and chemical properties of thiophene and benzene, and of corresponding derivatives of the two parent compounds are very similar aroused an interest with respect to the biochemistry and pharmacology of these substances. Does the metabolism of a thiophene derivative resemble that of corresponding benzene compounds, and do both types of compounds produce similar effects on an animal organism? The desire to find the answers to these questions and many others is the stimulus to continue research with thiophene compounds. Biochemical studies were begun almost as soon as thiophene derivatives became available, and to a limited extent, have been continued to the present time, but during recent years the pharmacology of thiophene analogs of pharmacologically active benzene derivatives has attracted special interest.

The interest in compounds containing thiophene rings as potential biologically active agents stems largely from the ideas inherent in the receptor theory of drug action, the theory of biological antagonism, and finally the concept of bioisosterism. These three concepts may be said to represent the latest approach to the problem of securing a correlation between chemical structure and biological activity. Because of large numbers of variables existing in biological systems, it is not possible to establish a direct relationship between a single pair of these variables such as chemical structure and a particular biological action without taking into consideration simultaneous variation in other factors such as solubilities, distribution coefficients, electrical fields, acid and base strengths, detoxification mechanisms in the organism, etc.

The advantage of an approach to the problem of structure-action relationships based on the concepts of biological antagonism and bioisosterism is that while not eliminating variation in such factors it does minimize their variation. Thus, these concepts provide us with a promising basis for observing changes in biological activity with somewhat limited changes in chemical structure.

The idea that drugs exert their effects by interacting with certain receptors in the tissues has been unquestionably accepted by many workers in pharmacology and chemotherapy and related fields for many years.

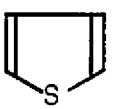
The concept of biological antagonism (1,2,3,4) states that certain compounds which possess similar chemical structure and similar physical properties to an "essential metabolite" of the organism will, by virtue of their similarities, possess a degree of affinity for the receptor sites at which the metabolite is believed to elicit a response. The antagonist usually is chemically similar to the metabolite and appears to inhibit it by competing for a common receptor in the cells. Initially, this concept was applied to the phenomenon of competitive inhibition. In such cases it was assumed that the metabolite analogue was unable to elicit a response on combining with receptor and, by competing reversibly with the natural metabolite for the available receptors, it was able to prevent the metabolite from fulfilling its normal function. Recently, however, the concept has been modified (5,6,7) to include cases where the analogue is itself able to elicit a response, a measure of its ability to do so being termed as intrinsic activity.

Where a thiophene derivative is prepared as an isologue of a known metabolite, one can expect it to intensify, mimic, or oppose the

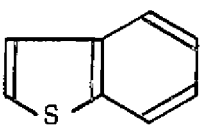
biological effect of its natural analogue depending on its affinity for the receptor and upon its intrinsic activity. Biochemical and pharmacological studies have shown that the thiophene and benzene nuclei are, in general, biologically equivalent.

It is recognized that the properties of benzene, furan, pyrrole, pyridine, and thiophene are similar. The similarities in properties of these rings, each with its π electrons, have been expressed in the concept of isosterism (8) developed by Erlenmeyer (9), Friedman (10), and other scientists (11,12,13,14). Friedman coined the term bioisosterism, which refers to two isosters having the same type of biological activity.

A general conclusion to be drawn regarding the biological properties of thiophene (I) and its higher ring homolog, thionaphthene (II), is that these compounds usually possess activities similar to those of benzene and naphthalene but less pronounced and often more toxic.



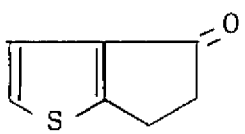
I



II

In addition to their established use as antihistamines, certain thiophene derivatives have shown substantial activity as pressor compounds, local anesthetics, hypnotics, analgesics, anticholinergics, antispasmodics, anticonvulsants, tuberculostats, antibacterials, antimalarials, and germicidals.

This investigation was undertaken to prepare amino derivatives of thiophene isosters [thiaindanones (III, IV)] of indanone (V) and thiophene isosters [4-keto-4,5,6,7-tetrahydrothionaphthenes (VI)] of tetralone (VII). It was also anticipated that this investigation would lead to additional knowledge and increased understanding of the biological effects of isosters.



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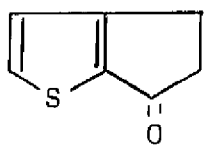

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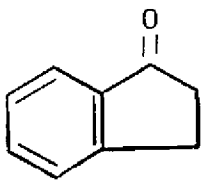

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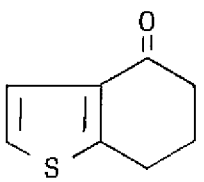
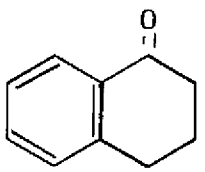


VI



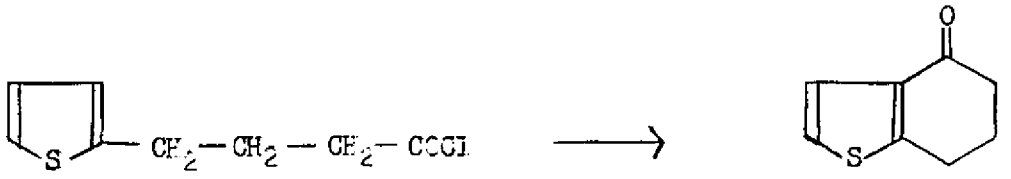
VII

The preparation of isosters with biological activity similar to or opposite to the model compounds (V, VII) was not the sole purpose of this investigation. It was speculated that compounds possessing unusual or unique biological activity might be obtained.

HISTORICAL

A. Intramolecular Acylation of Thiophene Aliphatic Acids

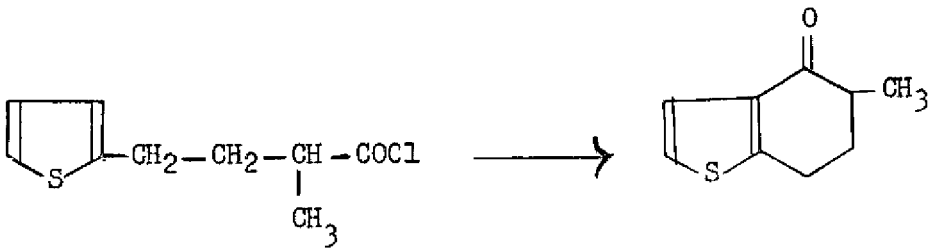
The ring closures of the thiophene-substituted aliphatic acids have been carried out either by the direct cyclization of the acid itself or the cyclization of the acid chloride by the intramolecular Friedel-Crafts reaction (15). Fieser and Kennelly (16) used stannic chloride as the cyclizing agent. They were able to convert γ-(2-thienyl)-butyryl chloride (VIII) to 4-keto-4,5,6,7-tetrahydrothionaphthene (VI) in 90% yield.



VIII VI

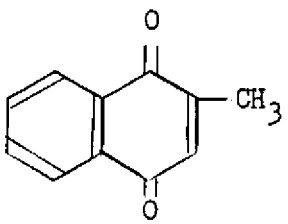
Cagniant (17) using the above method of cyclization carried out the ring closure of the acid chloride of α-methyl-γ-(2-thienyl)-butyric acid (IX) to give 2-methyltetrahydrothionaphthanone (X). This bicyclic ketone was prepared as an intermediate in the synthesis of the thiophene analog (XI) of menadione (XII), a structural relative of vitamin K.

Fabrichnyi et al., (18) prepared both six-and seven-membered bicyclic thiophene ketones (XIII and XIV) from the corresponding thienyl butyric and thienyl valeric acids, respectively.

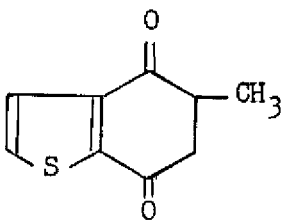


IX

X

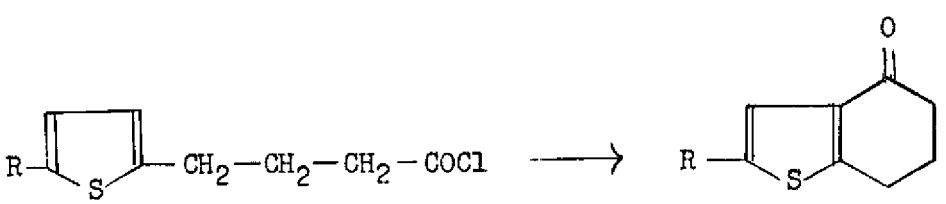


XII

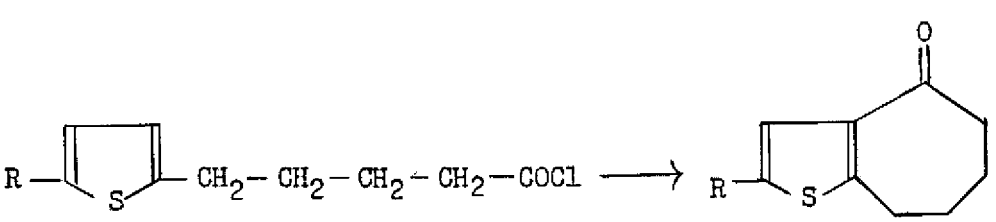


XI

Cyclization was carried out by the action of stannic chloride on the appropriate acid chloride in benzene solution.



