[CONTRIBUTION NO. 196 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. X. SYNTHESES OF THENAL- AND THENYL-BARBITURIC ACIDS

LOUIS J. OWEN AND F. F. NORD[1,2]

Received February 13, 1950

The progress of syntheses in thiophene chemistry has been handicapped by the cumbersome methods of obtaining a pliable starting material. This situation was alleviated with the advent of the one-step preparation of 2-thiophenealdehyde (1). Some recent work (2) in this laboratory has been conducted with the purpose of utilizing this versatile reactant for the preparation of various 2-thienyl-substituted compounds.

In this communication are described the syntheses of several new 2-thenal- and 2-thenyl-substituted barbituric acids.

It was known that 2-thiophenealdehyde, I, can be condensed with malonic acid in the presence of pyridine and piperidine (3), with the formation of 2-thenylacrylic acid. It was found that if milder conditions were employed, this modification could be applied for the synthesis of 2-thenalmalonic acid (II). However, because of the danger of decarboxylation, it was necessary to keep the reaction temperature below 55°. By so doing, the yield of the dicarboxylic acid amounted to 45%. Prolonging the reaction time served to increase only the extent of decarboxylation but not the yields. We found that by employing alcoholic ammonia (4), 2-thenalmalonic acid could be obtained in excellent yield. The successful synthesis of this dicarboxylic acid facilitated the preparation of the new thenyl-substituted barbituric acids.

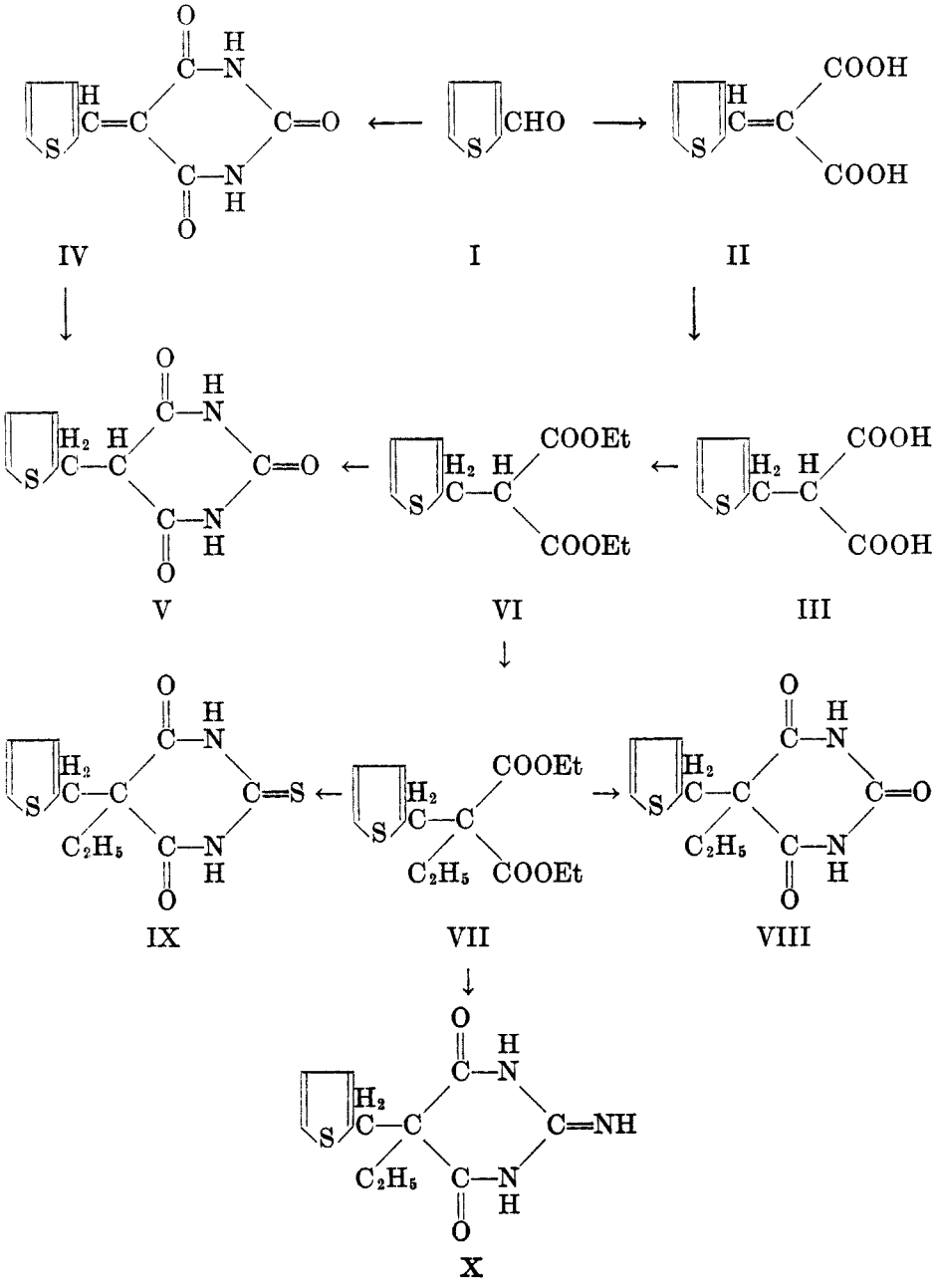
Upon reduction of II with sodium-amalgam in the presence of carbon dioxide, 2-thenylmalonic acid (III) was obtained. Maintaining the *p*H between 8 and 9, in this manner, reduced the reaction time from 72 hours to 24 hours. When mixed with an authentic sample of this saturated dicarboxylic acid, prepared according to an earlier method (5), a mixed melting point showed no depression. Esterification of 2-thenylmalonic acid and subsequent alkylation with ethyl bromide resulted in the formation of diethyl ethyl-(2-thenyl)malonate (VII). Upon condensation of this ester with urea, thiourea, and guanidine (as the carbonate) there was obtained 5-ethyl-5-(2-thenyl)barbituric acid (VIII), 5-ethyl-5-(2-thenyl)-2-thiobarbituric acid (IX), and 5-ethyl-5-(2-thenyl)-2-iminobarbituric acid (X), respectively.

