[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

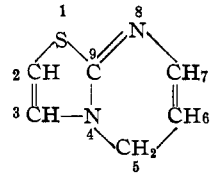
Researches on Thiazoles. XXV. Some New Thiazolidinopyrimidines of Barbituric Acid Type

BY EDWARD J. MASTERS AND MARSTON TAYLOR BOGERT

Since the proof of the structure of vitamin B_1,[1] great interest has been shown in compounds containing the thiazole or thiazoline ring. A miscellany of such compounds having therapeutic value appears in the patent and regular literature. These compounds are characterized by relatively low toxicity when introduced into the body.

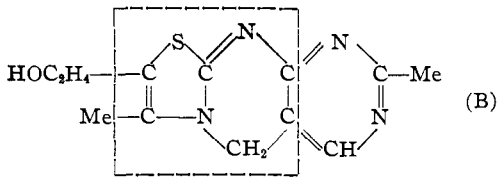
Thus, sulfathiazole[2] is an example of this type of compound and is useful in the treatment of certain types of bacterial infection. More recently, its thiazoline analog, sulfathiazoline,[3] has been synthesized. A variety of compounds containing the thiazole or thiazoline ring and possessing local anesthetic activity has been prepared.[4-9]

The immediate object of this investigation was the synthesis of compounds related to the structure (A)



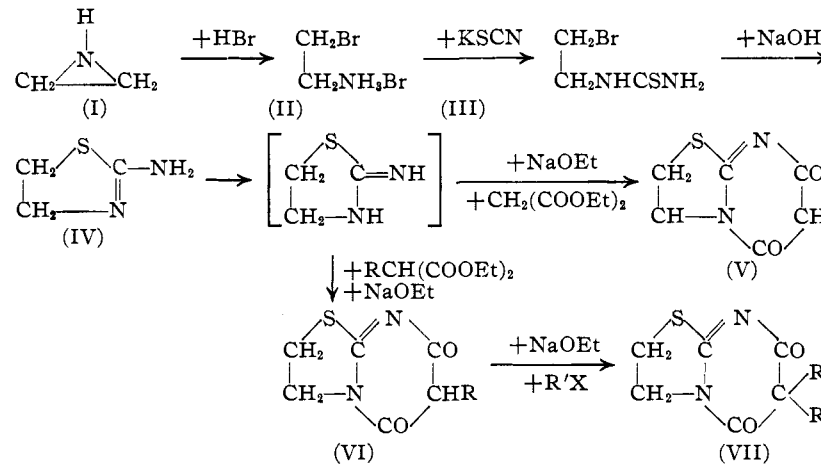
(A)

Compounds containing this skeletal structure are as yet unknown in the literature. The nearest approach to it is found in the thiochrome molecule[10] (B), the thiazolopyrimidine portion of which is enclosed in broken lines.



(B)

FLOW SHEET



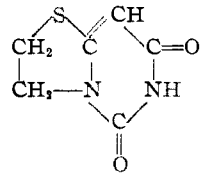
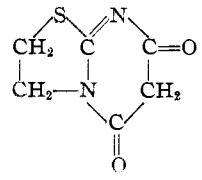
R = Me, Et, *i*-Pr, Ph, and $PhCH_2$
R′ = Et, *i*-Pr, *n*-Bu, Ph, and $PhCH_2$

The 5,7-dioxo derivatives of constitution (A) present an interesting variation in the barbituric acid structure, and the analogs of the more important barbituric acids might be expected to possess hypnotic or anesthetic activity. The flow sheet for the reactions involved includes standard methods for the synthesis of barbituric acids.

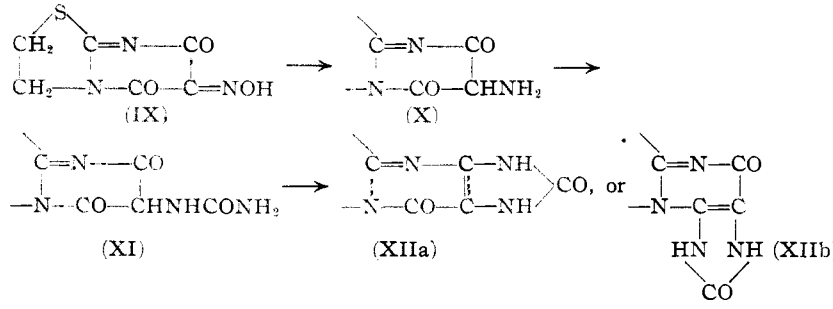
As will be noted in this flow sheet, 2-aminothiazoline (IV) is assumed to react in its tautomeric 2-iminothiazolidine form under the conditions employed.