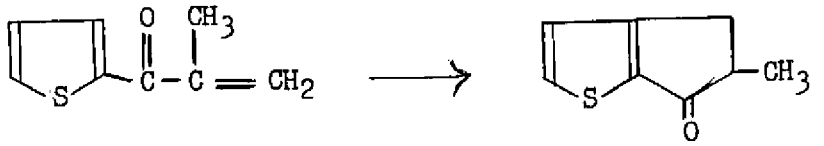
XIII



XIV

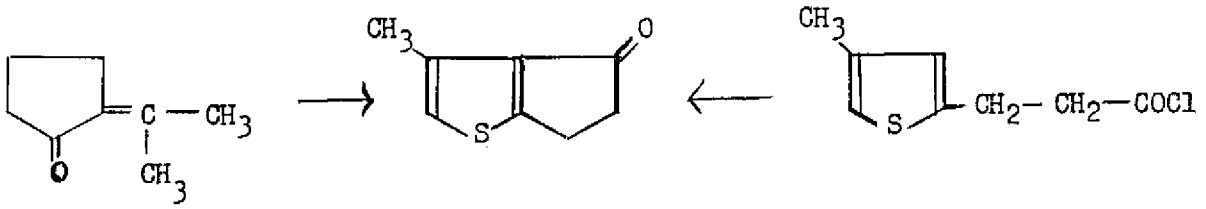
Cagniant and Cagniant (19) obtained 70-80% yield of ketone (XIV) by carrying out the cyclization of δ-(5-alkyl-2-thienyl)valeric acid chlorides with stannic chloride in carbon bisulfide for two hours. They reported a decrease in the yield of the ketone if the reaction time is prolonged or the chain length is increased.

Burckhalter and Sam (20) were successful in preparing the five-membered bicyclic thiophene system (XVI). The cyclization of α-methyl-2-acrylothienone (XV) was accomplished by the use of concentrated sulfuric acid at room temperature.

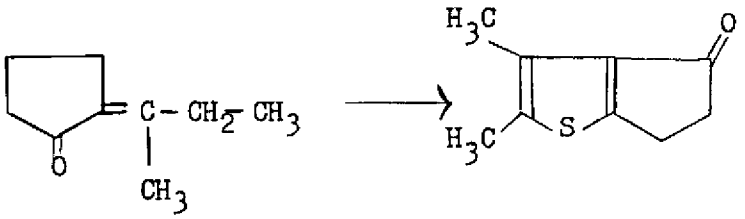


XV XVI

An attempt was made by Burckhalter and Sam to cyclize the unsubstituted acrylothienone with concentrated sulfuric acid to give the unsubstituted thiaindanone. This resulted in the formation of intermolecular condensation products. Several substituted thiaindan-4-ones have been prepared using different procedures. Christakis (21) prepared 3-methylthiaindan-4-one (XIX) and 2,3-dimethylthianindan-4-one (XX) from 2-isopropylidenecyclopentanone (XVII) and 2-(sec-butylidene)cyclopentanone (XVIII), respectively. The cyclization was accomplished by heating the appropriate cyclopentanone with sulfur at 200°C. The 3-methylthiaindan-4-one also was prepared by cyclization of β-(4-methyl-2-thienyl)propionyl chloride (XXI) with phosphoric acid.

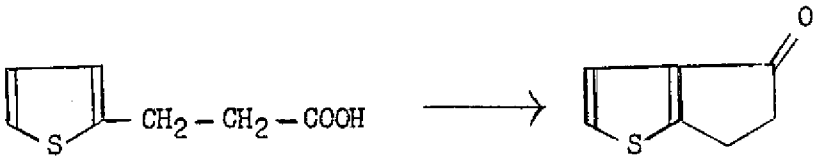


XVII XIX XXI

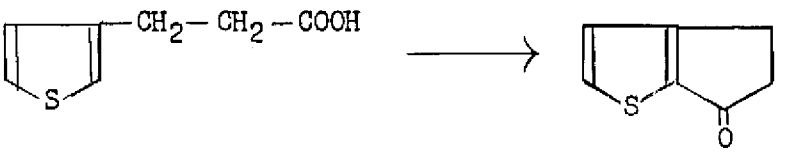


XVIII XX

Sam and Thompson (22) have devised methods for the cyclization of β-(2-and 3-thienyl)propionic acids to five-membered bicyclic thiophene ketones. The cyclization of β-(2-thienyl)propionic acid (XXII) to thiaindan-4-one (III) was accomplished with polyphosphoric acid whereas the cyclization of β-(3-thienyl)propionic acid (XXIII) to give thiaindan-6-one (IV) was carried out by the use of liquid hydrogen fluoride.



XXII III

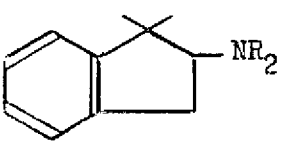


XXIII IV

B. Some Thiophene Derivatives of Biological Interest

For an extensive review of this subject the reader is referred to articles by Blanton and Nobles (23) and Martin-Smith and Reid (24).

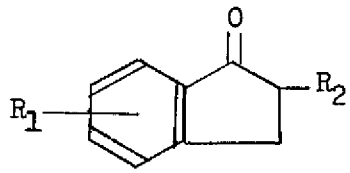
The physiological activity of compounds in the structurally related indan series has been studied extensively. A few of these as well as some of the related tetralones are mentioned because of their structural similarity to the compounds described in this thesis. Levin (25) has shown that indanamines (XXIV) are effective bronchodilators, the most active compounds in the series being 2-amino-1-indanones, 2-aminoindans, and 2-amino-indanols.



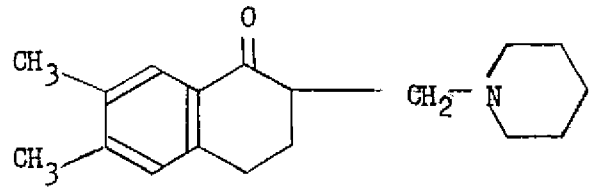
XXIV

Sam and Plampin (26) prepared a series of basic ethers from substituted indanones (XXV) which exhibited hypotensive activity characteristic of the veratrum ester alkaloids.

A series of Mannich bases prepared from 1-tetralone were observed to possess interesting biological properties (27). The 4-methyl derivative was found to be a potent anticonvulsant. Substitution at position 7, as well as at 6 and 7, enhance the tranquilizing effect. Of the derivatives produced thus far, the 6,7-dimethyl derivative (XXVI) proved to be a potent tranquilizing agent.

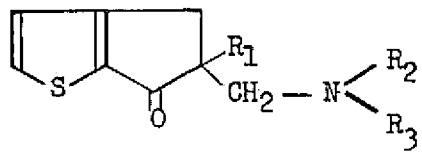


XXV



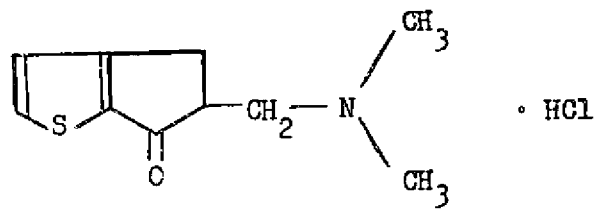
XXVI

A description of the biological properties of thiophene isosters of indanones is limited. Sam and Thompson (28) prepared a series of thiaindanones (XXVII) which exhibit some degree of anticonvulsant, antihypertensive and antibacterial activity.



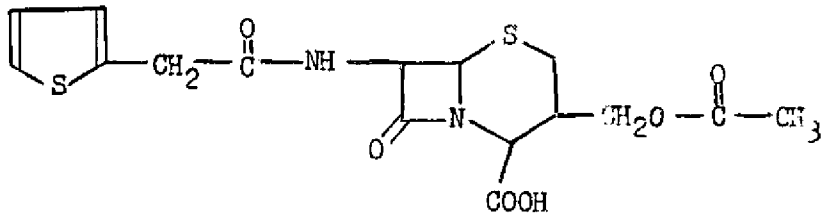
XXVII

Pronounced activity against both gram-positive and gram-negative bacteria was observed with 5-dimethylaminomethylthiaindan-6-one hydrochloride (XXVIII).



XXVIII

Preliminary studies (29) on cephalothin, sodium 7-(thiophene-4-acetamido)cephalosporamate (XXIX), have indicated that it has bactericidal activity and appears to be an effective drug for treating both gram-positive and gram-negative infections.

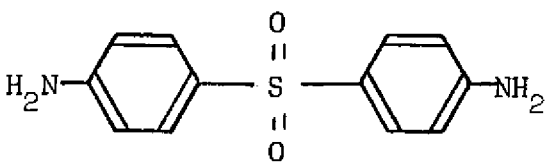


XXIX

The remainder of this discussion will be limited to some examples of the more important antimicrobial agents, antihistaminic agents and analgesics having thiophene nuclei.

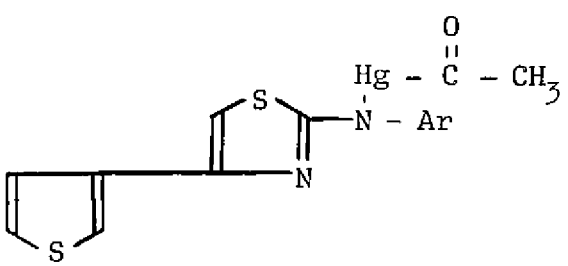
Antimicrobial Agents

The main chemical classes of drugs showing high antitubercular activity are sulfones, thiosemicarbazones, and certain acid hydrazides. Thiophene derivatives of each group have been prepared. The sulfone, XXX, possesses slight antitubercular and antistreptococcal activity (30).



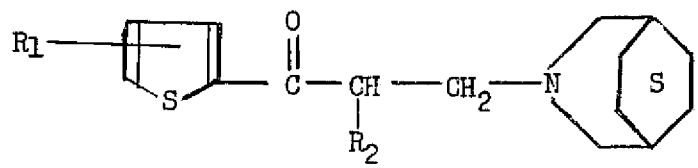
XXX

Antifungal activity has been reported (31) in many types of thiophene derivatives, especially those containing mercury (XXXI). Thiosemicarbazones of many substituted thiophene carboxaldehydes were synthesized



XXXI

as potential antiviral agents (32). Recently, certain β-amino ketones (Mannich bases) (XXXII) have been prepared (23) from 2-acetyl thiophene



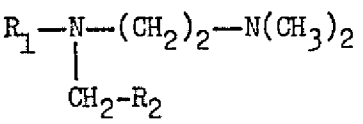
XXXII

and 3-azabicyclo [3.2.2] nonane. Results of the preliminary screening (23) indicated that significant antimicrobial activity against certain gram-positive and gram-negative bacteria, fungi, and protozoa is possessed by these compounds.

