SYNTHESIS OF 5-(2-THIENYL)BARBITURIC ACID

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SYNTHESIS OF 5-(2-THIENYL)BARBITURIC ACID

THESIS

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by

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CHAPTER I

INTRODUCTION

The similarity in the physical and chemical properties of benzene and thiophene is well known as is the similarity in the properties of the derivatives of the two compounds. In addition, analogies have been shown to exist in the physiological properties of the two compounds. Steinkopf and co-workers have prepared derivatives of cocaine, eucaine-A, and stovaine in which phenyl is replaced by thienyl and have found that no marked change in local anesthetic power is associated with the introduction of thiophene nucleus into the molecule.\(^1\) In some cases toxicity was reduced and anesthetic power augmented. They found in addition that the introduction of the thienyl group into quinine and phenacetine did not markedly change the antipyretic power of the molecule. Gilman and co-workers replaced the \(p\)-aminophenyl group in novocaine by thienyl and found the resulting compound to have an activity of one as compared with a value of ten for cocaine.\(^2\) Compounds of the type of \(\text{PhCOCH}_2\text{CH}_2\text{NC}_5\text{H}_4\) are anesthetics.

\(^1\) Wilhelm Steinkopf and Walter Ohse, \textit{Ann.}, CDXXXVII, 14 (1933).

Mannich and Lammering found that replacement of the phenyl by thienyl and other groups also gave anesthetic compounds. Levy and Nisbet have prepared 2-thienyl-B-piperidinoethyl ketone hydrochloride and have found its anesthetic action to be less than that of cocaine.

Various investigators have studied the effects of the thienyl group on pressor action. Thus Barger and Easson have prepared the thiophene isologs of B-phenylalanine and B-phenylethylamine. The pressor action of B-(2-thienyl)ethylamine was qualitatively and quantitatively the same as the above mentioned phenyl compound. Alles and Feigen also found that B-phenylisopropylamine and B-(2-thienyl)isopropylamine have pressor effects very similar in intensity and duration. The latter had a shorter duration of action.

2-Thienylquinoline-4-carboxylic acid has been found by Hartman and Wybert to have a therapeutic action similar to that of the phenyl compound (cinchophen). It was relatively

3. C. Mannich and D. Lammering, *Ber.*, LV, 3515 (1922); *C. A.*, XVII, 1795 (1923).


non-poisonous and had increased antiphlogistic and analgesic properties over the later.

Gilman has had certain ketones tested for hypnotic activity. Among these were two which contained the thienyl group: methyl thienyl ketone and 2-furoyl thiophene. These compounds showed no hypnotic activity and were somewhat toxic. Since methyl thienyl ketone is the thiophene isolog of acetophenone which has found some use as a hypnotic, this result would seem to indicate that the thienyl group has a depressing effect on hypnotic properties.

Spurlock has prepared a number of thienyl derivatives of hydantoin which have been tested for anticonvulsant action. Among others, these included the thiophene isologs of 5-ethyl-5-phenylhydantoin (Nirvanol) and 5,5-diphenylhydantoin (Dilantin) both of which have found some use as anticonvulsants in the treatment of epilepsy. The isolog of Nirvanol possessed only a fraction of the activity of Nirvanol, whereas the isolog of Dilantin, 5-phenyl-5-(2-thienyl)hydantoin, has approximately the same activity as Dilantin and in addition is less toxic and has certain other more desirable characteristics.

No record was found of the synthesis of thienyl substituted


9. Unpublished manuscript of J. J. Spurlock's research at North Texas State Teachers College.
barbituric acids. The barbituric acids are closely related to hydantoin derivatives in structure and physiological properties, and certain barbituric acids are of value therapeutically. Thus, Phenobarbital, 5-ethyl-5-phenylbarbituric acid, is a valuable hypnotic and in addition is useful in the treatment of epilepsy. However, the sedative action is undesirable in a compound to be used as an anticonvulsant. Such compounds must be administered daily and any sedative action would seriously restrict the performance of the duties of the patient in the workaday world. The ideal anticonvulsant, then, is one which possesses no sedative action and which is not toxic when administered over long periods of time. A perfect example of this type does not exist at the present. In view of the anticonvulsant activity of the above mentioned and other phenylbarbituric acids and the favorable effects secured by substitution of thienyl for phenyl, it seemed of interest to attempt the synthesis of 5-(2-thienyl)-substituted barbituric acids. The simplest of these would be 5-(2-thienyl)barbituric acid.