Bogert and Mills[11] in laying the groundwork for the synthesis of compounds of type (A) synthesized β,β′-di-(1-barbituryl)-ethyl disulfide, using β-mercaptoethylamine as the starting material. Bogert and Nathan[12] continued this work and by reduction of β,β′-di-(1-barbituryl)-ethyl disulfide, using zinc and hydrochloric acid, obtained a compound of the empirical formula $C_6H_6N_2O_2S$. Since condensation at two different positions was possible, it was not clear whether the structure of this compound was

(1) Cline, Williams and Finkelstein, THIS JOURNAL, **59**, 1052 (1937).
(2) Lott and Bergeim, *ibid.*, **61**, 3593 (1939).
(3) Raiziss and Clemence, *ibid.*, **63**, 3124–3126 (1941).
(4) Johnson, *ibid.*, **52**, 4141 (1930).
(5) U. S. Patent 1,970,656 (1931).
(6) Ballowitz, *Arch. Exptl. Path. Pharm.*, **163**, 687 (1932).
(7) Niederl, Hart and Scudi, THIS JOURNAL, **58**, 707 (1936).
(8) Hart and Niederl, *ibid.*, **61**, 1145 (1939).
(9) Adams, *ibid.*, **59**, 2264 (1937).
(10) Bergel and Todd, *J. Chem. Soc.*, 1601 (1936).
(11) Bogert and Mills, THIS JOURNAL, **62**, 1173–1180 (1940).
(12) Bogert and Nathan, *ibid.*, **63**, 2361–2366 (1941).

(VIII)  or  (V)

In the present work, it was thought that a more direct and unequivocal synthesis of (V) could be effected by condensation of 2-aminothiazoline (IV) with malonic ester, analogous to that used by Chichibabin[13] in which 2-aminopyridine was condensed with malonic ester to yield the bicyclic pyridinopyrimidine.



In the attempts to condense 2-aminothiazoline with malonic ester to form the desired pyrimidine (V), the conditions of Chichibabin's experiment were followed, *i. e.*, the slow heating of the reactants to 195°. Extensive decomposition occurred with the formation of a hard red resin. Lower temperatures were used without success. The condensation was finally effected in high yield using sodium ethylate with absolute ethyl alcohol as solvent. This synthesis of compound (V) proves that the compound synthesized from β,β′-di-(1-barbituryl)-ethyl disulfide by Bogert and Nathan[12] was (VIII), since the two products were not identical.

When mono-substituted alkyl or aryl malonic esters were used in the condensation with 2-aminothiazoline in the presence of sodium ethylate, the reaction proceeded readily with formation of the mono-substituted thiazolidinopyrimidines listed in Table I. The synthesis of the disubstituted pyrimidines was effected by alkylation of the appropriate monosubstituted pyrimidine containing the more sterically hindered group. The alkylations were conducted in absolute ethyl alcohol in the presence of sodium ethylate. The disubstituted pyrimidines synthesized in this series (Table II) are the analogs of the barbituric acids: Veronal, Neonal, Ipral and Phenobarbital.

Of the compounds described in Tables I and II, nos. 1, 2 and 6 formed white dendritic crystals; no. 3, white needles; nos. 4, 8, 10 and 11 colorless plates; nos. 5, 7 and 9, colorless needles.

Solubilities.—No. 1, 1% in hot absolute alcohol, 2% in hot water; no. 2, 1 g. in 150 cc. of hot water; no. 3, 1% in hot water, more soluble in alcohol; no. 4, 1 g. in 9 cc. of hot alcohol; no. 7, 0.25% in hot water.

From the thiazolidinobarbituric acid (V), the corresponding uric acid (XII) was synthesized via the usual oximino (IX), uramil (X), and pseudouric acid (XI) derivatives

The results of the pharmacological tests upon the compounds described in this paper will be reported later.

Acknowledgments.—We are greatly indebted to the Carbide & Carbon Chemicals Corp. of New York for their courtesy in supplying us with ethyleneimine and β-aminoethyl sulfate required for this investigation. We are also under obligations to Mr. Saul Gottlieb for the analysis of our products.