Antihistamines

Thiophene analogs of benzene derivatives are most prevalently used as antihistamines. Compounds with thiophene rings possessing antihistaminic activity are given in Table I. Most of the antihistamines used in clinical practice are structurally related to tripelennamine. The first two compounds in the table are included for comparison of structures.

TABLE I



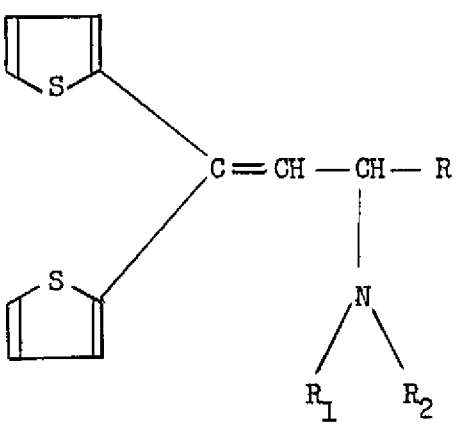
	R_1	R_2
Antergan	phenyl	phenyl
Tripelennamine	2-pyridyl	phenyl
Methapyrilene	2-pyridyl	2-thienyl
Chloromethapyrilene (chlorotheh)	2-pyridyl	2-(5-chlorothienyl)
Methaphenilene (diatrin)	phenyl	2-thienyl

Thiophene antihistamines in general have not shown any marked superiority over the antihistamines of other chemical groups (24). As with other antihistamines, the thiophene derivatives show local anesthetic activity, possess antifungal action, prolong blood clotting time, exert cardiodepressant activity, possess some oxytocic activity and demonstrate some atropine-like activity.

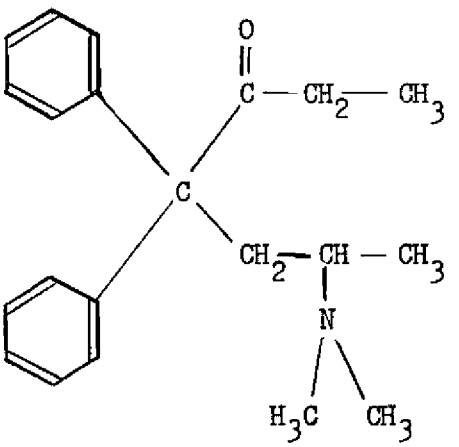
Methapyrilene is reported to possess hypnotic activity approximately equal to that of phenobarbital (33) and to potentiate the effect of other hypnotic drugs (34). The nicotinates of methapyrilene and thenyldiamine have been reported to be useful sedatives (35). Methapyrilene has also been employed in ophthalmology (36).

Analgesics

In the course of investigations of the biological properties of a series of 3-tertiaryamino-1,1-di(2-thienyl)but-1-enes (XXXIII) prepared as analogues of the 3,3-diphenylallylamines, which were known to have atropine-like, antihistaminic and local anesthetic properties (37), the important discovery was made that the thiophene compounds, in addition to having similar activity to the compounds on which they were modeled, also possessed pronounced analgesic activity (38). Unfortunately, they turned out to be addictive. This class of compounds has been named thiambutenes. They can be regarded as cogeners of methadone (XXXIV) in which the ketone side chain has been omitted with the introduction of a double bond, and the benzene rings replaced by thiophene rings.



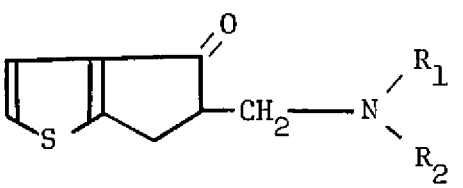
XXXIII



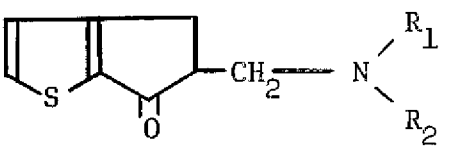
XXXIV

The compound, 3-piperidyl-1,1-di(2-thienyl)but-1-ene (XXXIII, NR_1R_2 = piperidino, R = CH_3) has been found to be very effective as an antitussive agent (39). The di(2-thienyl) isosters of both methadone and isomethadone in which the benzene rings have been replaced by thiophene rings have been prepared (40). Other compounds closely related in structure to methadone but which have only one of the benzene rings replaced by a thiophene ring have been tested and shown to be active analgesics (41).

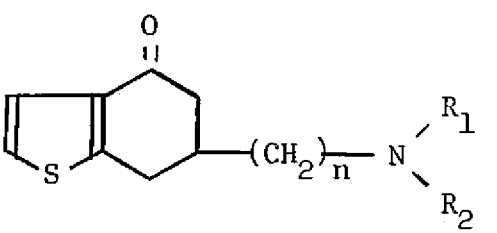
In view of the interesting pharmacological activity of the compounds described above, it was of interest to expand Sam and Thompson's work (42) on aminoketones (XXXV, XXXVI) derived from thiophene isosters of indanones and also to investigate aminoketones (XXXVII, n=0,1) derived from thiophene isosters of tetralone.



XXXV



XXXVI



XXXVII

DISCUSSION OF RESULTS

The primary objective of this investigation was the preparation of aminoketones of potential biological interest. Inasmuch as the ketones that were required were not readily available, considerable effort was devoted to their preparations. This section of the thesis, therefore, is divided into the following categories.

A. Preparation of 4-keto-4,5,6,7-tetrahydrothionaphthene

B. Preparation of thiaindan-4-one

C. Preparation of thiaindan-6-one

D. Preparation of α-aminoketones

E. Preparation of β-aminoketones (Mannich bases)

A. Preparation of 4-Keto-4,5,6,7-tetrahydrothionaphthene

The procedures described by Fieser and Kennelly (16) (Fig. 1) were followed. Acylation of thiophene (I) with succinic anhydride provided a 74% yield of β-(2-thenoyl)propionic acid (XXXVIII). This increase in yield (74% vs. 54%) over that obtained by Fieser and Kennelly was due to modified isolation procedures. Comparable yields of β-(2-thienyl)-butyric acid (XXXIX), β-(2-thienyl)butyryl chloride (VIII), and 4-keto-4,5,6,7-tetrahydrothionaphthene (VI) were obtained. No unusual problems were encountered in the preparation of these substances.

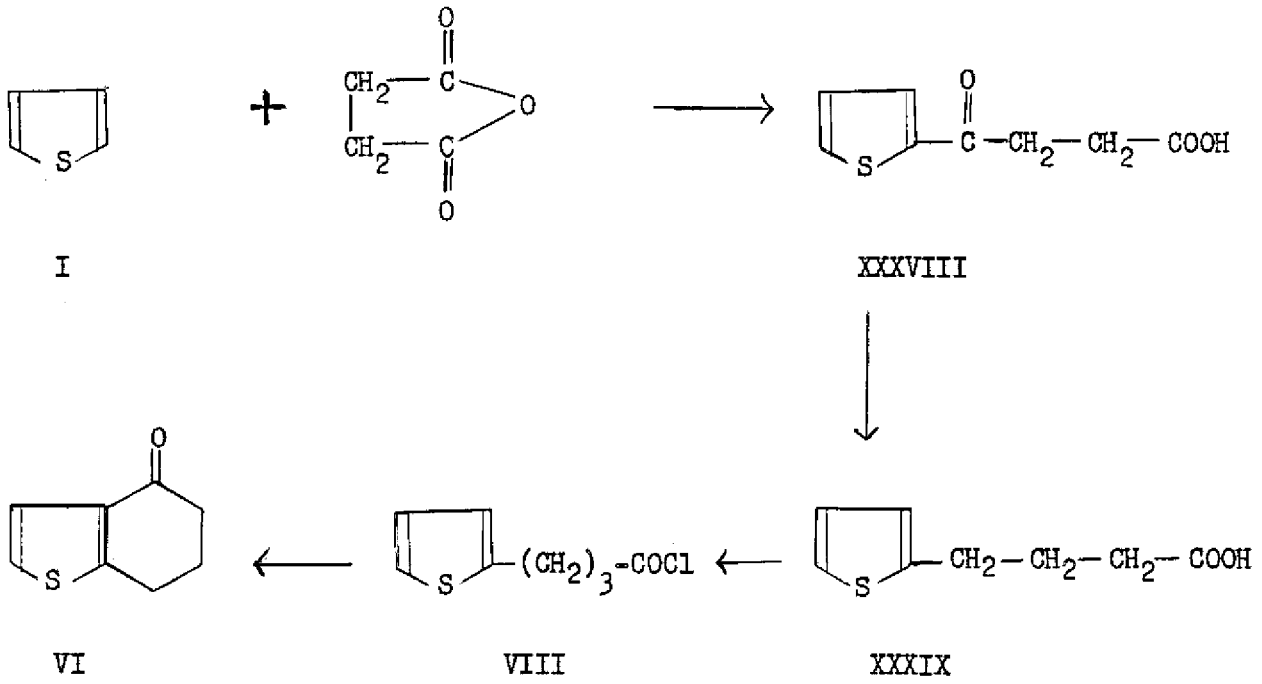


Fig. 1

B. Preparation of Thiaindan-4-one

The reactions shown in Figure 2 were employed for the preparation of thiaindan-4-one (III). The method employed by Rajagopalan and Raman (43) for the preparation of 2-furanacrylic acid was followed for the preparation of 2-thienylacrylic acid (XLI) from 2-thiophene aldehyde (XL).

