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 $C_6H_9O_5N_3S$: 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 $C_7H_8O_5N_4S$: 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 $C_7H_6O_4N_4S$: 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.

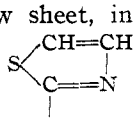
4. The physiological effects of these compounds are now being studied, to ascertain to what extent, if at all, their properties resemble those of the corresponding barbituric acids.

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, 

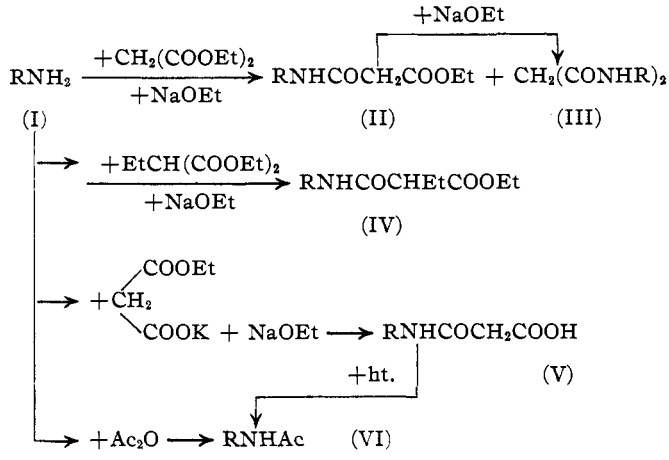
This difference in the behavior of 2-aminothiazole as compared with 2-aminothiazoline is probably due, as pointed out in our previous article,[1] to the fact that the thiazoline can react in its tautomeric iminothiazolidine form, a rearrangement which is less likely to occur with the more stable conjugated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



our own experiments, when the aminothiazole and malonic ester were heated together directly, a great deal of decomposition ensued, but both (II) and (III) were isolated from the crude product.

When the malonamate (II) was heated above its m. p., or was refluxed in absolute ethanol solution with sodium ethylate, the diamide (III) was formed.

By the use of a substituted ethyl malonate, instead of ethyl malonate itself, in the condensation with the aminothiazole, the corresponding substituted malonamate (IV) was obtained.

From the potassium salt of the malonic ester acid, 2-aminothiazole, and sodium ethylate, in absolute ethanol solution, the malonamic acid (V) was prepared. This acid when heated lost carbon dioxide, with formation of the same 2-acetaminothiazole as resulted from direct acetylation of the aminothiazole.

All attempts to cyclize the malonamic acid (V) to a thiazolopyrimidine have so far proved fruitless.

Acknowledgments.—Our thanks are due to the Monsanto Chemical Co., of St. Louis, Missouri, and to the Calco Chemical Division of the American Cyanamid Company, Bound Brook, New Jersey, for supplies of 2-aminothiazole; and to Mr. Saul Gottlieb for the analysis of our products.

Experimental

All melting points are corrected for exposed stem.

2-Aminothiazole (I) can be prepared readily from thiourea and dichloroethyl ether, by the method of Traumann,[3] if necessary, but it is also available commercially.

(3) Traumann, *Ann.*, **249**, 35 (1888).

Ethyl N-(2-Thiazolyl)-malonamate (II).—To a solution of 11.5 g. (0.5 mole) of clean sodium in 500 cc. of absolute ethanol, cooled to 50°, there was added 80 g. (0.5 mole) of ethyl malonate, followed by 50 g. (0.5 mole) of 2-aminothiazole. After refluxing the mixture for five hours, it was cooled, and acidified by the addition of 42 cc. of concentrated hydrochloric acid. The precipitate contained two products, the more soluble of which was extracted by leaching with large volumes of hot water. The total yield of this product, including some recovered from the original filtrate, was 34.5 g. Recrystallized from water, it formed white crystals, m. p. 149–149.5°, soluble in alcohol or benzene.

Anal. Calcd. for $C_8H_{10}O_3N_2S$: C, 44.8; H, 4.7; N, 13.1. Found: C, 45.0; H, 4.6; N, 13.1.

sym-**N-(2-Thiazolyl)-malonamide** (III), which was the less soluble product in the above reaction, was isolated in a yield of 34 g. The combined yield of (II) and (III) accounted for about 80% of the aminothiazole used.

The amide (III) was purified by precipitating its bicarbonate solution by dilute acid. It began to change color at about 258° and decomposed sharply at 271°.

Anal. Calcd. for $C_9H_8O_2N_4S_2$: C, 40.3; H, 3.0; N, 20.8. Found: C, 40.2; H, 3.0; N, 20.6.

N-(2-Thiazolyl)-malonamic acid (V) was prepared as described for (II), using the potassium salt of malonic ethyl ester acid in place of ethyl malonate. By acidification with dilute mineral acid, the free malonamic acid was obtained as white dendritic crystals, in a yield of 54%. At 185.8–186.8°, it melted with decomposition, losing carbon dioxide and forming the 2-acetaminothiazole (VI), m. p. 206.5–207° (lit.,[3] m. p. 203°), long needles, whose identity was checked by preparation of the same compound from the aminothiazole (I) and acetic anhydride.[3]

Anal. Calcd. for $C_6H_6O_3N_2S$: C, 38.8; H, 3.3; acid equivalent, 186. Found: C, 39.1; H, 3.6; acid equivalent, 186.

Ethyl N-(2-thiazolyl)-ethylmalonamate (IV), prepared by the same method as (II), using ethyl ethylmalonate in place of ethylmalonate, was obtained in a yield of 46%, m. p. 117.8–118.8°, as white dendritic crystals.

Anal. Calcd. for $C_{10}H_{14}O_3N_2S$: C, 49.6; H, 5.8. Found: C, 49.8; H, 5.8.

In this case, no diamide analogous to (III) was isolated.

Summary

1. The behavior of 2-aminothiazole when digested, in alcoholic solution, with ethyl malonate and sodium ethylate, is quite different from that of 2-aminothiazoline, in that there results a mixture of the thiazolylmalonamic ester and the *sym*-dithiazolylmalonamide, but no thiazolopyrimidine, nor could the latter be obtained by cyclization of the thiazolylmalonamic acid.

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