In addition to the above named disubstituted barbituric acids it was found possible to prepare a number of monosubstituted, unsaturated barbituric acids, such as IV, by the direct condensation of 2-thiophenealdehyde with barbituric acid. These barbituric acids, listed in Table I, are yellow solids which melt at

[1] This investigation was carried out under the auspices of the Office of Naval Research. The analyses were obtained through the courtesy of Dr. F. Bühler, formerly of this Department.

[2] For paper No. IX of this series, see Gilsdorf and Nord, *J. Org. Chem.*, **15**, 307 (1950).

SCHEME I



high temperatures with decomposition and are insoluble in most organic solvents (6).

As a corroboration of the structure of these barbiturates, 5-(2-thenal)barbituric

TABLE I

MONOSUBSTITUTED, UNSATURATED THIOPHENE DERIVATIVES OF BARBITURIC ACID[a]

THIOPHENE-2-ALDEHYDES	PRODUCT	M.P., °C.	YIELD, %	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
Thiophene-2-aldehyde	5-(2-Thenal)barbituric acid	330–333	98	48.64	2.72	48.45	2.57
3-Methylthiophene-2-aldehyde	5-(3-Methyl-2-thenal)barbituric acid	283–285	97	50.83	3.41	50.95	3.24
5-Bromothiophene-2-aldehyde[b]	5-(5-Bromo-2-thenal)barbituric acid	364–367	92	35.89	1.67	35.75	1.71
5-Chlorothiophene-2-aldehyde	5-(5-Chloro-2-thenal)barbituric acid	345–348	93	42.11	1.96	42.25	2.09
5-Methylthiophene-2-aldehyde[c]	5-(5-Methyl-2-thenal)barbituric acid	320–323	95	50.83	3.41	50.55	3.42
5-Ethylthiophene-2-aldehyde[c]	5-(5-Ethyl-2-thenal)barbituric acid	288–290	95	52.78	4.02	52.65	4.17
5-Propylthiophene-2-aldehyde[c]	5-(5-Propyl-2-thenal)barbituric acid	275–277	96	54.53	4.58	54.70	4.71

[a] In this series, melting points are not very characteristic, representing temperatures of decomposition that depend upon the rate of heating. [b] Ref. (8). [c] Ref. (9).

TABLE II

PHARMACOLOGICAL ACTIVITY

	COMPOUND	DOSE mg./kg. *per os*	No. DEAD / No. TREATED	LD_{50} mg./kg.	REMARKS
I	5-Ethyl-5-(2-thenyl)-barbituric acid	500 1000 1500	1/6 4/6 6/6	770	Light sleep, hyperexcitability, and convulsions
II	5-Ethyl-5-(2-thenyl)-2-thiobarbituric acid	500 1000 1500	2/6 3/6 5/6	950	Light sleep, hyperexcitability, and convulsions
III	5-Ethyl-5-(2-thenyl)-2-iminobarbituric acid	500 1000 1500 2000 3000 4000 5000	0/6 0/6 0/6 0/6 0/6 0/6 0/6	>5000	No hypnosis
IV	5-(5-Methyl-2-thenal)-barbituric acid	500 1000 2000 3000 4000 5000	0/6 0/6 0/6 0/6 0/6 0/6	>5000	No hypnosis

acid was reduced with zinc and acetic acid whereby 5-(2-thenyl)barbituric acid (V), was obtained. This saturated barbiturate was prepared subsequently by the condensation of VI with urea (7).

