

base strength of the system is  $K_B = 4 \times 10^{-3}$ . A decomposition takes place at a rate proportional to the first power of the concentrations of the pyrazinium and hydroxide ions. The rate of formation of the pseudo base is hypothesized as the controlling step in this reaction.

5. The solubility of 5-phenyl-10-methylacridinium hydroxide has been found to be  $1 \times 10^{-4}$  mole/liter at room temperature and solutions of the base appear to be highly ionized. The initial high value of the conductivity on mixing 5-phenyl-10-methylacridinium chloride and sodium hydroxide is shown to be due to supersaturation.

6. The significance of the results is discussed in the light of ring conjugation, which seems to be the determining factor in the quaternary base-pseudo base equilibria.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

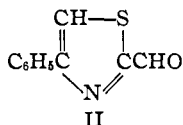
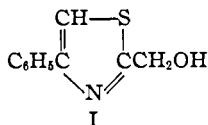
### SYNTHESIS OF 4-PHENYLTHIAZOLE-2-METHANOL AND SOME OF ITS DERIVATIVES. VIII

BY JOHN F. OLIN<sup>1</sup> AND TREAT B. JOHNSON

RECEIVED DECEMBER 8, 1930

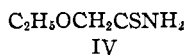
PUBLISHED APRIL 6, 1931

In the carrying out of our research program dealing with the chemistry of thiazoles, it was necessary to develop practical methods of synthesizing certain thiazoles containing the simplest primary alcohol and an aldehyde group in position 2 of the thiazole ring. The derivatives selected for synthesis were the alcohol and aldehyde of 4-phenylthiazole which are represented by formulas I and II, respectively. These have been prepared by



methods which undoubtedly will be of general application for further important syntheses in this series.

The starting points of our research were the thioamides of benzoylglycolic and ethoxyacetic acids, which are represented by formulas III and IV, respectively.



By interaction of these thioamides III and IV with bromoacetophenone, the benzoate and ethyl ether of the alcohol I are obtained easily in excellent yields. Both derivatives are convertible by hydrolysis into the alcohol I. The benzoate undergoes saponification with alkali easily, while acid hydroly-

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sis with 80% sulfuric acid proved to be the best method for converting the thiazole ether into the alcohol I.

In order to prepare the aldehyde II we applied the usual technique of oxidizing the alcohol in acetic acid solution with chromic acid. This aldehyde II and its precursor the alcohol I are the first representatives of their types to be described in the thiazole series. In the experimental part of this paper are described several derivatives of the alcohol I which are proving to be of immediate service for new synthetic operations now being carried on in our thiazole researches. The work is being continued.

### Experimental Part

**4-Phenylthiazole-2-methyl Alcohol**,  $C_6H_5T^2CH_2OH$ .—The benzoate of this alcohol was prepared as follows. Fifty grams of benzoyl-oxyacetthioamide,<sup>3</sup> 38 g. of bromol acetophenone and 20 cc. of pyridine were dissolved in 100 cc. of alcohol and the solution heated for one hour on a steam-bath. The mixture was then poured into ice water and the insoluble residue washed three times with dilute hydrochloric acid. The benzoate separated and solidified, and was purified by crystallization from 95% alcohol. It separated in the form of rosetts melting at 73–74° and the yield was 80% of the theoretical.

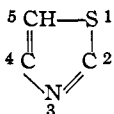
*Anal.* Calcd. for  $C_{17}H_{13}O_2NS$ : N, 4.74; C, 69.15; H, 4.40. Found: N, 4.52, 4.66; C, 68.95; H, 4.45.

Twenty grams of this benzoate was saponified by warming with potassium hydroxide in alcohol solution. On pouring the hydrolysate into water an oil separated which was extracted with ether, dried over sodium sulfate and finally distilled under diminished pressure. The alcohol boiled at 210–215° at 20 mm. and on cooling solidified immediately. It separated from hot dilute alcohol solution in the form of colorless cubical crystals melting at 88–89°.

*Anal.* Calcd. for  $C_{10}H_9ONS$ : N, 7.32; S, 16.77. Found: N, 7.27, 7.45; S, 16.55.

