Synthesis of 2-Thiophene Derivatives

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The objective of this present study is the synthesis of certain new 2-thiophene derivatives to be evaluated as potential antispasmodic, analgesic, or local anesthetic agents. The first part of this study concerns the synthesis of β-aminoketones (Mannich bases). The second segment concerns the synthesis of γ-amino secondary alcohols by chemical reduction of the corresponding β-aminoketones. The third portion describes the synthesis of a series of γ-amino tertiary alcohols by application of the Grignard reaction to the corresponding Mannich bases. The last section of the study involves the preparation of γ-aminoalkyl esters from the corresponding tertiary alcohols.

THE INTEREST in compounds containing thiophene rings as biologically active agents stems primarily from the similar physical and chemical properties of benzene and thiophene. The concept of preparing thiophene analogs of biologically active compounds has stimulated workers in medicinal chemistry to the point that by now it appears that at least one thiophene analog has been prepared for every important therapeutic group containing a benzene nucleus.

The physical and chemical characteristics of thiophene and benzene, as well as some of the biological activities of compounds of this type, can be reasonably well correlated by the application of the concept of isosterism as introduced by Langmuir (1) in 1919 and subsequently developed by Erlenmeyer (2) and others (3, 4). In the case of thiophene, the lower resonance energy and the presence of a hetero atom in the ring, along with the fact that a dipole moment exists, would logically lead one to postulate that thiophene compounds would be more easily degraded and detoxified in the human body. It is generally accepted from experimental evidence, however, that thiophene compounds are more toxic than their benzene analogs. There are important exceptions, however, and it is this realization that inspires further investigations in this field of endeavor.

The preparation of β-aminoketones requires the use of the Mannich reaction (5), which consists of the condensation of formaldehyde with ammonia, or a primary or secondary amine and a compound containing at least one active hydrogen atom. The amine is generally used in the form of its hydrochloride salt. An example of the reaction follows

$$C_6H_5COCH_3 + CH_2O + R_2NH.HCl \rightarrow C_6H_5COCH_2CH_2NR_2 \cdot HCl + H_2O$$

Mannich and Lammering (6) prepared a series of β-aminoketones and found that β-N-piperidinoethyl phenyl ketone, prepared from acetophenone, piperidine hydrochloride, and paraformaldehyde, possessed local anesthetic activity. Levvy and Nisbet (7) prepared a series of β-aminoketones from 2-acetylthiophene and found that 2-thienyl-β-piperidinoethyl ketone hydrochloride and the β-dimethylaminoethyl analog possessed local anesthetic activity, though considerably less than cocaine.

The work was extended by Denton and coworkers (8) who prepraed 22 β-aminoketones and evaluated them pharmacologically. In subsequent work by these investigators in which 23 additional β-aminoketones were prepared (9), it was concluded that, in general, a decrease in activity results from: (*a*) increasing the complexity of the amino group, and (*b*) the introduction of more complex aromatic radicals than the phenyl group.

Mannich bases from benzalacetone were prepared by Burckhalter and Johnson (10) as vinylogs of β-aminopropiophenones in an attempt to enhance their analgetic activity. While these compounds were devoid of analgetic activity, they did possess *in vitro* action against bacteria. Denton and co-workers (11) reported the preparation of a secondary alcohol, 3-(1-piperidyl)-1,2-diphenyl-1-propanol hydrochloride, and found that it ranked higher in antispasmodic activity than did the seven tertiary alcohols with which it was compared.

Mannich (12) was not able to obtain *m*-aminophenyl β-piperidinoethyl ketone monohydrochloride by chemical reduction of the nitro base; Wright and Freifelder (13) were able to obtain this compound, however, by catalytic reduction of the ketone monohydrochloride in aqueous solution with 5% palladium on activated charcoal.

Nobles (14) reported the preparation of 3-dimethylamino-1-phenyl-1-propanol hydrochloride by the reduction of the corresponding amino ketone with sodium borohydride.