In general the substituted barbituric acids are prepared by condensing the appropriately substituted malonic ester with urea in the presence of sodium ethylate or a related compound. The malonic esters are in most cases prepared by the alkylation

10. A few months after this work was started an article appeared, F. F. Blicke and M. F. Zienty, J. Am. Chem. Soc., LXIII, 2945, describing the preparation of 5-ethyl-5-(2-thienyl)-barbituric acid.
of diethyl malonate. However, this is not successful in the case of phenylmalonic esters since the phenyl halides are too inactive chemically. An indirect method is thus necessary for the preparation of phenylbarbiturates and because of the great similarity of benzene and thiophene derivatives, this same general method was chosen for the preparation of the thienylmalonic ester. This method may be expressed by the following equations: thiophene $\xrightarrow{I_2} 2$-iodothiophene $\xrightarrow{Mg + CH_2O} 2$-thienylcarbinol $\xrightarrow{SOCl_2} 2$-thienylmethyl chloride $\xrightarrow{KCN} 2$-thienylacetonitrile $\xrightarrow{NaNH_2 + CO(OC_2H_5)_2} \text{ethyl} 2$-thienylcyanoacetate $\xrightarrow{HCl + C_2H_5OH} \text{diethyl} 2$-thienylmalonate $\xrightarrow{Mg(OCH_3)_2 + CO(NH_2)_2} 5$-(2-thienyl)barbituric acid.
CHAPTER II

EXPERIMENTAL PROCEDURE

Preparation of Thiophene

\[ \text{CH}_2\text{COONa} + \text{P}_2\text{S}_3 = \text{HC-CH} + \text{other products} \]

An intimate mixture of 324 grams (2 moles) of anhydrous sodium succinate (dried in an oven at 100° C. for four hours) and 432 grams (2.8 moles) of finely ground phosphorus trisulfide was placed in a two-liter round-bottom flask. The flask was fitted with a two-holed cork and through one of the holes was passed a glass tube two centimeters in diameter leading to a condenser set for distillation. Through the other hole passed a small diameter glass tube extending to the bottom of the flask. The condenser was connected to a one-liter flask which in turn was connected in series to two three-hundred-milliliter flasks arranged so that any uncondensed vapors were bubbled through a twenty per cent solution of sodium hydroxide in each flask. The three receiving flasks were cooled in an ice-salt mixture.

The reaction flask was swept out with carbon dioxide for

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1. H. Gilman and H. Blatt, Organic Syntheses, XII, 72.
a few minutes to remove the air. The connections were then tightened and a slow stream of carbon dioxide passed through the system during the reaction. The flask was heated strongly in one spot until the reaction began and no further heating was required until the reaction was near completion. Then the flask was strongly heated and a more vigorous current of carbon dioxide was passed through the system until no more yellow vapors were produced. The contents of the three receiving flasks were then combined and steam-distilled from a two-liter distilling flask. The thiophene layer in the distillate was separated, dried over solid sodium hydroxide and sodium, and then fractionated. The fraction boiling between 83° and 86° C. was collected. The yield was 67-75 grams (40-45 per cent of the theoretical). $D_{20}^\circ 1.0618$; $n_{D}^\circ 1.5247$.

Preparation of 2-Iodothiophene

$$\begin{align*}
\text{HC-CH} & + \text{HgO} + \text{I}_2 = \\
\text{HC-CH} & + \text{HgI}_2 + \text{H}_2\text{O}
\end{align*}$$

A solution of thirty-five grams (0.42 mole) of thiophene and 50 milliliters of benzene was placed in a one-liter glass-stoppered bottle cooled in ice. With constant shaking and cooling, seventy-five grams (0.25 mole) of yellow mercuric oxide and 109 grams (0.43 mole) of iodine were added alternately

2. Gilman and Blatt, *Organic Synthesis*, XII, 44.
in small portions. The mixture was filtered and the residue washed several times with ether. The ether-benzene solution was then shaken with a dilute solution of sodium thiosulphate to remove the excess iodine, dried over calcium chloride, and filtered. After removal of the ether and benzene by distillation from a water bath, the oily residue was distilled under vacuum. The yield of 2-iodothiophene boiling at 72° C./9 mm. pressure was 55-63 grams (60-70 per cent). D₂₀ 2.0495.