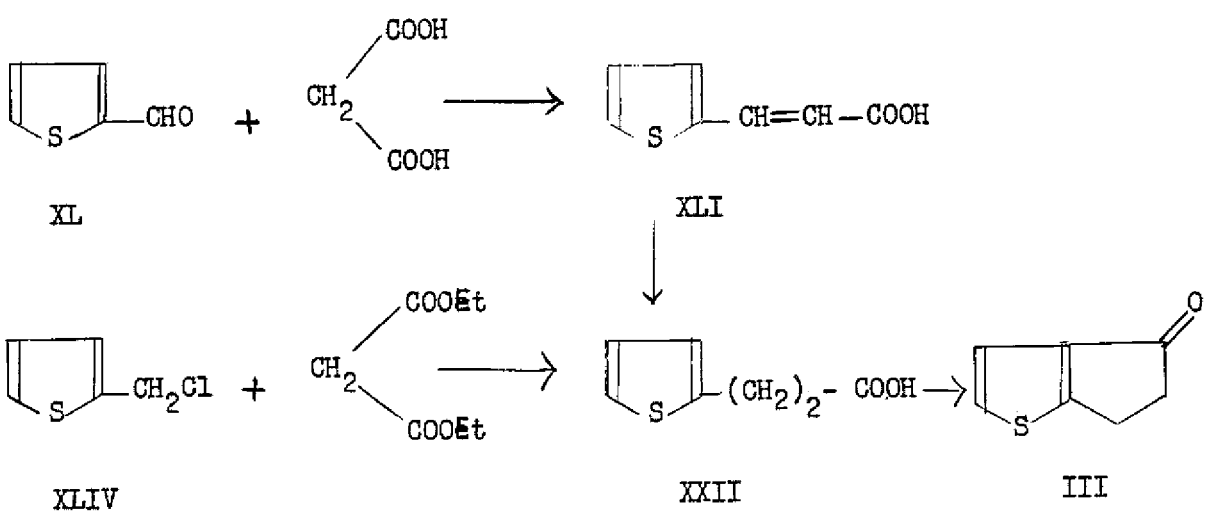
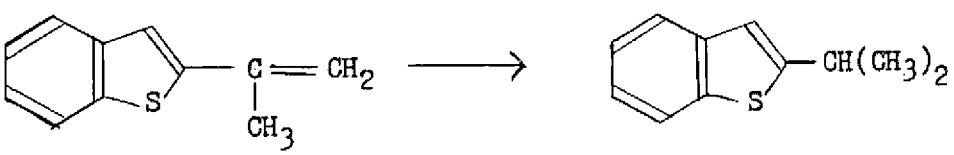


Fig. 2

Barger and Easson (44) employed sodium amalgam for the reduction of 2-thienylacrylic acid (XLI) to β-(2-thienyl)propionic acid (XXII), whereas we utilized sodium lead alloy.* Comparable yields (91%) were obtained.

Alternatively, 2-thienylacrylic acid was hydrogenated with 10% palladium-carbon catalyst by the method utilized by Bedell et al., (45) for the reduction of 2-isopropenylbenzo(b)thiophene (XLII) to 2-isopropylbenzo(b)thiophene (XLIII).



XLII XLIII

An alternate route to β-(2-thienyl)propionic acid involved the reaction of 2-chloromethylthiophene (XLIV) with diethylmalonate. The method of Blicke and Burckhalter (46) was followed for the preparation of 2-chloromethylthiophene and its condensation with diethylmalonate was performed according to the method of Campaigne and McCarthy (47). Both reactions, however, provided relatively low yields of product; consequently, this method was abandoned.

Considerable difficulty was encountered in repeating the work of Sam and Thompson (22) for the cyclization of β-(2-thienyl)propionic

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*Commercially available as dri-sodium, J. T. Baker Chemical Company.

acid (XXII) to thiaindan-4-one (III). They reported 36% yield of thiaindan-4-one from β-(2-thienyl)propionic acid.

The reaction was repeated many times, modifying the conditions as described by Sam and Thompson (22), however, only 7-10% yield of the product was obtained. The best yield (10%) was obtained when the reaction was carried out by adding as quickly as possible the solution of the acid (XXII) in methylene chloride to PPA* preheated to 130-135°, keeping the temperature of the reaction mixture between 120-130°. The use of chlorobenzene in place of methylene chloride with the same conditions as above gave 10% of thiaindan-4-one.

C. Preparation of Thiaindan-6-one

The reactions outlined in Figure 3 were employed for the preparation of thiaindan-6-one (IV). The method of Campaigne and Tullar (48) was followed for the bromination of 3-methylthiophene (XLV). Yields (65%) of the product (XLVI) comparable to those reported were obtained.

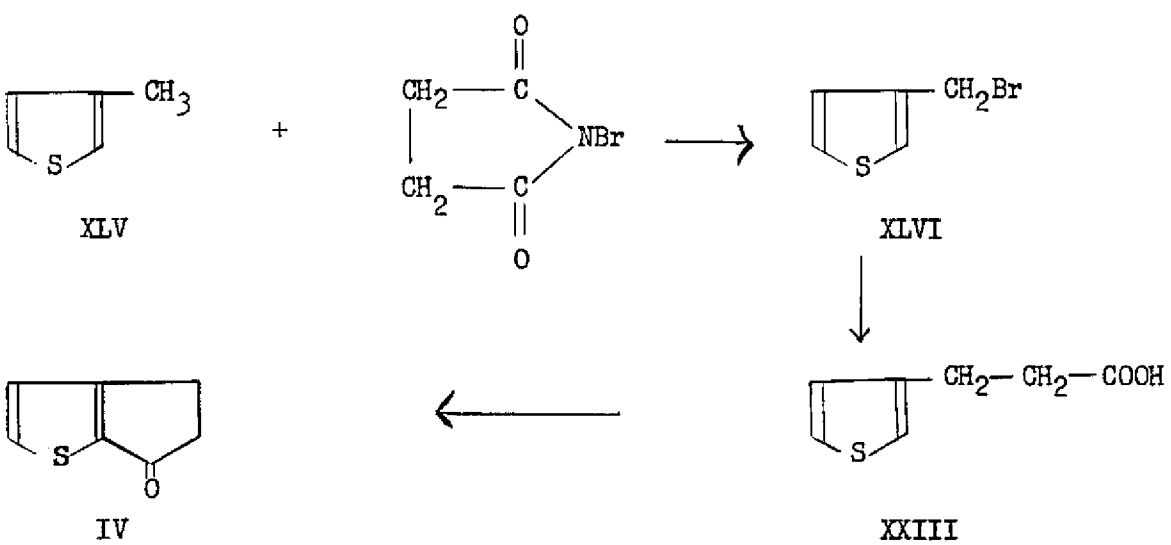


Fig. 3

*Polyphosphoric acid.

Comparable results also were obtained in the preparation of β-(3-thienyl) propionic acid (XXIII) from 3-thenylbromide (XLVI) by using the method of Campaigne and McCarthy (47) as modified by Sam and Thompson (22).

The cyclization of β-(3-thienyl)propionic acid to thiaindan-6-one was accomplished by using the method reported by Sam and Thompson (22). This was carried out by keeping β-(3-thienyl)propionic acid in contact with liquid hydrogen fluoride for approximately 18 hours. The yield of ketone was lower (29%) than reported (44%) by them.

D. Preparation of α-Aminoketones

The α-aminoketones that were investigated were limited to those prepared from 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene (XLVII). The bromination of 4-keto-4,5,6,7-tetrahydrothionaphthene (VI) was accomplished in good yield (93%) using bromine.

Aminoketones (Table II) were obtained by the condensation of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene with amines in a sealed tube according to the procedure used by Takahashi et al., (49) for the preparation of 2-aminocyclohexanones. Refluxing a mixture of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene with amines in benzene or in excess of amines was unsuccessful. Limited success was realized in the preparation of the ketones, either because of the instability of the products or the hygroscopic character of the salts.

Thus far the preparation of 5-amino-4-keto-4,5,6,7-tetrahydrothionaphthene (XLIX) has not been accomplished. Procedures (Fig. 4) involving the preparation of the isonitrosoketone, the Delepine, and the Gabriel reactions were unsuccessful.