The data regarding the effectiveness of four of these new barbiturates are recorded in Table II and were obtained in the pharmacology laboratories of Hoffmann-La Roche Inc., Nutley, N. J., through the courtesy of Dr. L. O. Randall.

EXPERIMENTAL[3]

2-Thenalmalonic acid. Freshly distilled 2-thiophenealdehyde (28 g.) and 52.0 g. of malonic acid, previously dried over phosphorus pentoxide and 250 cc. of absolute ethyl alcohol saturated with anhydrous ammonia, were heated at 70–75° for four hours. Then 500 cc. of water was added and the solution was acidified with concentrated hydrochloric acid. The precipitate, recrystallized from dilute alcohol, gave faintly yellow plates of 2-thenalmalonic acid (85%), m.p. 206–207°.

Anal. Calc'd for $C_8H_6O_4S$: C, 48.47; H, 3.05.

Found: C, 48.55; H, 3.41.

2-Thenylmalonic acid. 2-Thenalmalonic acid (19.82 g.) was dissolved in 250 cc. of water with the aid of 10% sodium hydroxide until the solution was neutral. Finely divided 4% sodium-amalgam (400 g.) was added, the entire mixture was vigorously agitated, and a stream of carbon dioxide was passed into the liquid. At the end of 24 hours, the solution was carefully acidified with hydrogen chloride. The acidified solution was extracted three times with 150 cc. of ether, the ether extract washed successively with water and 10% sodium bicarbonate solution, and dried over Drierite. Upon removal of the ether, a yellow oil was obtained which, after cooling and scraping, solidified. Recrystallization from acetone-benzene gave white needles of 2-thenylmalonic acid (85%), m.p. 136–137°.[4]

Anal. Calc'd for $C_8H_8O_4S$: C, 48.20; H, 4.03.

Found: C, 48.25; H, 4.02.

Diethyl 2-thenylmalonate. 2-Thenylmalonic acid (40 g.) was esterified by refluxing gently for four hours with 200 cc. of absolute ethyl alcohol and 6 cc. of sulfuric acid. At the end of this time the excess alcohol was removed *in vacuo* and 250 cc. of water was added. The resulting solution was extracted twice with 150-cc. portions of ether, washed with water and 10% sodium bicarbonate, and dried over Drierite. Fractionation yielded diethyl 2-thenylmalonate (80%), b.p.[5] 125–128°/1–2 mm.

Anal. Calc'd for $C_{12}H_{16}O_4S$: C, 56.22; H, 6.29.

Found: C, 56.10; H, 6.01.

Diethyl ethyl-(2-thenyl)malonate. Diethyl 2-thenylmalonate (128.2 g.) was refluxed gently for one to two minutes in a solution of 14.0 g. of sodium and 500 cc. of absolute ethyl alcohol, and 75.0 g. of ethyl bromide was added dropwise. When the addition was completed, the mixture was refluxed vigorously until the solution was no longer alkaline. Excess ethyl alcohol was removed *in vacuo* and the oil was taken up in ether. Fractionation yielded diethyl ethyl-(2-thenyl)malonate (72%), b.p. 130–135°/1–2 mm.

Anal. Calc'd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.08.

Found: C, 59.05; H, 7.06.

Ethyl (2-thenyl)malonic acid. Diethyl ethyl-(2-thenyl)malonate (3 g.) was refluxed for two hours with 20.0 g. of potassium hydroxide pellets, 40.0 g. of ethyl alcohol, and 40.0 g. of water. After acidification with sulfuric acid, the acid was treated in the manner described for 2-thenylmalonic acid, m.p. 127.5–128.5°.

Anal. Calc'd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30.

Found: C, 52.80; H, 5.43.

---

[3] Melting points were obtained with the Fischer-John apparatus.

[4] Blicke and Leonard reported 138–139°.

[5] Blicke and Leonard reported 149–152°/6 mm.

5-Ethyl-5-(2-thenyl)barbituric acid. Diethyl ethyl-(2-thenyl)malonate (10 g.), 2.43 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 10.55 g. of urea were refluxed gently for 18 hours. The alcohol was removed *in vacuo*, the residue was dissolved in water and acidified with 2 *N* hydrochloric acid. The precipitate was filtered and recrystallized from toluene. The white needles of 5-ethyl-5-(2-thenyl)barbituric acid (62%) melted at 207–208°.