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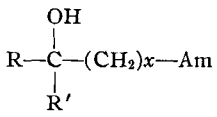
Denton and co-workers (15–19) have prepared more than 100 γ-amino tertiary alcohols, a majority of which have exhibited physiological activity. The general structure of the γ-amino-alcohols prepared by these workers is represented as follows

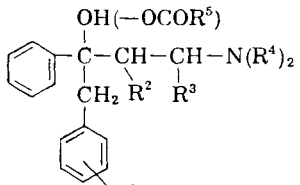


Cunningham and co-workers (20) prepared 3-(N - piperidyl) - 1 phenyl - 1 - cyclohexy - 1 - propanol hydrochloride[1] and related compounds. These compounds were found to be potent antispasmodics.

Adamson (21) found that the intermediates for the preparation of compounds with antihistaminic properties may be obtained by treating tertiary aminoethyl ketones or their salts with 2-pyridyllithium and hydrolyzing the organo-lithium compound formed. One of the compounds mentioned was a 2-thiophene derivative: 3-dimethylamino-1-(2-thienyl)-1-propanol.

Pohland and Sullivan (22) demonstrated the formation of tertiary alcohols from the reaction of a β-aminoketone with a Grignard reagent and hydrolysis of the addition product to form 4-dimethylamino - 1,2 - diphenyl - 3 - methyl - 2-butanol and its hydrochloride salt and related compounds.

Pohland and Sullivan (22) were interested in the preparation of 4-dialkylamino-1,2-diphenyl-2-butanols and their esters. The general structure of these compounds may be represented as



Preliminary pharmacological evaluation of *dl*-4 - dimethylamino - 1,2 - diphenyl - 3 - methyl - 2-propionyl oxybutane hydrochloride indicated that the α-isomer possessed a high order of analgesic activity in animals and was found to be an effective analgesic in human beings (23).

DISCUSSION

The preparation of three β-aminoketones, 3-dimethylamino - 2 - methyl - 1 - (2 - thienyl) - 1 - propanone hydrochloride and the 3-piperidyl and 3-morpholinyl analogs, was accomplished by the reaction of 2-propionylthiophene and paraformaldehyde with the appropriate secondary amine hydrochloride. The starting compound, 2-propionylthiophene, was prepared by following the method of Kosak and Hartough (24) for the preparation of 2-acetylthiophene.

A different procedure was followed in the synthesis of each of the three β-aminoketones rather than following one general procedure. 3-Dimethylamino-2-methyl-1-(2-thienyl)-1-propanone had previously been prepared by Blicke and Burckhalter (25). Harradence and Lions (26) described a procedure for the production of Mannich bases using morpholine hydrochloride. This method was followed in the synthesis of 4-morpholinyl-3-methyl-1-(2-thienyl)-1-propanone hydrochloride. The method of Levvy and Nisbet (7) was utilized for the synthesis of the 4-piperidyl analog.

As a result of the relatively low yield (33%) of 4-piperidyl-3-methyl-1-(2-thienyl)-1-propanone hydrochloride obtained by following the method outlined by Levvy and Nisbet, the present authors found it necessary to prepare an additional quantity of this Mannich base salt. The method of Maxwell (27) was followed for this second preparation and a yield of 49% was obtained. Levvy and Nisbet (7) stated that a 1 molar quantity of paraformaldehyde is used in the initial reaction mixture and the mixture is refluxed for 15 minutes. A second mole of paraformaldehyde is added and refluxing is continued for an additional 15 minutes. Maxwell (27) uses a 1.5 molar equivalent of paraformaldehyde, which is placed in the reaction mixture at the onset of the reaction, and the reaction mixture is refluxed for 3 hours.

Table I indicates pertinent data with respect to the Mannich bases utilized in this study.

The preparation of the three γ-amino secondary alcohols, 3-dimethylamino-2-methyl-1-(2-thienyl)-1-propanol hydrochloride and the 3-piperidyl and 3-morpholinyl analogs, was patterned after the method of Chaikin and Brown (28) as modified by Nobles (14).

The secondary alcohols were obtained by reduction of the corresponding Mannich bases with sodium borohydride. Sodium borohydride is reported (29) to react quite vigorously with aldehydes and ketones at temperatures as low as −40° in methyl alcohol solution, but a quite gentle reaction is obtained at room temperature in an aqueous solution. A moderately vigorous, but easily controllable reaction was obtained at 20–30° when the ketone in methyl alcohol solution was reacted with a 50% methyl alcohol solution of sodium borohydride.