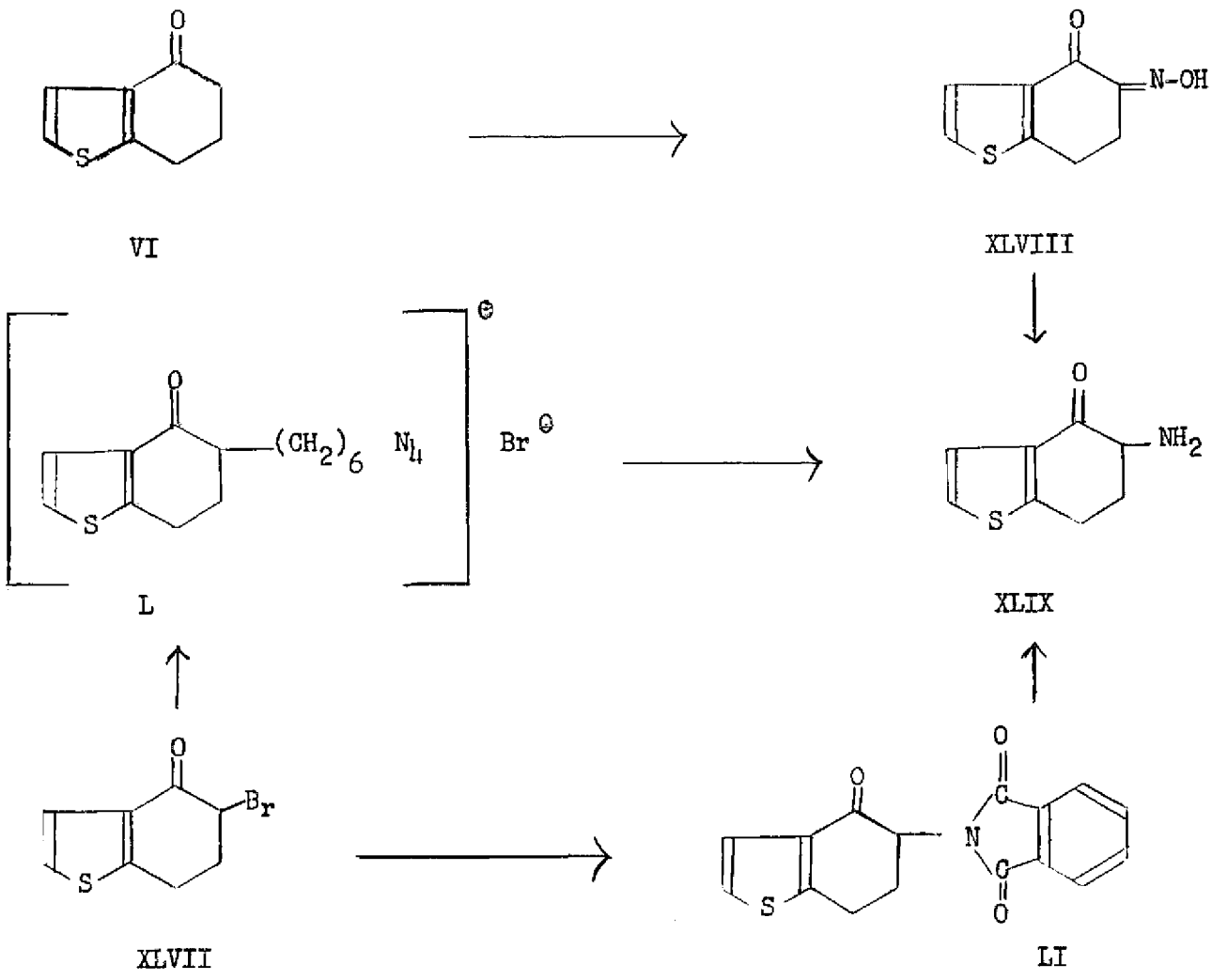


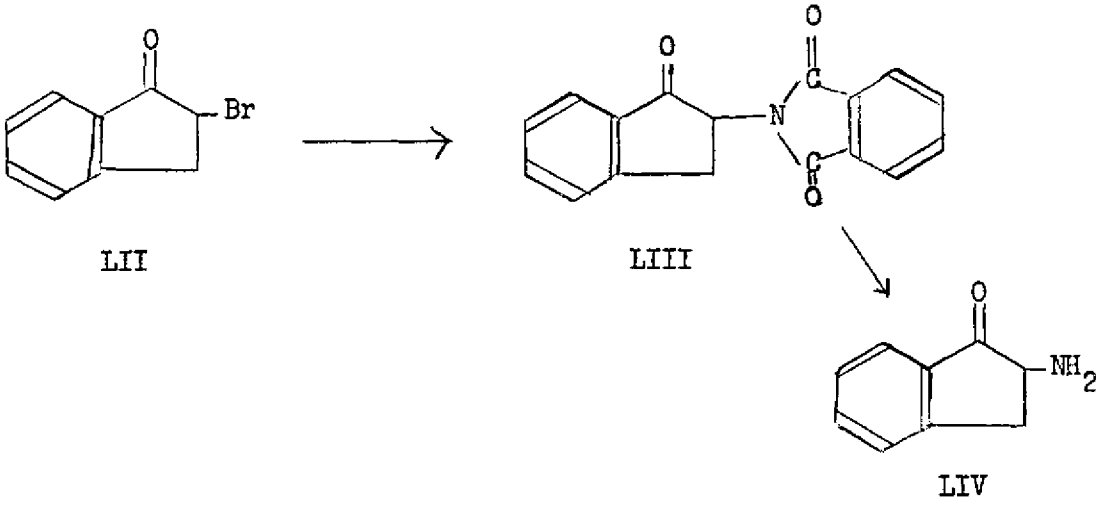
Fig. 4

The method of Friedrich and Werner (50) for the preparation of 2-isonitroso-1-indanones was followed in an attempt to prepare 5-isonitroso-4-keto-4,5,6,7-tetrahydrothionaphthene (XLVIII) and consequently 5-amino-4-keto-4,5,6,7-tetrahydrothionaphthene.

The method of Covello et al., (51) for the preparation of α-aminoacetophenone was followed in an attempt to prepare 5-amino-4-keto-4,5,6,7-tetrahydrothionaphthene via the Delépine reaction (XLVIII ⟶ L ⟶ XLIX). The method of Sheehan and Bolhofer (52) for the

preparation of α-phthalimidoacetophenone and the method of Sam and Plampin (26) for the preparation of an aminoindanone were followed in an attempt to prepare 5-amino-4-keto-4,5,6,7-tetrahydrothionaphthene via the Gabriel reaction (XLVII → LI →XLIX).

A model experiment involving the preparation of 2-phthalimido-1-indanone (LIII) from 2-bromo-1-indanone (LII) was performed. The hydrolysis with hydrazine hydrate of 2-phthalimido-1-indanone (LIII) to 2-amino-1-indanone (LIV) was unsuccessful.

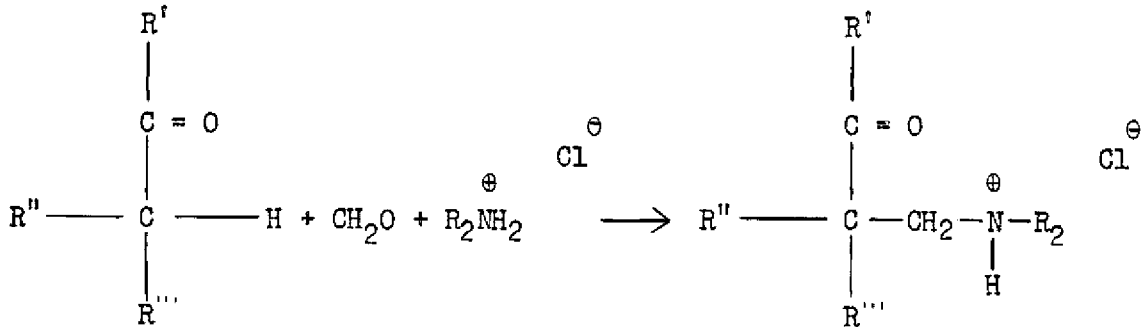


LII LIII LIV

E. Preparation of β-Aminoketones (Mannich bases)

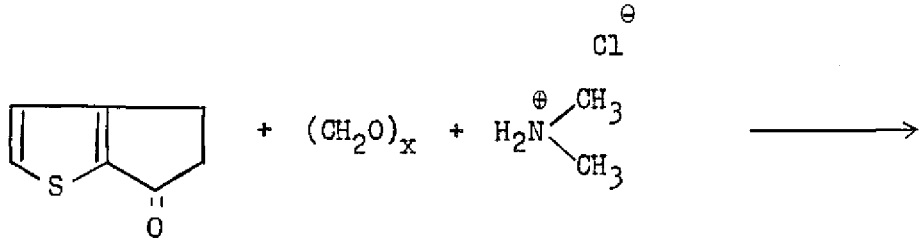
The Mannich reaction which consists in the condensation of ammonia or a primary or a secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity, was used for the preparation of β-aminoketones. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl group. The following example is illustrative of the Mannich reaction. A series of Mannich bases, made

as indicated below are listed in Table II, III, IV. The Mannich bases of the ketones, with the exception of thiaindan-6-one, were prepared (28)

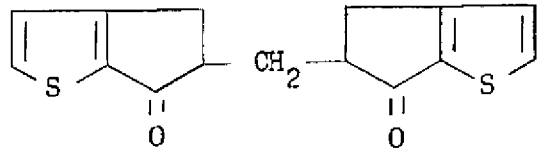


generally by refluxing the particular ketone, paraformaldehyde, the amine hydrochloride and concentrated hydrochloric acid in absolute ethanol for 4 hours.

The Mannich reaction involving thiaindan-6-one mostly was carried out in a 1:1 benzene-nitrobenzene mixture. Sam and Thompson (42) reported the formation of a bis product (LV) when the reaction was carried out with unsubstituted thiaindan-6-one (IV), paraformaldehyde and dimethylamine hydrochloride in 95% ethanol. From his studies of the



IV

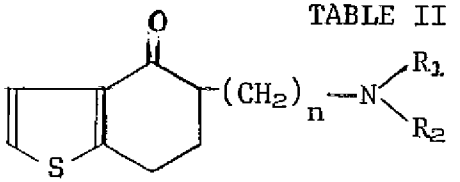


LV

Mannich reaction with 1-indanone, Fry (53) suggested that the amine hydrochloride and paraformaldehyde be heated together for 20 minutes in a 1:1 benzene-nitrobenzene mixture followed by the addition of the ketone. According to him, the nitrobenzene, having valuable solvent properties, aids in the formation of a complex between the amine hydrochloride and formaldehyde.

The Mannich bases of thiaindan-6-one were thus prepared by heating the mixture of appropriate amine hydrochloride, paraformaldehyde, concentrated hydrochloric acid in a 1:1 benzene-nitrobenzene mixture for 20 minutes followed by addition of the ketone and refluxing the mixture for an additional 30 minutes.