**Preparation of 2-Thienylcarbinol**

\[
\begin{align*}
\text{HC-CH} & \quad \text{Mg} \quad \text{HC-CH} \\
\text{HC-C-I} & \quad \text{HC-C-MgI} \\
& \quad \text{CH}_2\text{O} + \text{H}_2\text{O} \\
& \quad \text{HC-C-CH}_2\text{OH}
\end{align*}
\]

2-Thienylcarbinol was prepared by a method similar to that used for the preparation of cyclohexylcarbinol.³ A one-liter, three-necked, round-bottom flask was fitted with a dropping funnel, a Hopkins reflux condenser fitted with a calcium chloride drying tube, and a mercury-sealed stirrer. 25 grams (1.03 moles) of magnesium turnings, 140 milliliters of dry ether and a small crystal of iodine were added to the flask. Stirring was begun and 210 grams (1.0 mole) of 2-iodothiophene in 140 milliliters of dry ether added as follows: a few milliliters of the solution of the halide were added, the solution stirred until the reaction began, and the

remainder of the solution added dropwise. Due to the vigorous reaction it was necessary to keep the flask cooled in ice-water. The solution became dark and a precipitate formed as the reaction proceeded. After the 2-iodothiophene had been added, the solution was refluxed for one hour.

The dropping funnel was now replaced by a glass tube, two centimeters in diameter, to which was sealed a one-hundred-twenty-five milliliter flask. The flask contained 50 grams of paraformaldehyde which had been dried in a vacuum desiccator over phosphorus pentoxide for two days. The flask containing the Grignard reagent was immersed in an ice bath, the stirrer started, and the flask containing the paraformaldehyde heated by an oil bath on a hot-plate in order to depolymerize the paraformaldehyde. The temperature of the bath was increased slowly until, at the end of six hours, the temperature was about 210°C. The reaction was then tested for completeness using Gilman's test for a Grignard reagent.\(^4\) When no color was produced, the reaction was assumed complete.

The mixture was transferred to a two-liter distilling flask and three-hundred grams of cracked ice added all at once. The flask was shaken until the reaction was complete and then a solution of ammonium chloride (2 molar) was added to dissolve the magnesium hydroxide. The mixture was distilled

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with steam until no more oily droplets were seen in the distillate. The distillate was saturated with sodium chloride and extracted with ether. The ether solution of the alcohol was then dried over potassium carbonate, filtered, and the ether evaporated on a water bath. The crude alcohol was warmed thirty minutes with 0.5 grams of dehydrated lime, filtered, washed with ether, and distilled under vacuum. The yield of 2-thienylcarbinol distilling at 90-92° C./3 mm. pressure was 63-65 grams (55 per cent of the theoretical). D20 1.1969; nD 1.5380; molecular refractivity, found: 29.81; calc.: 31.15.

Preparation of 2-Thienylmethyl Chloride

\[
\begin{align*}
\text{HC-CH} & + \text{SOCl}_2 = \text{HC-CH} \\
\text{HC-S-C-C-CH}_2\text{OH} & \quad \text{HC-S-C-C}_2\text{Cl}
\end{align*}
\]

2-Thienylmethyl chloride was prepared by a method used for the preparation of 2-furylmethyl chloride from 2-furylcarbinol.5 A five-hundred milliliter three-necked flask was fitted with a dropping funnel, a thermometer, and a stirrer. The flask was placed in an ice bath and 65.4 grams (0.574 mole) of thienylcarbinol and 54.4 grams (0.688 mole) of pyridine added. The solution was stirred until the temperature dropped to 2-3° C and then 74.8 grams (0.63 mole) of thionyl chloride were added dropwise at such a rate that

the temperature did not rise above 10° C. As each drop was added, there was hissing and sputtering and a great deal of heat was evolved. When all of the thionyl chloride had been added, the solution was stirred for a half-hour. The lumps which formed were broken up with a glass rod and the stirring continued another half-hour. The solution was transferred to a separatory funnel, the flask rinsed with water, and the washings added to the separatory funnel. The water layer was removed and the ether solution extracted with ten per cent sodium hydroxide until the aqueous layer remained basic to litmus. The ether layer was dried over anhydrous sodium sulphate and the ether evaporated on a water bath. The yellow oil which remained was distilled under vacuum. The yield was 58.6 grams (74 per cent of the theoretical) distilling at 60-61° C./9 mm. pressure. \( \mu^2 \) 1.2531; \( n^2 \) 1.5654; molecular refractivity, found: 34.49; calc.: 34.49.