Anal. Calc'd for $C_{11}H_{12}N_2O_3S$: C, 52.36; H, 4.79.
Found: C, 52.55; H, 4.67.

5-Ethyl-5-(2-thenyl)-2-thiobarbituric acid. Ten grams of diethyl ethyl-(2-thenyl)malonate, 2.43 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 13.35 g. of thiourea were treated as in the procedure described for the preparation of 5-ethyl-5-(2-thenyl)barbituric acid. After recrystallization from *o*-xylene the yellow plates of 5-ethyl-5-(2-thenyl)-2-thiobarbituric acid (49.5%) melted at 216–217°.

Anal. Calc'd for $C_{11}H_{12}N_2O_2S_2$: C, 49.26; H, 4.50.
Found: C, 49.55; H, 4.53.

5-Ethyl-5-(2-thenyl)-2-iminobarbituric acid. Ten grams of diethyl ethyl-(2-thenyl)-malonate, 7.29 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 15.00 g. of guanidine carbonate were treated as described in the two proceding sections. Purification was accomplished by repeated acidifications from alkaline solutions, m.p. 365–368°. The yield was 58%.

Anal. Calc'd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21.
Found: C, 52.55; H, 5.59.

GENERAL PROCEDURE FOR THE PREPARATION OF THENALBARBITURIC ACIDS

The procedure utilized was identical for all the thenalbarbituric acids.

5-(2-Thenal)barbituric acid. Barbituric acid (13 g.) was vigorously shaken with 2 liters of water at room temperature until solution was effected (usually from one to two hours). At the end of this time, 11.22 g. (0.1 mole) of freshly distilled 2-thiophenealdehyde was added and shaking was resumed. Within a short time, a lustrous, yellow solid was formed, but shaking was continued for an hour to insure the completeness of the reaction. After the addition of 250 g. of sodium chloride, the mixture was shaken for an additional one-half hour. After 12 hours in the refrigerator, the yellow, amorphous 5-(2-thenal)barbituric acid was filtered, washed with water to remove any unreacted barbituric acid, and washed with ether to remove any unreacted 2-thiophenealdehyde. The product (98%) was recrystallized from glacial acetic acid.

5-(2-Thenyl)barbituric acid. a. 5-(2-Thenal)barbituric acid (10 g.) was dissolved in 250 cc. of hot glacial acetic acid. An excess of zinc dust was added and the temperature was maintained at 70–75° until the intense, yellow color no longer persisted (usually from 10–20 minutes). The solution was cooled, filtered, and evaporated *in vacuo* yielding a faintly yellow mixture of zinc acetate and 5-(2-thenyl)barbituric acid. Upon recrystallization from water, there was obtained 8.8 g. of 5-(2-thenyl)barbituric acid, m.p. 214–215°.

Anal. Calc'd for $C_9H_8N_2O_3S$: C, 48.20; H, 3.59.
Found: C, 48.15; H, 3.71.

b. Diethyl 2-thenylmalonate (25.6 g.), 2.2 g. of sodium, and 6.0 g. of urea were refluxed for 7 hours in 100 cc. of absolute ethyl alcohol. The resulting crystals were dissolved in 80 cc. of hot water and acidified with concentrated hydrochloric acid. Upon recrystallization from water there was obtained 5-(2-thenyl)barbituric acid in 55% yield, m.p. 214–215°.

Anal. Calc'd for $C_9H_8N_2O_3S$: C, 48.20; H, 3.59.
Found: C, 48.25; H, 3.45.

SUMMARY

The syntheses of several 2-thenal- and 2-thenyl-barbituric acids are reported.

NEW YORK 58, N. Y.

REFERENCES

(1) KING AND NORD, *J. Org. Chem.*, **13,** 635 (1948).
(2) CROWE AND NORD, *J. Org. Chem.*, **15,** 81 (1950).
(3) BARGER AND EASSON, *J. Chem. Soc.*, 2100 (1938).
(4) (a) KNOEVENAGEL, *Ber.*, **31,** 2596 (1898); (b) ADAMS, *Org. Reactions*, **1,** 222 (1942).
(5) BLICKE AND LEONARD, *J. Am. Chem. Soc.*, **68,** 1934 (1946).
(6) CONRAD AND REINBACH, *Ber.*, **34,** 1339 (1901).
(7) KAST, *Ber.*, **45,** 3124 (1912).
(8) KING AND NORD, *J. Org. Chem.*, **14,** 405 (1949).
(9) KING AND NORD, *J. Org. Chem.*, **14,** 638 (1949).