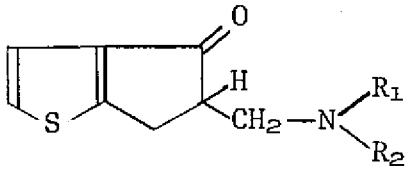
TABLE II



					Analyses %									
					Calculated					Found				
$N\begin{matrix}R_1\\R_2\end{matrix}$	n	M.P. °C	% Yield	Molecular Formula	C	H	Cl	N	S	C	H	Cl	N	S
$-C_8H_4NO_2$ [a]	0	183-185	17	$C_{16}H_{11}NO_3S$ [b]	64.5	3.7	--	4.7	10.8	64.8	3.8	--	4.6	10.7
$-C_4H_8NO$ [c]	0	205-206	56	$C_{12}H_{16}ClNO_2S$ [b,d]	52.6	5.9	13.0	5.1	11.7	52.8	5.9	13.0	4.8	11.7
-NHCH$_3$	1	205-206	73	$C_{10}H_{14}ClNOS$ [b,d]	51.8	6.1	15.3	6.1	13.8	52.0	6.1	15.2	6.0	13.7
$-N(CH_3)_2$	1	186-188	69	$C_{11}H_{16}ClNOS$ [b,d]	53.7	6.6	14.4	5.7	13.0	53.7	6.5	14.4	5.7	12.9
$-C_4H_8NO$ [c]	1	184-186	80	$C_{13}H_{18}ClNO_2S$ [b,d]	54.2	6.30	12.3	4.9	11.1	54.1	6.3	12.3	4.9	11.0
$-C_5H_{10}N$ [e]	1	180-182	53	$C_{14}H_{20}ClNOS$ [b,d]	58.8	7.1	--	4.9	11.2	58.8	7.0	--	5.1	11.5
$-NH-CH_2C_6H_5$	1	172-174	49	$C_{16}H_{18}ClNOS$ [b,d]	62.4	5.9	--	4.6	10.4	61.6	5.8	--	4.7	10.5

[a]Phthalimido. [b]Recrystallized from absolute ethanol. [c]Morpholino. [d]Hydrochloride. [e]Piperidino.

TABLE III

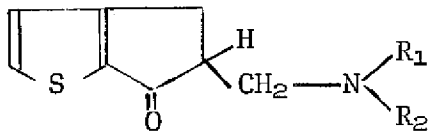


HCl

No.	$N\begin{matrix}R_1\\R_2\end{matrix}$	M.P. °C.	% Yield	Molecular Formula	Analyses % Calculated C	H	Cl	N	Found C	H	Cl	N
LXII	$-N(CH_3)_2$	169-170	65	$C_{10}H_{14}ClNOS$[a]	51.8	6.1	15.3	6.1	52.0	6.1	15.2	6.0
LXIII	$-NHCH_2C_6H_5$	199-201	85	$C_{15}H_{16}ClNOS$[a]	61.3	5.5	--	4.8	61.6	5.5	--	4.8
LXIV	$-C_5H_{10}N$[b]	194-195	96	$C_{13}H_{18}ClNOS$[a]	57.7	6.7	13.0	5.2	57.4	6.9	12.8	5.1
LXV	$-NHCH_3$	197-199	46	$C_9H_{12}ClNOS$[a]	49.7	5.6	--	6.4	50.5	5.7	--	5.9
LXVI	$-C_4H_8NO$[c]	199-201	58	$C_{12}H_{16}ClNO_2S$[a]	52.6	5.9	--	5.1	52.8	5.8	--	5.0

[a]Recrystallized from absolute ethanol. [b]Piperidino. [c]Morpholino

TABLE IV



·HCl

Number	$N\begin{matrix}R_1\\R_2\end{matrix}$	M.P. °C	% Yield	Molecular Formula	Analyses % Calculated C	H	N	Found C	H	N
LXVII	$-NH-CH_2C_6H_5$	188-190	68	$C_{15}H_{16}ClNOS$[a]	61.3	5.5	4.8	61.1	5.6	4.9
LXVIII	$-C_4H_8NO$[b]	160-161	88	$C_{12}H_{16}ClNO_2S$[a]	52.6	5.9	5.1			
LXIX	$-NHCH_3$	202-203	51	$C_9H_{12}ClNOS$[c]	49.7	5.6	6.4			

[a]Recrystallized from absolute ethanol. [b]Morpholino. [c]Recrystallized from methanol.

EXPERIMENTAL*

The reactions for the preparation of α -aminoketones and β-aminoketones (Mannich bases) were carried out with 4-thiaindanone, m.p. 115-117°; 6-thiaindanone m.p. 89-90°; and 4-keto-4,5,6,7-tetrahydrothionaphthene, m.p. 35-36°. The preparation of Mannich bases was accomplished using well known procedures. The reactions were performed either in ethanol using the method of Sam and Thompson (28) or in a mixture of benzene and nitrobenzene using the method of Fry (53).

β-(2-Thenoyl)propionic Acid (XXXVIII). The procedure described by Fieser and Kennelly (16) with some modifications was followed. Aluminum chloride (288 g., 2.16 moles) was added in small portions over a period of one hour to a stirred mixture at 0-5°C of 98 g. (0.98 mole) of succinic anhydride, 80 g. (0.95 mole) of thiophene, and 880 ml. of nitrobenzene. After stirring for an additional 4 hours the mixture was poured slowly into a mixture of ice and 200 ml. of concentrated hydrochloric acid. The resulting mixture was steam-distilled and the residual material was heated with water. The aqueous solution was decanted from the material and cooled in an ice bath. The solid which separated was removed by filtration, dissolved in 10% sodium carbonate solution, filtered and thereafter acidified with 1:1 hydrochloric acid. The yield of product was 130 g. (74%); m.p. 120°C. (Lit. (16) m.p. 119-120°).

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*All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer Model 137G infracord spectrophotometer using KBr pellets.

γ-(2-Thienyl)butyric Acid (XXXIX). The procedure described by Fieser and Kennelly (16) with some modifications was followed. To a mixture of amalgamated zinc (prepared from 250 g. of mossy zinc by shaking for five minutes with 700 ml. of 5% mercuric chloride and 12.5 ml. of concentrated hydrochloric acid) and 450 ml. of 1:1 hydrochloric acid, cooled to 25°, was added in one portion 25 g. (0.136 mole) of powdered β-(2-thenoyl)propionic acid. The mixture was allowed to stand with occasional shaking for 50 hours, 250 ml. of 1:1 hydrochloric acid being added at intervals during this period. The solid keto acid became oily and formed a film over zinc. To complete the reaction, the mixture was refluxed for 35 minutes. After cooling, the reaction product was extracted with ether, dried over sodium sulfate and distilled in vacuum. Seventeen grams (72%) of product was obtained; b.p. 124° (0.6 mm.).

γ-(2-Thienyl)butyryl Chloride (VIII). The procedure described by Fieser and Kennelly (16) was followed. The acid chloride was prepared by refluxing for 5 hours a solution of γ-(2-thienyl)butyric acid, 27.5 ml. of thionyl chloride, and 9 drops of pyridine in 68 ml. of anhydrous ether. Distillation of the residual solution gave 43.4 g. (83%) of product; b.p. 105-110°C. (at 1.5-2 mm.).

4-Keto-4,5,6,7-tetrahydrothionaphthene (VI). The procedure described by Fieser and Kennelly (16) was followed. A solution of 43.4 g. (0.23 mole) of γ-(2-thienyl)butyryl chloride in 132 ml. of carbon disulfide was added during 20 minutes to a stirred solution at 0° of 68.15 g. (0.262 mole) of anhydrous stannic chloride in 352 ml. carbon disulfide. A yellow addition compound separated which after refluxing for 2 hours became orange and pasty. After cooling

and adding ice, the mixture was steam-distilled. An ethereal extract of the distillate, after drying over sodium sulfate and evaporation yielded 35.3 g. (100%) of the product; m.p. 35-36°. (Lit.(16) m.p. 35.5-37°)

5-Bromo-4-keto-4,5,6,7-tetrahydrothionaphthene (XLVII). The method used by Wilds (54) for the bromination of 1-keto-1,2,3,4-tetrahydrophenanthrene was modified and used for this preparation. To a solution of 5.66 g. (0.037 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene in 400 ml. of anhydrous ether kept at 0°C was added dropwise with stirring 5.33 g. (0.033 mole) of bromine. Thereafter the mixture was stirred at room temperature until the yellow insoluble addition complex which had formed dissolved completely. The ethereal solution was poured into ice water, separated from the aqueous layer, and washed with water and dilute sodium bicarbonate solution, respectively. Evaporation of the ether left 8 g. (93%) of product which was recrystallized from petroleum ether (b.p. range 30-60°C); m.p. 79-81°.

Anal. Calcd. for C_8H_7BrOS: C, 41.59; H, 3.05; Br, 34.57; S, 13.88. Found: C, 41.51; H, 3.15; Br, 34.37; S, 13.8.

4-Keto-5-phthalimido-4,5,6,7-tetrahydrothionaphthene (LI). The procedure devised by Sheehan and Bolhofer (52) for the preparation of phthalimidoacetophenone was used. Potassium phthalimide (1.98 g., 0.0107 mole) was added in one portion to a stirred solution of 2.31 g. (0.01 mole) of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene in 20 ml. of N,N-dimethylformamide. After the mixture was stirred for 12 hours at room temperature, 15 ml. of chloroform were added and the mixture poured into 50 ml. of water. The aqueous phase was separated and extracted with two 5-ml. portions of chloroform. The combined chloroform

extract was washed with 10 ml. of 0.2 N sodium hydroxide and 10 ml. of water and thereafter dried over anhydrous sodium sulfate. After removal of the chloroform by distillation, the residual solid was triturated with 20 ml. of ether. The solid (0.5 g., 17%) was recrystallized several times from absolute ethanol; m.p. 183-185°.

Anal. Calcd. for $C_{16}H_{11}NO_3S$: C, 64.45; H, 3.73; N, 4.71; S, 10.78. Found: C, 64.79; H, 3.82; N, 4.56; S, 10.66.

