[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

5-Ethyl-5-(α-thienyl)-barbituric Acid

BY F. F. BLICKE AND M. F. ZIENTY[1]

It has been shown that the pharmacological activity of many compounds, at least in a qualitative sense, is not changed by the replacement of a phenyl group by α-thienyl. The substitution of phenyl by α-thienyl has been effected in local anesthetics,[2] pressor agents,[3] cinchophen[4] and in β-phenylalanine.[5]

This paper deals with the preparation of 5-ethyl-5-(α-thienyl)-barbituric acid, the α-thienyl analog of phenobarbital (luminal). Based on a preliminary examination of the product by J. W. Nelson in the laboratories of The Upjohn Company, it may be stated that the "thienylbarbital" exhibits the same order of activity as phenobarbital when injected intraperitoneally into rats.

	M.L.D.[a] Mg./kg.	M.H.D.[a] Mg./kg.	M.L.D. / M.H.D.
Phenobarbital sodium	150	80	1.8
"Thienylbarbital" sodium	200	100	2.0

[a] The results are expressed in terms of the free barbituric acid although the products were injected as solutions of the sodium salts.

The disubstituted barbituric acid was synthesized by the general procedure employed for alkylarylbarbituric acids. In this instance it involved preparation of the following series of compounds: thiophene-α-carboxylic acid → α-thenoyl chloride → α-thienyl diazomethyl ketone → ethyl α-thienylacetate → ethyl ethoxalyl-α-thienylacetate → diethyl α-thienylmalonate → diethyl ethyl-α-thienylmalonate → 5-ethyl-5-(α-thienyl)-barbituric acid.

We found that the time required for the elimination of carbon monoxide from ethyl ethoxalyl-α-thienylacetate is shortened by the use of powdered glass and that condensation of diethyl ethyl-α-thienylmalonate with urea is effected best by the use of magnesium methylate.[6]

(1) The Upjohn Company Fellow.

(2) Steinkopf and Ohse, *Ann.*, **437**, 14 (1924); **448**, 205 (1926); Gilman and Pickens, THIS JOURNAL, **47**, 252 (1925); Mannich and Lämmering, *Ber.*, **55**, 3515 (1922); Levy and Nisbet, *J. Chem. Soc.*, 1053 (1938).

(3) (a) Tainter, *Quart. J. Pharm. Pharmacol.*, **3**, 584 (1930); (b) Alles, *J. Pharm. Exp. Therap.*, **47**, 339 (1933); (c) Barger and Easson, *J. Chem. Soc.*, 2100 (1938); (d) Alles and Feigen, *J. Pharm. Exp. Therap.*, **72**, 267 (1941).

(4) Hartmann and Wybert, *Helv. Chim. Acta*, **2**, 60 (1919).

(5) Yuan and Li, *J. Chinese Chem. Soc.*, **5**, 214 (1937); ref. 3c.

(6) Lund, *Kgl. Dan. Vid. Selsk. Math.-fys. Medd.*, **13**, 13 (1935).

Experimental Part

Ethyl α-Thienylacetate and α-Thienylacetic Acid.—Thiophene-α-carboxylic acid was obtained in 92% yield from an ether–benzene solution of α-thienylmagnesium bromide and solid carbon dioxide.[7] The acid chloride, α-thenoyl chloride, was prepared in 85% yield with the aid of thionyl chloride.[8]

(a) A dry ether solution of diazomethane,[9] prepared by treatment of 52.5 g. of N-methyl-N-nitrosourea[10] with 40% potassium hydroxide solution, was maintained at 5° while 20.0 g. of α-thenoyl chloride,[11] dissolved in 100 cc. of dry ether, was added during the course of one-half hour. Before the addition of the acid chloride, a few small fragments of porous plate were added to the diazomethane solution in order to facilitate the evolution of nitrogen. After all of the gas had been evolved, the reaction mixture was placed in a bath heated to 30–40° and the ether was removed under reduced pressure. A small portion of the yellow, crystalline residue, α-thienyl diazomethyl ketone, was recrystallized from absolute ether; m. p. 67–68°.