Experimental

All melting points recorded are corrected for stem exposure.

β-Bromoethylamine hydrobromide (II) was prepared most satisfactorily as follows: 174 g. (4 mols) of 99% ethyleneimine was added dropwise to 1250 cc. (11.1 mols) of 48% HBr. The temperature of the reaction mixture was maintained at 0–5°, and the solution was stirred vigorously during the addition. It was then concentrated to a thick sirup under vacuum, allowed to cool, the crystalline mass filtered off and washed with a little absolute alcohol. The filtrate and washings were concentrated further to yield more of the product. The product after drying weighed 660 g. or a yield of 80%. After recrystallization from absolute alcohol, the compound melted at 173.3–174.3° (lit.,[14] m. p. 172–173°).

Anal. Calcd. for $C_2H_7Br_2N$: C, 11.7; H, 3.4. Found: C, 11.7; H, 3.3.

It is stated by Gabriel,[15] and in "Organic Syntheses,"[16] that the above compound can be prepared "by the addition of hydrogen bromide to ethyleneimine," but if the reaction is carried out in that way the compound sought will not be obtained.

β-Bromoethylthiourea (III) was prepared from β-bromoethylamine hydrobromide and potassium thiocyanate by

(13) Chichibabin, *Ber.*, **57**, 1168 (1924).

(14) Leffler and Adams, THIS JOURNAL, **59**, 2255 (1937).

(15) Gabriel, *Ber.*, **21**, 1054 (1888).

(16) "Organic Syntheses," XVIII, 14 (1938).

TABLE I

6-MONOSUBSTITUTED 2,3,6,7-TETRAHYDRO-5,7-DIOXO-5-THIAZOLO[3,2-a]PYRIMIDINES

No.	Formula	Group at 6	Yield, %	M. p. (cor.), °C.	Calcd. C	Calcd. H	Found C	Found H
1	$C_6H_6O_2N_2S$	H	88	244.5–245.5	42.5	3.6	42.6	3.8
2	$C_7H_8O_2N_2S$	Me	72	272–276	45.7	4.4	45.9	4.5
3	$C_8H_{10}O_2N_2S$	Et	70	224.4–224.7	48.5	5.1	48.7	5.2
4	$C_9H_{12}O_2N_2S$	*i*-Pr	76	262.3–262.8	51.1	5.7	51.5	6.0
5	$C_{12}H_{10}O_2N_2S$	Ph	45	247.2–247.7	58.5	4.1	58.5	4.1
6	$C_{13}H_{12}O_2N_2S$	$PhCH_2$	82	241.9–242.3	60.0	4.7	60.0	4.8

TABLE II

6,6-DISUBSTITUTED 2,3,6,7-TETRAHYDRO-5,7-DIOXO-5-THIAZOLO[3,2-a]PYRIMIDINES

No.	Formula	Groups at 6	Yield, %	M. p. (cor.), °C.	Calcd. C	Calcd. H	Found C	Found H
7	$C_{10}H_{14}O_2N_2S$	Et, Et	29	138.2–138.7	53.1	6.2	53.4	6.4
8	$C_{11}H_{16}O_2N_2S$	Et, *i*-Pr	33	92.6–93.1	55.0	6.7	55.3	6.8
9	$C_{12}H_{18}O_2N_2S$	Et, *n*-Bu	31	89.7–90.3	56.7	7.1	56.8	7.1
10	$C_{14}H_{14}O_2N_2S$	Et, Ph	36	120.3–121.3	61.3	5.2	61.4	5.2
11	$C_{15}H_{16}O_2N_2S$	Et, $PhCH_2$	30	136.0–136.4	62.5	5.6	62.7	5.7

the method of Gabriel,[17] and melted at 173.6–174.2° (lit.,[17] m. p. 172.5–173.5°); yield, 60%.

The 2-aminothiazoline (IV) used was obtained by treating (III) with caustic soda solution.[17] The m. p. was 84–85° (lit.,[17] m. p. 84–85°); yield, 86%; over-all yield from ethyleneimine was 41%.

2,3,6,7-Tetrahydro-5,7-dioxo-5-thiazolo[3,2-a]pyrimidine (V).—2.3 g. (0.10 mole) of clean metallic sodium was dissolved in 50 cc. of absolute ethyl alcohol. This solution was cooled to 50° and 8 g. (0.05 mol) of ethyl malonate was added, followed by a solution of 5 g. (0.05 mol) of 2-aminothiazoline in 20 cc. of absolute ethyl alcohol. The reaction mixture was refluxed for three hours, during which period a white solid separated rapidly.