Preparation of 2-Thienylacetonitrile

\[
\begin{align*}
HC-CH & + NaCN = HC-CH \\
S-\text{C-CH}_2\text{Cl} & \quad \text{HC-CH} \\
& \quad \text{S-\text{C-CH}_2\text{CN}}
\end{align*}
\]

A five-hundred-milliliter, three-necked, round-bottomed flask was fitted with a dropping funnel, reflux condenser, and a mercury-sealed stirrer. A mixture of fifteen grams

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(0.31 mole) of sodium cyanide, 100 milliliters of ninety-five per cent alcohol, and 100 milliliters of water was stirred and heated to boiling and 40 grams (0.30 mole) of thienylmethyl chloride in 50 milliliters of alcohol were added over a period of one hour. The mixture was heated with stirring for five hours, during which time it became very dark brown in color. The alcohol was evaporated on a water bath and the oily mixture extracted with ether. The ether extract was dried over anhydrous sodium sulphate and distilled at reduced pressure. The yield of 2-thienylacetonitrile distilling at 100-103$^\circ$ C./9 mm. pressure was 16 grams (40 per cent). $D_{20}^0$ 1.1732; $n_D^0$ 1.5408; molecular refractivity, found: 32.96; calc.: 34.06.

In several of the preparations, a product was obtained which contained neither chlorine nor nitrogen. The material distilled at 64$^\circ$ C./9 mm. pressure. $D_{20}^0$ 1.0597; $n_D^0$ 1.5070. The product was saved for later identification.

Preparation of Ethyl 2-Thienylcyanoacetate

A mixture of 200 milliliters of anhydrous ether, dried over sodamide, and 6 grams (0.153 mole) of powdered sodamide

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was placed in a dry five-hundred milliliter three-necked flask equipped with a dropping funnel, reflux condenser, and a mercury-sealed stirrer. A solution of 18 grams (0.147 mole) of redistilled 2-thienylacetonitrile in 20 milliliters of dry ether was added slowly. Ammonia was given off and the mixture began to reflux due to the heat given off by the reaction. When about half of the nitrile solution had been added, the mixture became light blue and turned darker as the remainder of the nitrile was added. When all of the nitrile had been added, the solution was refluxed for one hour, during which time the mixture became a dark purple and a fine precipitate was formed. The mixture was cooled to room temperature and 21.6 grams (0.182 mole) of redistilled ethyl carbonate was added dropwise with constant stirring. Some heat was given off during the course of this addition. When all the ethyl carbonate had been added, the mixture was heated on a water bath for one hour. At the end of this time, the material was very dark purple in color and contained some tarry material. The mixture was filtered into a separatory funnel and acidified with dilute hydrochloric acid. The ether layer was removed, dried over calcium chloride, and distilled as usual. The yield was 7 grams (24 per cent of the theoretical) of ethyl 2-thienyl-cyanoacetate boiling from 140° to 143° C. /8 mm. pressure.
Preparation of Diethyl 2-Thienylmalonate

\[ \text{HC-CH} + \text{C}_2\text{H}_5\text{OH} + \text{HCl} = \text{HC-CH} \]
\[ \text{HC-S-C-CH} \text{CO(OOC}_2\text{H}_5) \]

A rapid stream of dry hydrogen chloride was passed into a solution of 7 grams (0.0359 mole) of ethyl 2-thienylcyanooacetate, 35 grams of ninety-five per cent alcohol, and 0.5 grams of water in a one-hundred-twenty-five milliliter flask. The flask was fitted with a condenser and the hydrogen chloride passed into the solution until it was saturated. There was little evidence of reaction for some time but soon a precipitate of ammonium chloride appeared. The reaction mixture was cooled in an ice bath and the cold solution saturated with hydrogen chloride. The mixture was allowed to stand overnight at room temperature and the following morning was heated on a water bath for one hour to evaporate the alcohol. After cooling, sufficient water was added to dissolve the ammonium chloride. The ester was extracted with ether, washed with water, and dried over calcium chloride. After removal of the ether on a water bath the residual liquid was distilled under vacuum. The yield was 4 grams (21.3 per cent of the theoretical) of the product distilling at 154-157°C./9 mm. pressure.