The crude ketone was dissolved in 200 cc. of absolute alcohol, 0.5 g. of silver oxide added and the mixture heated on a steam-bath for two hours. During this time 0.3-g. portions of silver oxide were added at one-half hour intervals. After the last addition of silver oxide, the mixture was heated one-half hour longer and the alcohol then removed under reduced pressure. The residue, ethyl α-thienylacetate, boiled at 124–129° (26 mm.); yield 15 g. (68%).[12]

When methyl alcohol was employed in the synthesis described above, methyl α-thienylacetate was obtained; b. p. 115–118° (23 mm.). Upon hydrolysis of the ester with alcoholic potassium hydroxide, α-thienylacetic acid was produced; m. p. 75–76°[13] after recrystallization from a mixture of carbon tetrachloride and petroleum ether (30–40°).

(b) A mixture of 15 g. (0.31 mole) of sodium cyanide, 100 cc. of alcohol and 100 cc. of water was stirred and heated until it began to reflux; 40 g. (0.30 mole) of α-thienylmethyl chloride,[14] dissolved in 50 cc. of alcohol, was added

(7) Schlenk and Ochs [*Ber.*, **48**, 679 (1915)] isolated the acid, in about the same yield, after interaction of α-thienylmagnesium iodide and gaseous carbon dioxide.

(8) Jones and Hurd, THIS JOURNAL, **43**, 2444 (1921).

(9) "Organic Syntheses," Vol. 15, p. 3.

(10) Arndt, Lowe and Avan, *Ber.*, **73**, 606 (1940).

(11) The acid chloride must be entirely free from thionyl chloride.

(12) The preparation of this ester was patented by Arndt and Eistert [German Patent 650,706 (1937); *C. A.*, **32**, 595 (1938)] but they used platinum instead of silver oxide and the boiling point of the ester was not reported.

(13) The same melting point was reported by Arndt and Eistert (ref. 12). The melting point is stated incorrectly in *Chemical Abstracts* (ref. 12) to be 270°.

(14) Obtained by the chloromethylation of thiophene. The process will be described soon in another publication. The chloride was prepared previously from α-thienylmethanol and hydrogen chloride by Biedermann, *Ber.*, **19**, 639 (1886).

at such a rate that the addition was complete in one hour. The mixture was stirred and heated for three hours longer, the alcohol removed, the oily α-thienylmethyl cyanide dried over fused sodium sulfate and distilled; b. p. 115–120° (22 mm.); yield 23 g. (60%).

Five grams of the cyanide, 5 g. of potassium hydroxide, 25 cc. of alcohol and 25 cc. of water were refluxed for eighteen hours, the alcohol removed and the solution acidified. The oily precipitate was extracted with ether, the solution dried and the ether removed whereupon the residue soon crystallized. The α-thienylacetic acid melted at 75–76° after recrystallization from a mixture of carbon tetrachloride and petroleum ether; yield 2 g.

Diethyl Ethyl-α-thienylmalonate.—Two and three-tenths grams of sodium was added to 100 cc. of absolute alcohol and after the solution had cooled to 55°, it was stirred and 14 g. of diethyl oxalate was added rapidly, followed by the addition of 18 g. of ethyl α-thienylacetate. The alcohol was removed under reduced pressure and the cold residue treated with 18% hydrochloric acid. The oily ethyl ethoxalyl-α-thienylacetate [C_2H_5OOC-CO-CH-(C_4H_3S)-$COOC_2H_5$] was extracted with ether, the solution dried with fused sodium sulfate and the ether removed. After the addition of 1 g. of powdered glass, the material was heated in an oil-bath at 155–160° under 20 mm. pressure; the evolution of gas was complete after two hours. Upon distillation 9 g. (38%) of a pale yellow liquid, diethyl α-thienylmalonate, was obtained; b. p. 145–148° (5 mm.).