The mixture was cooled, brought to acidity by the addition of 11 cc. of concentrated hydrochloric acid, the precipitate filtered off and washed with a few cc. of alcohol. It was then slurried with about 30 cc. of water, to remove any sodium chloride, filtered, dried at 105° for an hour, and then weighed. The yield was 6.8 g. From the original filtrate, 0.7 g. more was obtained, making a total yield of 7.5 g. or 88%. Recrystallized from alcohol, it formed small dendritic crystals, which melted with decomposition at 244.5–245.5°.

Anal. Calcd. for $C_6H_6O_2N_2S$: C, 42.5; H, 3.6. Found: C, 42.6; H, 3.8.

The mono-R derivatives of (V) were synthesized in a manner analogous to the above, using the appropriate mono-substituted malonic ester in the place of malonic ester. Data concerning them appear in Tables I and II. The phenyl malonic ester employed was prepared from phenyloxaloacetic ester.[18]

6,6-Diethyl-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (VII).—4 g. (0.020 mole) of the monoethyl derivative (VI) was added to an alcoholic solution of sodium ethylate prepared by dissolving 0.50 g. (0.022 mole) of clean metallic sodium in 50 cc. of absolute ethyl alcohol, and the temperature was kept at 50°.

3.9 g. (0.025 mole) of ethyl iodide was added, and the solution refluxed until neutral. The time of refluxing was about two hours. It was then concentrated to about 15 cc., 100 cc. of water added slowly with shaking, and small white feathery crystals precipitated. The crystals were collected on a Büchner funnel, washed with a few cc. of dilute bicarbonate solution, to dissolve any unreacted (VI), then with a few cc. of alcohol, and finally with water. Dried at 105°, the yield was 1.3 g., or 29%.

Recrystallization of the product from a large volume of hot water resulted in the formation of beautiful long needles, m. p. 138.2–138.7°.

Anal. Calcd. for $C_{10}H_{14}O_2N_2S$: C, 53.1; H, 6.2. Found: C, 53.4; H, 6.4.

The other 6,6-disubstituted products were prepared similarly, using the appropriate halide. Analyses and other data are given in Tables II and III. These compounds were quite soluble in various organic solvents, but dissolved only slightly in water. A convenient method of isolating them consisted in removing all of the alcohol from the reaction mixture, when the residual oil congealed on standing and cooling. Unaltered initial mono-substituted esters were then easily removed by washing with a potassium carbonate solution.

6-Isonitroso-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (IX).—A suspension of 7 g. (0.041 mol) of (V) in 100 cc. of 30% alcohol was stirred vigorously and 6.3 g. (0.054 mol) of isoamyl nitrite added dropwise over a period of a half hour. After further vigorous stirring for an hour, the temperature was slowly raised to 50° and the stirring continued for another hour. The white suspension slowly changed into the purple of the nitroso compound. The mixture was chilled, the nitroso compound removed, washed with alcohol and air dried; yield, 5 g., or 61%; m. p. 175–178°. As some difficulty was experienced in purifying this compound, it was used without further purification in the subsequent reactions. It dissolved readily in alkali to a deep purple solution.

6-Amino-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a] pyrimidine (X).—To a solution of 4 g. (0.02 mol) of (IX) in 10 cc. of concentrated ammonium hydroxide diluted with 10 cc. of water, 7 g. of sodium hydrosulfite, dissolved in 15 cc. of water containing a few drops of ammonia, was added slowly until the purple color disappeared. The

(17) Gabriel, *Ber.* **22**, 1141 (1889).

(18) "Organic Syntheses," XVI, 33 (1936).

solution was chilled and neutralized with dilute hydrochloric acid. The precipitate was filtered off, washed with water and crystallized from hot water. The yield was 2 g. or 54%. The compound turned red at 174° and decomposed at 194°. Not unlike other uramils, this compound was very troublesome to purify, changed color rapidly in the air or on drying *in vacuo*, and burned with difficulty in the microanalytical apparatus, so that it was felt that not much reliance could be placed upon the analytical results, although these indicated that the substance was the impure monohydrate.