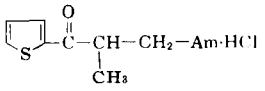
Data with respect to these alcohols are listed in Table II.

The preparation of γ-amino tertiary alcohols involves the reaction of a β-aminoketone with a Grignard reagent. Three different Grignard reagents were utilized in the preparation of this series of compounds: benzylmagnesium chloride, methylmagnesium bromide, and ethylmagnesium bromide. Only the first of the three Grignard reagents was prepared in this laboratory. The remaining two reagents were obtained commercially. The procedure of Gilman and Catlin (30) was followed for the preparation of benzylmagnesium chloride.

The synthesis of 4-dimethylamino-3-methyl-1-phenyl-2-(2-thienyl)-2-butanol hydrochloride and

[1] Marketed as Artane hydrochloride by Lederle Laboratories.

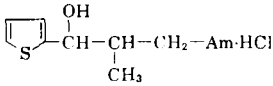
TABLE I.—β-AMINOKETONES



Am	Yield, %	M.p., °C.	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	49	155–157[a]	$C_{10}H_{16}ClNOS$			Not analyzed[a]			
Morpholino	67	178.5–180.5	$C_{12}H_{18}SClNO_2$	52.26	52.27	6.58	6.79	5.08	5.15
Piperidino	33[b]	168–170	$C_{13}H_{20}ClNOS$	57.02	56.51	7.36	7.59	5.12	5.49

[a] Blicke and Burckhalter (25) report a melting point of 154–156°. [b] A later synthesis following the method of Maxwell (30) yielded 49%.

TABLE II.—3-DIALKYLAMINO-2-METHYL-1-(2-THIENYL)-1-PROPANOL HYDROCHLORIDE



Am	Yield, %	M.p., °C.	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	48[a]	152–156	$C_{10}H_{18}ClNOS$	50.94	51.12	7.69	7.84	5.94	5.79
Piperidinyl	83	199–200	$C_{13}H_{22}ClNOS$	56.60	56.34	8.04	7.92	5.08	5.19
Morpholinyl	87	178–181	$C_{12}H_{20}ClNO_2S$	51.87	51.96	7.26	7.38	5.04	4.87

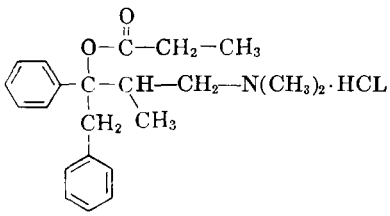
[a] Hydrochloride salt is extremely hygroscopic until washed free of impurities.

the 4-piperidyl and 4-morpholinyl analogs were carried out by following the procedure of Pohland and Sullivan (31). An attempted synthesis of 4-morpholinyl-3-methyl-1,2-diphenyl-butanol hydrochloride was conducted by following the procedure of Denton and his associates (11). The main difference in this method and the method of Pohland and Sullivan is the method of decomposing the addition complex. Denton's method advocates the use of hydrochloric acid to effect the decomposition. The probable reason for the failure of the present authors to obtain the γ-morpholinyl tertiary alcohol is that, after the addition complex was decomposed with dilute hydrochloric acid, the reaction mixture was allowed to stand overnight. The presence of the mineral acid in the reaction mixture for an extended time was undoubtedly sufficient to cause dehydration of the tertiary alcohol. The reaction product gave a positive test for unsaturation when treated with bromide in carbon tetrachloride and aqueous potassium permanganate. This portion of the work will be modified correspondingly in subsequent work.

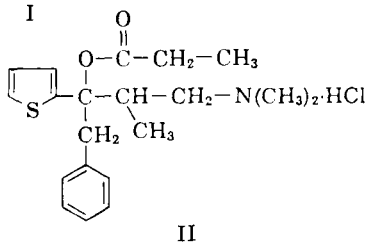
The tertiary alcohols are listed in Table III.