4-Keto-5-morpholino-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LVI). The method used by Takahashi, et al. (49) was employed. Two and three-tenths grams (0.01 mole) of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene, 1.642 g. (0.02 mole) of morpholine, and 30 ml. of anhydrous benzene contained in a pressure bottle were heated in an oil bath for 3 hours at 100°C. The precipitated morpholine hydrochloride was removed by filtration and the benzene distilled in vacuo. The residue was treated with 10% hydrochloric acid and extracted with ether. The aqueous layer was neutralized with excess sodium bicarbonate and extracted with ether. The ethereal solution was dried over sodium sulfate and thereafter treated with hydrogen chloride. The precipitate (1.5 g., 56%) was removed by filtration and recrystallized from absolute ethanol; m.p. 205-206°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2S$: C, 52.62; H, 5.89; Cl, 12.95; N, 5.12; S, 11.70. Found: C, 52.84; H, 5.88; Cl, 13.01; N, 4.81; S, 11.60.

4-Keto-5-methylaminomethyl-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LVII). A mixture of 1.52 g. (0.01 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene, 0.375 g. (0.0125 mole) of paraformaldehyde, 0.743 g. (0.011 mole) of methylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was

refluxed on a steam bath for 4 hours. The alcohol was removed *in vacuo* and the residual solid was washed several times with ether leaving 1.7 g. (73%) of product which was recrystallized from absolute ethanol; m.p. 205-206°.

Anal. Calcd. for $C_{10}H_{14}ClNOS$: C, 51.83; H, 6.09; Cl, 15.31; N, 6.05; S, 13.84. Found: C, 51.97; H, 6.13; Cl, 15.24; N, 5.98; S, 13.74.

4-Keto-5-dimethylaminomethyl-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LVIII). A mixture of 3.04 g. (0.02 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene, 0.751 g. (0.025 mole) of paraformaldehyde, 1.794 g. (0.022 mole) of dimethylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed *in vacuo* and the residual solid was washed several times with ether leaving 3.4 g. (69%) of product which after recrystallization several times from absolute ethanol melted at 186-188°.

Anal. Calcd. for $C_{11}H_{16}ClNOS$: C, 53.74; H, 6.56; Cl, 14.42; N, 5.7; S, 13.04. Found: C, 53.70; H, 6.47; Cl, 14.38; N, 5.67; S, 12.86.

4-Keto-5-morpholinomethyl-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LIX). A misture of 2.0 g. (0.0131 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene, 0.495 g. (0.0165 mole) of paraformaldehyde, 1.788 g. (0.0145 mole) of morpholine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed *in vacuo* and the residual solid was washed several times with ether leaving 3.0 g. (80%) of product which was recrystallized from absolute ethanol; m.p. 184-186°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2S$: C, 54.24; H, 6.30; Cl, 12.32; N, 4.87; S, 11.14. Found: C, 54.12; H, 6.28; Cl, 12.27; N, 4.94; S, 11.04.

4-Keto-5-piperidinomethyl-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LX). A mixture of 3.04 g. (0.02 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene, 0.75 g. (0.025 mole) of paraformaldehyde, 2.44 g. (0.022 mole) of piperidine hydrochloride, 15 ml. of absolute ethanol, and two drops of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with ether leaving 3.0 g. (53%) of the product which was recrystallized from absolute ethanol; m.p. 180-182°.

Anal. Calcd. for $C_{14}H_{20}ClNOS$: C, 58.83; H, 7.06; N, 4.9; S, 11.22. Found: C, 58.79; H, 6.97; N, 5.05; S, 11.45.

4-Keto-5-benzylaminomethyl-4,5,6,7-tetrahydrothionaphthene Hydrochloride (LXI). A mixture of 1.52 g. (0.01 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene, 0.375 g. (0.0125 mole) of paraformaldehyde, 1.58 g. (0.011 mole) of benzylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with ether leaving 1.5 g. (49%) of the product which was recrystallized from absolute ethanol; m.p. 172-174°.

Anal. Calcd. for $C_{16}H_{18}ClNOS$: C, 62.44; H, 5.89; N, 4.55; S, 10.42. Found: C, 61.63; H, 5.81; N, 4.65; S, 10.53.

2-Thienylacrylic Acid (XLI). The method of Rajalopalan and Raman (43) for the preparation of 2-furanacrylic acid was used. In a 1-liter round-bottomed flask fitted with a reflux condenser was placed 112.14 g. (1 mole) of freshly distilled 2-thiophene aldehyde, 104 g. (1 mole) of malonic acid, and 48 ml. (0.6 mole) of pyridine. The flask was heated for 2 hours on a water bath, cooled and diluted with 100 ml. of water. The precipitated solid was treated with concentrated ammonium hydroxide, filtered and washed with 100 ml. of water. The filtrate and washings were combined and while stirring acidified to congo red with dilute hydrochloric acid. The mixture was cooled in an ice bath for 1 hour. The precipitate was removed by filtration, washed with 200 ml. 50-ml. portions) of ice cold water and dried leaving 130 g. (84%) of 2-thienylacrylic acid; m.p. 145-147°. (Lit. (44) m.p. 143-145°.

2-Chloromethylthiophene (XLIV). The method devised by Blicke and Burckhalter (46) was utilized. In a 2-liter beaker immersed in an ice-salt bath, fitted with a mechanical stirrer and a thermometer was placed 420 g. (5 moles) of thiophene and 200 ml. of concentrated hydrochloric acid. A rapid stream of hydrogen chloride was passed into this solution continuously with vigorous stirring. When the temperature reached 0°C. 165 g. (5.5 moles) of paraformaldehyde was added at such a rate that the temperature remained between 0-5°. The addition of paraformaldehyde was regulated by the clearing up of the solution after each addition (about 10 minutes). When the addition was complete, the reaction was stirred for 15 minutes and then extracted with four 500 ml. portions of ether. The combined extracts were washed once with water (500 ml.) and once with saturated sodium bicarbonate solution,

respectively. The ether extract was then dried over anhydrous calcium chloride. After evaporation of solvent, the residue was distilled under vacuum yielding 187.3 g. (28%) of product, b.p. 56-58°/4.75 mm. (Lit. (46) b.p. 80-81°/18 mm.).

β-(2-Thienyl)propionic Acid (XXII). Method A. The method devised by Barger and Easson (44) for the reduction of 2-thienylacrylic acid was modified and used for the preparation of the β-(2-thienyl) propionic acid. A solution of 2-thienylacrylic acid (215.86 g., 1.4 moles) in 2 liters of 2.8% sodium hydroxide was maintained at 10-15° and treated portionwise over a two-hour period with stirring with 1400 g. of sodium-lead alloy. The solution was filtered and made acidic. The precipitated acid was removed by filtration and distilled to give 200 g. (91%) of product, b.p. 116-124°/0.45-0.75 mm.; m.p. 42-44° (Lit. (44) m.p. 43-45°).

Method B. The method used by Bedell et al. (45) was employed. A solution of 15.4 g. (0.1 mole) of 2-thienylacrylic acid in 200 ml. of methanol was treated with 2 g. of 10% palladium-carbon catalyst and hydrogenated at 42 psi. Only 6.5 lbs. of hydrogen were taken up during the next 20 hours. An additional gram of 10% palladium-carbon catalyst was added and hydrogenation continued for another hour at 42 psi. During this time it took 1.5 lbs. of hydrogen. No further uptake of hydrogen was observed during an additional half hour. The catalyst was removed by filtration and the solvent distilled in vacuo leaving 12.6 g. (80%) of product melting at 48-49°.

Method C. The method employed by Campaigne and McCarthy (47) was used. To a solution of 253 g. (1.53 moles) of diethylmalonate in sodium ethoxide, made by reacting 31.63g. (1.375g.-at.) of sodium with

688 ml. of absolute ethanol, was added through a dropping funnel and with constant shaking, 182.2 g. (1.375 moles) of 2-chloromethylthiophene. The resulting mixture was heated at reflux on a water bath for 5 hours. At the end of this time, 280 g. (5 moles) of potassium hydroxide in 245 ml. of water was added carefully to the mixture and the mixture refluxed for a further period of 16 hours in an oil bath. The ethanol was distilled in vacuo and the residue was diluted with 500 ml. of water, cooled in an ice bath and made acidic with concentrated hydrochloric acid. The acidic solution was extracted with two 500-ml. portions of ether. Evaporation of the ether left a brown oil which was distilled to yield 54 g. (25%) of product, b.p. 142/4mm; m.p. 42-44°.

Thiaindan-4-one (III). The method of Sam and Thompson (22) was modified for this preparation. A solution of 31.2 g. (0.2 mole) of β-(2-thienyl)propionic acid in 50 ml. of methylene chloride was added as quickly as possible to a well-stirred solution of 400 g. of PPA preheated to 130-135°. The temperature of the mixture during the addition of the acid was maintained between 120-130°. When the addition of the organic acid was complete the mixture was cooled to 95° and poured, with vigorous stirring, into 600 ml. of ice water. The brown precipitate obtained was removed by filtration; the filtrate was saturated with sodium chloride and extracted with ethyl acetate. The combined extract was washed with water and 10% sodium bicarbonate solution, respectively, and then dried over anhydrous sodium sulfate. Distillation of the solvent left 3.0 g. (10.4%) of product melting at 115-117°.

5-Dimethylaminomethylthiaindan-4-one Hydrochloride (LXII).

A mixture of 1.38 g. (0.01 mole) of thiaindan-4-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 0.897 g. (0.011 mole) of dimethylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with ether leaving 1.5 g. (65%) of product which was recrystallized from absolute ethanol; m.p. 169-170°.

Anal. Calcd. for $C_{10}H_{14}ClNOS$: C, 51.83; H, 6.09; Cl, 15.31; N, 6.05. Found: C, 52.03; H, 6.1; Cl, 15.15; N, 6.02.

5-Benzylaminomethylthiaindan-4-one Hydrochloride (LXIII).

A mixture of 1.38 g. (0.01 mole) of thiaindan-4-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 1.58 g. (0.011 mole) of benzylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with ether leaving 2.5 g. (85%) of product which was recrystallized from absolute ethanol; m.p. 199-201°.