A solution of sodium ethylate was prepared from 1 g. of sodium and 50 cc. of absolute alcohol; 9 g. of diethyl α-thienylmalonate was added, the mixture refluxed and 5 g. of ethyl bromide dropped gradually into the solution. The mixture was heated for two hours, 20 cc. of water added and the alcohol removed under reduced pressure. The oily ester layer was separated, dissolved in ether, the solution dried, the solvent removed and the diethyl ethyl-α-thienylmalonate distilled; b. p. 148–150° (5 mm.); yield 7 g. (64%).

5-Ethyl-5-(α-thienyl)-barbituric Acid.—A mixture of 0.5 g. of magnesium ribbon, which had been cleaned with steel wool and cut into small pieces, and 100 cc. of absolute methyl alcohol was heated until all of the magnesium had dissolved; 3.5 g. of diethyl ethyl-α-thienylmalonate and 2.0 g. of urea were added and the material refluxed for twelve hours. After removal of the alcohol, the residue was treated with 18% hydrochloric acid. The barbituric acid was obtained as an oil which soon crystallized; m. p. 179–180° after recrystallization from dilute alcohol; yield 1.7 g. (58%).

Anal. Calcd. for $C_{10}H_{10}O_3N_2S$: N, 11.76; S, 13.44 Found: N, 11.80; S, 13.56.

Summary

The preparation of 5-ethyl-5-(α-thienyl)-barbituric acid has been described. As far as hypnotic activity is concerned, preliminary results indicate that it is as active as phenobarbital.

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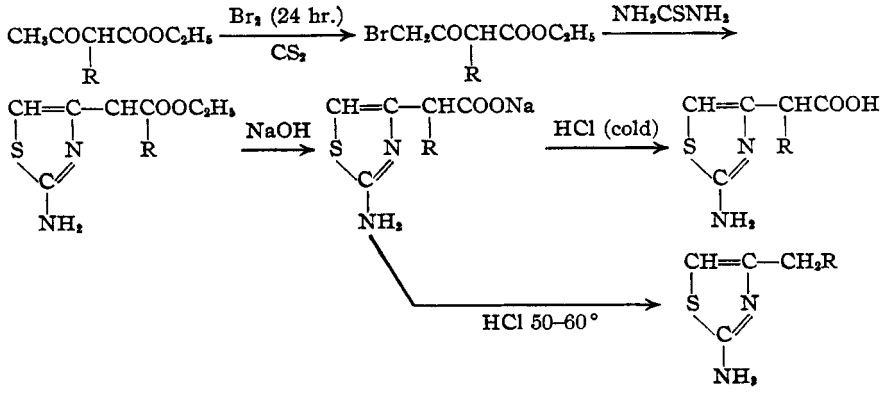
[CONTRIBUTION FROM THE SAMUEL BELL, JR., LABORATORY OF THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH IN THE PHILADELPHIA GENERAL HOSPITAL]

Preparation of 2-Amino-4-alkylthiazoles from Esters of Substituted 2-Aminothiazyl-4-acetic Acids

BY WILLIAM M. ZIEGLER

During a search for new sulfanilamide derivatives several interesting 2-aminothiazoles have been prepared. These contain a fatty acid ester in the 4 position, and lead to 2-amino-4-alkylthiazoles by saponification and decarboxylation.

The steps involved are



The reactions proceed smoothly and good yields of 4-alkylthiazoles are obtained without the usual preparation of the intermediate alkylhaloketones. Since the latter are often hard to obtain and at best unpleasant substances to work with, a method that avoids their use is desirable.

Although 2-amino-4-thiazylacetic acid has been reported to decarboxylate at its melting point,[1] no mention is made of the decarboxylation of this type of compound at a lower temperature. Since the amines turn dark at higher temperatures very

(1) Steude, *Ann.*, **261**, 33 (1891).