The attempted synthesis of γ-aminoalkyl esters was patterned after the work of Pohland and Sullivan (22, 23, 31). These workers prepared a compound, α - *d* - 4 - dimethylamino - 1,2 - diphenyl - 3 - methyl-2-propionyloxybutane hydrochloride (I).[2] This drug is reported to be an effective analgesic which is comparable to codeine in analgetic activity and is nontoxic and nonaddicting.

Various procedures for the esterification of tertiary alcohols were utilized by the present authors in the attempted synthesis of 4-dimethylamino-3-methyl-1-phenyl-2-propionyloxy-2-(2-thienyl)-butane hydrochloride (II) and the γ-morpholinyl and γ-piperidyl analogs.



I



II

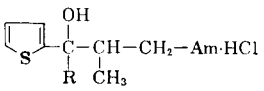
Each attempt met with failure. An examination of the infrared spectrum of each of the reaction products did not reveal the presence of the characteristic alkyl ester absorption in the region of 1735-1750 cm.$^{-1}$ and, in most cases, no absorption peaks of any consequence could be observed from 1650-2000 cm.$^{-1}$.

The reason for the failure to obtain the γ-amino esters is not absolutely clear, although Campaigne and Diedrich (32) stated that their inability to obtain esters of secondary alcohols, derived from 2-acylthiophenes, was due to the relative inactivity of the hydroxyl group. They claimed that this inactivity was due to hindrance of the α-carbon in 2-substituted thiophenes.

Some of the reaction products from the attempted esterifications were tested for unsaturation with bromine in carbon tetrachloride and dilute permanganate solution. The tests indicated that dehydration had occurred. The location of the unsaturation in the olefinic products has not been

[2] Commercially available from Eli Lilly and Co. as Darvon.

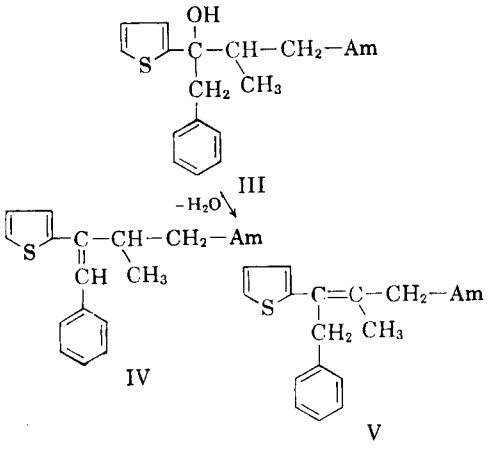
TABLE III.—γ-AMINO TERTIARY ALCOHOLS (HYDROCHLORIDE SALTS)



R	Am	Yield, %	M.p., °C.	Formula	Analyses—Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	Diethylamino	55	170–172	$C_{11}H_{20}ClNOS$	52.89	52.64	8.07	8.18	5.61	5.52
Methyl	Morpholinyl	68	167–172	$C_{13}H_{22}ClNO_2S$	53.50	53.36	7.60	7.68	4.80	4.91
Ethyl	Dimethylamino	50	174.5–175	$C_{12}H_{22}ClNOS$	54.63	54.58	8.41	8.31	5.31	5.52
Ethyl	Morpholinyl	55	163–167	$C_{14}H_{24}ClNO_2S$	55.12	55.26	7.86	7.76	4.57	4.63
Benzyl	Dimethylamino	57	180–184	$C_{17}H_{24}ClNOS$	62.65	62.80	7.42	7.55	4.29	4.27
Benzyl	Piperidinyl	32	169–177	$C_{19}H_{28}ClNOS$	65.64	65.84	7.71	7.95	3.83	3.59

determined, but, by consideration of resonance stabilization, it would be possible to predict the principle product of the dehydration of III as being that represented by structure IV.

Both the dehydration in preference to esterification and the suggested structure, IV, are in accord with the modern theories of this facet of organic chemistry as suggested by Morrison and Boyd (33). This is true despite the success of Pohland and Sullivan (22) in obtaining the tertiary alcohol esters in the *d*-propoxyphene hydrochloride series.