8. Ibid.
Preparation of 5-(2-Thienyl)barbituric Acid

\[ \text{HC-CH} \quad \begin{array}{c} \text{CO(OC}_2\text{H}_5) \\ \text{HC-C-CH} \\ \text{CO(OC}_2\text{H}_5) \end{array} + \text{CO(NH}_2)_2 + 4\text{Mg(OCH}_3)_2 = \text{HC-C-CH} \quad \begin{array}{c} \text{CO-N} \\ \text{S-C-CH-CO} \end{array} \]

The method employed was that of F. F. Blicke and M. F. Zienty for the preparation of 5-ethyl-(2-thienyl)barbituric acid. Twenty-eight hundredths gram of magnesium ribbon and forty milliliters of absolute methyl alcohol were heated in a 125-milliliter flask until all the magnesium dissolved. Two grams (0.0082 mole) of diethyl 2-thienylmalonate and 1.4 grams (0.029 mole) of urea were added to the flask. The flask was covered with a fifty-milliliter beaker and placed in a steel autoclave and sealed tightly. The autoclave was heated in an oven at 105°C for fifteen hours and then removed and permitted to cool. The contents of the flask, when removed from the autoclave, were greenish in color. The alcohol was removed on a water bath, the mixture acidified and extracted with ether. The ether solution was extracted with ten per cent sodium hydroxide and the alkaline layer removed and acidified with concentrated hydrochloric acid to precipitate the barbituric acid. Very little precipitate was noticed. About 0.3 gram of an oily material was obtained by evaporation of the ether solution. This was probably unreacted ester.

However, a dark green precipitate was noticed in the original acid solution which had been extracted with ether. This material was found to be soluble in sodium hydroxide and was reprecipitated on acidification with concentrated hydrochloric acid. A total of about 0.6 gram of this material was obtained. This material did not possess a definite melting point, was only slightly soluble in hot alcohol or hot water and was insoluble in ether. A positive test was obtained for nitrogen and sulfur.
CHAPTER III

DISCUSSION OF RESULTS

The preparation of thiophene resulted in yields of from forty to forty-five per cent as compared with twenty-six to thirty-one per cent predicted for the preparation in "Organic Syntheses". The time of heating for the reaction, as carried out by this investigator, was materially less than that specified in the directions followed. This was the only change made. The reason for it was that the reaction proceeded so rapidly that it was completed in a short time, and longer heating did not result in an increased amount of product.

The preparation of 2-thienylacetoneitrile was accompanied by the formation of varying amounts of an unknown substance. This substance contained sulfur but no nitrogen or chlorine and gave no test for an alcohol group or a carbonyl group. When the compound is assumed to be 2-thienyl-methyl ethyl ether, the molecular refractivity is 39.94 as compared with a calculated value of 40.49. This structure is pure speculation, and more work, including analytical data, is needed in order to characterize the compound.

In the preparation of ethyl 2-thienylcyanoacetate the presence of traces of moisture was found to result in increased tar formation and decreased yields of the product.
The ether used for this preparation was refluxed with sodamide and distilled directly into the reaction vessel in order to minimize the amount of water present.

The condensation of diethyl 2-thiencylmalonate with urea should have resulted in a white product of high melting point, readily soluble in alkali. The product obtained was a microcrystalline material which was dark purple and which dissolved in alkali to give a green solution. The substance had no definite melting point. The nature of the compound is not known at the present time.

The molar refractivities measured show considerable deviation from the calculated value in two cases. This is wholly in accord with the observed behavior of compounds containing the thiophene nucleus. For a given homologous series of thiophene derivatives, variation may be fairly constant.
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Unpublished manuscript of J. J. Spurlock's research at North Texas State Teachers College.