Anal. Calcd. for $C_{15}H_{16}ClNOS$: C, 61.31; H, 5.49; N, 4.77; Found: C, 61.55; H, 5.53; N, 4.75.

5-Piperidinomethylthiaindan-4-one Hydrochloride (LXIV).

A mixture of 1.38 g. (0.01 mole) of thiaindan-4-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 1.22 g. (0.011 mole) of piperidine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid

was washed several times with ether leaving 2.6 g. (96%) of product which after recrystallization several times from absolute ethanol melted at 194-195°.

Anal. Calcd. for $C_{13}H_{18}ClNOS$: C, 57.74; H, 6.67; Cl, 13.04; N, 5.15; Found: C, 57.38; H, 6.87; Cl, 12.8; N, 5.06.

5-Methylaminomethylthiaindan-4-one Hydrochloride (LXV). A mixture of 1.38 g. (0.01 mole) of thiaindan-4-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 0.743 g. (0.011 mole) of methylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with either leaving 1.0 g. (46%) of product which after recrystallization several times from absolute ethanol melted at 197-199°.

Anal. Calcd. for $C_9H_{12}ClNOS$: C, 49.65; H, 5.56; N, 6.43. Found: C, 50.49; H, 5.66; N, 5.87.

5-Morpholinomethylthiaindan-4-one Hydrochloride (LXVI). A mixture of 1.38 g. (0.01 mole) of thiaindan-4-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 1.46 g. (0.011 mole) of morpholine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed in vacuo and the residual solid was washed several times with either leaving 1.6 g. (58%) of product which after recrystallization several times from absolute ethanol melted at 199-201°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2S$: C, 52.62; H, 5.89; N, 5.12; Found: C, 52.82; H, 5.82; N, 5.043.

3-Thienyl Bromide (XLVI). The method used by Campaigne and Tullar (48) was followed. A 5-liter three-necked flask was fitted with two regular condensers and a large bore condenser in the center neck. A solution of 220 g. (2.24 moles) of 3-methylthiophene and 4.0 g. of benzoyl peroxide in 700 ml. of dry benzene was brought to vigorous reflux in this flask, and a mixture of 356 g. (2 moles) of N-bromosuccinimide and 4 g. of benzoyl peroxide was added portionwise through the large bore condenser; the addition was done as rapidly as violent foaming permitted. When the addition was complete, the flask was cooled first in a water bath and then in an ice bath. The succinimide was removed by filtration and washed once with dry benzene. The filtrate and the washing were transferred to a distilling flask and benzene removed in vacuo. The residue was distilled yielding 231 g. (65%) of product; b.p. 75-87°/1-3 mm.; n_D^{27} 1.60375. (Lit. n_D^{25} 1.6030).

β-(3-Thienyl)propionic Acid (XXIII). The method described by Campaigne and McCarthy (47), as modified by Sam and Thompson (28), was followed. To a solution of 216 g. (1.35 moles) of diethylmalonate in sodium ethoxide, made by reacting 30.02 g. (1.305 g.-at.) of sodium and 450 ml. of absolute ethanol, was added through a dropping funnel and with constant shaking 231 g. (1.305 moles) of 3-thienylbromide. The resulting mixture heated at reflux on a water bath for 5 hours. At the end of this time, 270 g. of potassium hydroxide in 360 ml. of water was added to the mixture and the mixture refluxed for an additional 24 hours. The resulting mixture was concentrated to 400 ml. in vacuo, treated with 250 ml. of water, cooled in an ice bath, and made acidic to pH of 1-2 with concentrated hydrochloric acid.

The acidic solution was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of ether left a brown oil which was distilled at 120-125° at 5 mm. yielding a liquid which solidified on cooling. Recrystallization from cyclohexane gave 77 g. (38%) of product melting at 59-60° (Lit. (28) m.p. 61-62°).

Thiaindan-6-one (IV). The method of Sam and Thompson (22) was used. In a copper retort containing 50 g. (0.32 mole) of β -(3-thienyl)-propionic acid was added 400 g. of liquid hydrogen fluoride and the mixture, with occasional shaking, was allowed to stand overnight (approximately 18 hours) in a fume hood. The contents of the retort were poured into a copper beaker and the hydrogen fluoride was evaporated in the hood. The residual brown solid was washed with water and 10% sodium bicarbonate solution, respectively, and extracted with ether. The ethereal layer was washed again with water and 10% sodium bicarbonate, respectively, and thereafter dried over anhydrous potassium carbonate. Evaporation of the solvent left 13 g. (29%) of product melting at 89-90° (Lit. (22) m.p. 90-91°).

5-Benzylaminomethylthiaindan-6-one Hydrochloride (LXVII). A mixture of 1.38 g. (0.01 mole) of thiaindan-6-one, 0.375 g. (0.0125 mole) of paraformaldehyde, 1.58 g. (0.011 mole) of benzylamine hydrochloride, 10 ml. of absolute ethanol, and one drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hours. The alcohol was removed *in vacuo* and the residual solid was washed several times with ether leaving 2 g. (68%) of product which after recrystallization several times from absolute ethanol melted at 188-190°.

Anal. Calcd. for $C_{15}H_{16}ClNOS$: C, 61.31; H, 5.49; N, 5.77. Found: C, 61.06; H, 5.60; N, 4.89.

5-Morpholinomethylthiaindan-6-one Hydrochloride (LXVIII). A mixture of 3.09 g. (0.025 mole) of morpholine hydrochloride, 0.75 g. (0.025 mole) of paraformaldehyde, two drops of concentrated hydrochloric acid, 4 ml. of benzene, and 4 ml. of nitrobenzene was refluxed in an oil bath for 20 minutes. This solution was treated with 3.45 g. (0.025 mole) of thiaindan-6-one and refluxed for an additional 30 minutes. During the last 12 minutes of reflux the water was distilled from the reaction mixture. The residue was cooled and washed several times with ether leaving 3.09 g. (88%) of product which after recrystallization several times from absolute ethanol melted at 160-161°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2S$: C, 52.62; H, 5.89; N, 5.12. Found:

5-Methylaminomethylthiaindan-6-one Hydrochloride (LXIX). A mixture of 5.52 g. (0.04 mole) of thiaindan-6-one, 2.7 g. (0.04 mole) of methylamine hydrochloride, 1.2 g. (0.04 mole) of paraformaldehyde, 8 ml. of benzene, 8 ml. of nitrobenzene, and two drops of concentrated hydrochloric acid was refluxed in an oil bath for 50 minutes. During the last 12 minutes of the reflux water was distilled from the reaction mixture. The residue was cooled and washed several times with ether leaving 4.45 g. (51%) of product which after recrystallization several times from methanol melted at 202-203°.

Anal. Calcd. for $C_9H_{12}ClNOS$: C, 49.65; H, 5.56; N, 6.43. Found:

Potassium Phthalimide. The method of Salzberg and Supniewski (55) was followed. In a 500 ml. round-bottomed flask fitted with a reflux condenser were placed 20 g. (0.135 mole) of phthalimide and 400 ml.

of absolute ethanol. The mixture was gently boiled until no more of phthalimide dissolved. The hot solution was decanted from the solid into a solution of 7.63 g., (0.135 mole) of potassium hydroxide in 7.5 ml. of water and 22.5 ml. of absolute ethanol. A precipitate of potassium phthalimide separated at once. The mixture was stirred and rapidly cooled to room temperature and the precipitate removed by filtration. The precipitate was washed with 25 ml. of acetone. The yield of air dried potassium phthalimide was 20 g. (80%).

2-Bromo-1-indanone. (LII). The method of Johnson and Shelberg (56) was used. To a solution of 26.4 g. (0.2 mole) of 1-indanone in 400 ml. of ether kept at 0°C. was added with stirring over a 10 minute period 32 g. (0.2 mole) of bromine. Thereafter the mixture was stirred at room temperature for 6 hours and kept aside overnight. The ethereal solution was poured into ice water, separated from the aqueous layer, and washed with water and dilute sodium bicarbonate solution, respectively. Evaporation of the ether left 34 g. (81%) of product. Part of the product was recrystallized from petroleum ether (b.p. range 30-60°); m.p. 38-39° (Lit. (56) m.p. 36-37°).

2-Phthalimido-1-indanone (LIII). The method of Curtin and Schmukler (57) was used. To 3.89 g. (0.021 mole) of potassium phthalimide in 15 ml. of N,N-dimethylformamide was added 6.34 g. (0.03 mole) of 2-bromo-1-indanone (crude). The mixture was heated on a steam bath with stirring for 8 hours. At the end of this period the reaction mixture was poured into 120 ml. of water. The product (3.0 g., 36%) was removed by filtration and recrystallized several times from ethanol; m.p. 200-201°.

Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.62; H, 4.00; N, 5.05. Found: C, 73.79; H, 4.03; N, 5.07.

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A STUDY OF AMINO DERIVATIVES OF THIOPHENE ISOSTERS OF INDANONE AND TETRALONE

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This investigation was undertaken to prepare amino derivatives of thiophene isosters of indanone and tetralone.

One new α-bromoketone was prepared from 4-keto-4,5,6,7-tetrahydrothionaphthene.

One new α-aminoketone was prepared from 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene and morpholine.

Two new α-imidoketones were prepared by the reactions of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene and 2-bromo-1-indanone with potassium phthalimide.

Five new β-aminoketones were prepared from 4-keto-4,5,6,7-tetrahydrothionaphthene by the application of the Mannich reaction.

Five new β-aminoketones were prepared from thiaindan-4-one by the application of the Mannich reaction.

Three new β-aminoketones were prepared from thiaindan-6-one by the application of the Mannich reaction.

Preliminary attempts to prepare α- and β-primaryaminoketones were unsuccessful.

The new compounds as described in this thesis have been sent for biological testing. However, at the time of submission of the thesis, the results were not received and hence could not be included in the discussion.