EXPERIMENTAL

The Mannich bases were prepared according to the general methods already indicated in this paper, according to the well-known methods of the chemical literature.

3 - Dimethylamino - 2 - methyl - 1 - (2 - thienyl)-1 propanol Hydrochloride.—Following the general procedure of Chaikin and Brown (30) as employed by Nobles (14), 10.0 Gm. (0.043 mole) of 3-dimethylamino-2-methyl-1-(2-thienyl)-1-propanone hydrochloride was dissolved in a minimum amount of water and made basic with ice cold 20% sodium hydroxide. The basic mixture was then extracted with ether. The ether was removed by evaporation at the water aspirator, and the free base was dissolved in 50 ml. of methyl alcohol. Meanwhile, 1.615 Gm. (0.427 mole) of sodium borohydride in 100 ml. of 50% methyl alcohol, cooled to 20°, was prepared and placed in a 300-ml. round-bottom flask, equipped with a magnetic stirrer, reflux condenser, and dropping funnel. The flask containing the sodium borohydride solution was surrounded by a cooling bath, and the alcoholic solution of the aminoketone was added, dropwise, with stirring and cooling so as to maintain the temperature below 30°. After the addition was complete, the mixture was stirred for an additional 30 minutes. The flask was removed from the cooling bath and warmed to 40–50° so as to decompose the excess sodium borohydride. The solution was then concentrated *in vacuo* to remove the alcohol. The residue was ether extracted and dried overnight with anhydrous magnesium sulfate. The drying agent was removed by filtration. The ether extract was chilled by means of an ice-water bath and treated with anhydrous hydrogen chloride while being stirred with a magnetic stirrer. The hydrochloride salt was collected on a sintered-glass funnel and washed with ether. Recrystallization from ethyl alcohol-ethyl acetate yielded 4.8 Gm. (48%) of white crystals, m.p. 152–156°.

3 - Piperidyl - 2 - methyl - 1 - (2 - thienyl) - 1-propanol Hydrochloride.—Following the above described procedure, 2.8 Gm. (0.074 mole) of sodium borohydride in 150 ml. of 50% methyl alcohol and 17.3 Gm. (0.073 mole) of 3-piperidyl-2-methyl-1-(2-thienyl)-1-propanone in 100 ml. of methyl alcohol yielded 16.8 Gm. (83%) of white crystals, m.p. 150–185°. A small sample, after recrystallization from ethyl alcohol-ethyl acetate, melted at 199–200°.

3 - Morpholinyl - 2 - methyl - 1 - (2 - thienyl) - 1-propanol Hydrochloride.—By the method outlined previously, 1.37 Gm. (0.036 mole) of sodium borohydride in 75 ml. of 50% methyl alcohol and 8.7 Gm. (0.036 mole) of 3-morpholinyl-2-methyl-1-(2-thienyl)-1-propanone in 75 ml. of methyl alcohol yielded 6.7 Gm. (67%) of white crystals, m.p. 172–180°. A sample after recrystallization from ethyl alcohol-ethyl acetate, melted at 178–181°.

4 - Dimethylamino - 3 - methyl - 2 - (2 - thienyl)-2-butanol Hydrochloride.—The general method of Pohland and Sullivan (23) for the preparation of γ-amino tertiary alcohols was used for this preparation. In a dry 500-ml. three-neck flask fitted with a mercury-sealed stirrer, a dropping funnel, and a condenser provided at its upper end with a drying tube containing a mixture of calcium chloride and soda lime, was placed 0.214 mole of methylmagnesium bromide and 50 ml. of dry ether. 3-Dimethylamino-2-methyl-1-(2-thienyl)-1-propanone, 21.1 Gm. (0.107 mole) in 200 ml. of dry ether was

pipetted into the dropping funnel and added dropwise with stirring to the Grignard solution. After the addition was completed, the reaction mixture was refluxed with stirring for 1 hour and cooled to room temperature. The reaction mixture was decomposed by the dropwise addition of a saturated ammonium chloride solution. The ether solution was decanted from the granular solid and the solid material was washed with 100 ml. of ether. The combined ether solutions were dried overnight with anhydrous magnesium sulfate. The drying agent was removed by filtration, and the ether solution was treated with anhydrous hydrogen chloride. The hydrochloride salt formed as a sticky mass and adhered to the walls of the flask. The ether was quickly decanted from the sticky mass and 10 ml. of acetone was added to the mass. The flask was restoppered and allowed to stand for 1 hour. After the mass had solidified, it was collected on a sintered-glass funnel and washed with a small quantity of acetone yielding 15.3 Gm. (55%) of white crystals m.p. 160–167°. A sample, after recrystallization from ethyl alcohol, melted at 170–172°.