Anal. Calcd. for $C_6H_9O_3N_3S$: C, 35.5; H, 4.5. Found: C, 36.4; H, 4.5.

6-Ureido-2,3,6,7-tetrahydro-5,7-dioxo-5-thiazolo[3,2-a]pyrimidine (XI).—To a solution of 0.5 g. of (X) (0.0027 mol) in 30 cc. of hot water, there was added a solution of 0.32 g. (0.0040 mol) of potassium cyanate in 10 cc. of water, and the solution was warmed to the disappearance of its purple color. It was then chilled, acidified with dilute hydrochloric acid, the yellow precipitate collected and dried; yield, 0.5 g., or 80%. Recrystallized from hot water containing a little Norit, a white crystalline product resulted, m. p. 261–263°.

Anal. Calcd. for $C_7H_8O_3N_4S$: C, 36.9; H, 3.5. Found: C, 37.2; H, 3.5.

The thiazolidinouric acid (XIIa or XIIb) was obtained from the corresponding pseudouric acid (XI) by an adaptation of the classic method of Fischer and Ach.[19]

A mixture of 46 mg. of the pseudouric acid (XI) with 1 g. of anhydrous oxalic acid was placed in a test-tube and heated in an oil-bath, the temperature of which was brought to 185° in the course of ten minutes. Most of the oxalic acid volatilized, and some of the pseudouric acid was decomposed with liberation of hydrogen sulfide. The residue when cold was extracted with alcohol, to remove any oxalic acid still present, and the undissolved material was dissolved in dilute sodium hydroxide solution, boiled with activated carbon, the filtrate acidified with dilute hydrochloric acid and chilled. The precipitate, removed and dried, weighed 15 mg., *i. e.*, a yield of 36%. Recrystallized from a large volume of water, it separated in glistening white microscopic crystals, which remained unmelted at 300°.

Anal. (on 1 mg. of product). Calcd. for $C_7H_6O_2N_4S$: C, 40.0; H, 2.9. Found: C, 39.7; H, 2.7.

Not enough material was available to determine whether the constitution of this product should be represented by formula XIIa or XIIb, either one of which could be formed by the elimination of water from the initial pseudouric acid.

(19) Fischer and Ach, *Ber.*, **28**, 2473 (1895).

Summary

1. Thiazolidinopyrimidines of barbituric acid type are easily prepared pure and in satisfactory yields from 2-aminothiazoline as initial material by familiar reactions.

2. Among the compounds so prepared are analogs of Veronal, Neonal, Ipral and Phenobarbital.

3. From the thiazolidinobarbituric acid, the corresponding thiazolidinouric acid has been synthesized via the oximino, uramil and pseudouric acid derivatives.

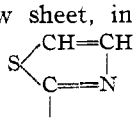
4. The physiological effects of these compounds are now being studied, to ascertain to what extent, if at all, their properties resemble those of the corresponding barbituric acids.

NEW YORK, N. Y. RECEIVED JULY 18, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Thiazoles. XXVI. Some Acyl Derivatives of 2-Aminothiazole

BY EDWARD J. MASTERS AND MARSTON TAYLOR BOGERT

The behavior of 2-aminothiazole (I) when digested with ethyl malonate and sodium ethylate, in alcoholic solution, is quite different from that of 2-aminothiazoline under similar conditions,[1] as can be seen from the following flow sheet, in which R represents the thiazole residue, 

This difference in the behavior of 2-aminothiazole as compared with 2-aminothiazoline is probably due, as pointed out in our previous article,[1] to the fact that the thiazoline can react in its tautomeric iminothiazolidine form, a rearrangement which is less likely to occur with the more stable conjugated system of the thiazole.

Refluxing of the thiazole, in alcoholic solution, with sodium ethylate and ethyl malonate, resulted in the formation of both the thiazolylmalonamic ester (II), and the *sym*-dithiazolylmalonamide (III).

Some years ago, the I. G. Farbenind. A.-G.[2] took out patents for the manufacture of acetoacetyl derivatives of 2-aminothiazole by heating together the aminothiazole and acetoacetic ester (and analogous esters) without any solvent. In

(1) Masters and Bogert, THIS JOURNAL, **64**, 2709 (1942).

(2) I. G. Farbenind. A.-G., German Patent 603,623, Oct. 8, 1934; *C. A.*, **29**, 814 (1935); and addition thereto, Jan. 3, 1935; *C. A.*, **29**, 4024 (1935).