

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

5-Ethyl-5-( $\alpha$ -thienyl)-barbituric AcidBY F. F. BLICKE AND M. F. ZIENTY<sup>1</sup>

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  $\alpha$ -thienyl. The substitution of phenyl by  $\alpha$ -thienyl has been effected in local anesthetics,<sup>2</sup> pressor agents,<sup>3</sup> cinchophen<sup>4</sup> and in  $\beta$ -phenylalanine.<sup>5</sup>

This paper deals with the preparation of 5-ethyl-5-( $\alpha$ -thienyl)-barbituric acid, the  $\alpha$ -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. <sup>a</sup> Mg./kg.	M.H.D. <sup>a</sup> Mg./kg.	M.L.D. M.H.D.
Phenobarbital sodium	150	80	1.8
"Thienylbarbital" sodium	200	100	2.0

<sup>a</sup> 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 alkyl-arylbarbituric acids. In this instance it involved preparation of the following series of compounds: thiophene- $\alpha$ -carboxylic acid  $\rightarrow$   $\alpha$ -thenoyl chloride  $\rightarrow$   $\alpha$ -thienyl diazomethyl ketone  $\rightarrow$  ethyl  $\alpha$ -thienylacetate  $\rightarrow$  ethyl ethoxalyl- $\alpha$ -thienylacetate  $\rightarrow$  diethyl  $\alpha$ -thienylmalonate  $\rightarrow$  diethyl ethyl- $\alpha$ -thienylmalonate  $\rightarrow$  5-ethyl-5-( $\alpha$ -thienyl)-barbituric acid.

We found that the time required for the elimination of carbon monoxide from ethyl ethoxalyl- $\alpha$ -thienylacetate is shortened by the use of powdered glass and that condensation of diethyl ethyl- $\alpha$ -thienylmalonate with urea is effected best by the use of magnesium methyrate.<sup>6</sup>

(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.*, **18**, 13 (1935).

## Experimental Part

**Ethyl  $\alpha$ -Thienylacetate and  $\alpha$ -Thienylacetic Acid.**—Thiophene- $\alpha$ -carboxylic acid was obtained in 92% yield from an ether-benzene solution of  $\alpha$ -thienylmagnesium bromide and solid carbon dioxide.<sup>7</sup> The acid chloride,  $\alpha$ -thenoyl chloride, was prepared in 85% yield with the aid of thionyl chloride.<sup>8</sup>

(a) A dry ether solution of diazomethane,<sup>9</sup> prepared by treatment of 52.5 g. of N-methyl-N-nitrosourea<sup>10</sup> with 40% potassium hydroxide solution, was maintained at 5° while 20.0 g. of  $\alpha$ -thenoyl chloride,<sup>11</sup> 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,  $\alpha$ -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  $\alpha$ -thienylacetate, boiled at 124–129° (26 mm.); yield 15 g. (68%).<sup>12</sup>

When methyl alcohol was employed in the synthesis described above, methyl  $\alpha$ -thienylacetate was obtained; b. p. 115–118° (23 mm.). Upon hydrolysis of the ester with alcoholic potassium hydroxide,  $\alpha$ -thienylacetic acid was produced; m. p. 75–76°<sup>13</sup> 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  $\alpha$ -thienylmethyl chloride,<sup>14</sup> 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  $\alpha$ -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  $\alpha$ -thienylmethanol and hydrogen chloride by Biedermann, *Ber.*, **19**, 639 (1886).