4 - Morpholinyl - 3 - methyl - 2 - (2 - thienyl)-2-butanol Hydrochloride.—Following the above described procedure, 0.15 mole of methylmagnesium bromide in 50 ml. of dry ether and 16.15 Gm. (0.068 mole) of 3-morpholinyl-2-methyl-1-(2-thienyl)-1-propanone in 150 ml. of dry ether yielded 13.4 Gm. (68%) of white crystals, m.p. 160–166°. A sample, after recrystallization from ethyl alcohol, melted at 167–172°.

1-Dimethylamino - 2-methyl-3-(2-thienyl)-3-pentanol Hydrochloride.—By the method outlined previously, 0.214 mole of ethylmagnesium bromide in 50 ml. of dry ether and 21.1 Gm. (0.107 mole) of 3-dimethylamino-2-methyl-1-(2-thienyl)-1-propanone in 200 ml. of dry ether yielded 14.0 Gm. (50%) of white crystals, m.p. 170–173°. A sample, after recrystallization from ethyl alcohol-acetone, melted at 174.5–175°.

1 - Morpholinyl - 2 - methyl - 3 - (2 - thienyl) - 3-pentanol Hydrochloride.—By the method outlined previously, 0.182 mole of ethylmagnesium bromide in 50 ml. of ether and 21.7 Gm. (0.091 mole) of 3-morpholinyl-2-methyl-1-(2-thienyl)-1-propanone in 150 ml. of dry ether yielded 15.3 Gm. (55%) of white crystals, m.p. 154–160°. A sample, after recrystallization from ethyl alcohol-acetone, melted at 163–165°.

4 - Dimethylamino - 3 - methyl - 1 - phenyl - 2-(2-thienyl)-2-butanol Hydrochloride.—By the previously described method of Gilman and Catlin (31), 0.152 mole of benzylmagnesium chloride was prepared in a 2-L. three-neck flask equipped with a mercury-sealed stirrer, a dropping funnel, and a condenser provided with a drying tube containing a mixture of calcium chloride and soda lime. Following the method of Pohland and Sullivan (23) for the preparation of the tertiary alcohol, the Grignard solution was stirred during the dropwise addition of a solution of 14.9 Gm. (0.76 mole) of 3-dimethylamino-2-methyl-1-(2-thienyl)-1-propanone in 200 ml. of dry ether. After the addition of the ketone was completed, the reaction mixture was refluxed for 1 hour and then allowed to cool to room temperature. The reaction mixture was decomposed by the dropwise addition of a saturated ammonium chloride solution. The ether was decanted from the granular solid, and the solid material was washed with 50–75 ml. of ether. The combined ether solutions were dried overnight with anhydrous magnesium sulfate. The drying agent was removed by filtration, and the ether solution was treated with anhydrous hydrogen chloride. The white precipitate was collected on a sintered-glass funnel yielding 14 Gm. (57%) of white crystals, m.p. 156–165°. A sample, after recrystallization from methyl alcohol-ethyl acetate (1:3 ratio) melted at 180–184°.

4 - Piperidyl - 3 methyl - 1 - phenyl - 2 - (2-thienyl)-2-butanol Hydrochloride.—By the method outlined above, 0.38 mole of benzylmagnesium chloride and 30.0 Gm. (0.126 mole) of 3-piperidyl-2-methyl-1-(2-thienyl)-1-propanone in 200 ml. of dry ether yielded 15 Gm. (32%) of white crystals, m.p. 120–170°. A sample, after recrystallization from methyl alcohol-ethyl acetate, melted at 169–177°.

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