**Ethyl Ether of 4-Phenylthiazole-2-methyl Alcohol**,  $C_6H_5TCH_2OC_2H_5$ .—Ethoxyacetonitrile was first prepared according to the method of Gauthier<sup>4</sup> by the action of cuprous cyanide on chloromethyl ethyl ether. The corresponding thioamide was then made by Sommelet's procedure<sup>5</sup> and allowed to react in alcohol with the calculated quantity of bromoacetophenone. After two hours of heating on the steam-bath the excess solvent was removed by distillation, the residue washed with dilute sodium hydroxide solution and the thiazole extracted with ether and dried over sodium sulfate. The thiazole ether boiled at 187–188° at 15 mm. and was obtained as an amber-colored oil which is feebly basic. The ether was not altered by digesting with 40% hydrobromic acid solution for four hours.

*Anal.* Calcd. for  $C_{12}H_{13}ONS$ : N, 6.39; S, 14.63. Found: N, 6.29, 6.26, 6.30, 6.21; S, 14.51.



<sup>2</sup> T is the thiazole nucleus.

<sup>3</sup> Olin and Johnson, *Rec. trav. chim.*, **50**, 72 (1931).

<sup>4</sup> Gauthier, *Ann. chim. phys.*, [8] **16**, 302 (1909).

<sup>5</sup> Sommelet, *Compt. rend.*, **142**, 828 (1906).

**Conversion of the Ether into its Alcohol.**—Fifty grams of the above ether was dissolved in 150 g. of 80% sulfuric acid and the solution heated in an oil-bath at 145–150° for half an hour. The liquid was then poured upon crushed ice and the resulting solution made alkaline with sodium hydroxide. The thiazole separated as an oil and was extracted by ether and purified by distillation. It was obtained in these experiments as a pale yellow, viscous oil which boiled as follows: 210° at 20 mm., 202° at 12 mm. and 178° at 4 mm. The oil solidified on cooling and was purified further by crystallization from dilute alcohol. It separated in the form of cubical crystals melting at 89°. The yield was 65% of the theoretical.

**Acetate**,  $C_6H_5TCH_2OCOCH_3$ .—Prepared by heating the thiazole methanol with acetic anhydride. It distilled at 193° at 4 mm. and crystallized from petroleum ether in the form of colorless plates melting at 40°.

*Anal.* Calcd. for  $C_{11}H_{11}O_2NS$ : N, 6.33. Found: N, 6.15.

**Benzoate**,  $C_6H_5TCH_2OCOC_6H_5$ .—This is formed by heating the thiazole methanol with benzoyl chloride at 120°. It crystallized from 80% alcohol in the form of rosetts melting at 73–74°.

**4-Phenylthiazole-2-methyl Bromide**,  $C_6H_5TCH_2Br$ .—Nineteen grams of the above methanol was dissolved in 75 cc. of acetic anhydride and hydrogen bromide gas bubbled through the solution, while being warmed on a steam-bath, until saturated. After standing for two hours, the solution was then boiled for forty-five minutes and finally poured into cold water. The bromide separated as an oil. It was washed with sodium carbonate solution, dried in ether over sodium sulfate and finally purified by distillation. It boiled at 195° at 15 mm. The yield was 90% of the theoretical.

*Anal.* Calcd. for  $C_{10}H_8NSBr$ : N, 5.51; Br, 31.46. Found: N, 5.38; Br, 31.58.

The corresponding **4-phenylthiazole-2-methyl chloride**,  $C_6H_5TCH_2Cl$ , is easily obtained by the action of phosphorus oxychloride on the thiazole methanol and boils at 184° at 16 mm.

**4-Phenylthiazole-2-aldehyde**,  $C_6H_5TCHO$ .—This is easily obtained by oxidation of the thiazole methanol with sodium dichromate in acetic acid solution. This was accomplished by dissolving 19 g. of the methanol and 20 g. of sodium dichromate in 135 cc. of acetic acid and digesting the mixture at 100° for two hours. After pouring into water and extracting the aldehyde with ether, it was then purified by fractional distillation. It was obtained as a colorless oil possessing a fragrant odor and boiling at 160–162° at 14 mm.

*Anal.* Calcd. for  $C_{10}H_7ONS$ : N, 7.40; C, 63.49; H, 3.70. Found: N, 7.48, 7.55; C, 63.37; H, 3.62.

The **phenylhydrazone** crystallizes in canary yellow prisms melting at 131–132°.

*Anal.* Calcd. for  $C_{16}H_{13}N_3S$ : N, 15.06. Found: N, 15.28.

**4-Phenylthiazole-2-aldoïn**,  $C_6H_5TCHOHC_6H_5$ .—The above aldehyde behaves normally as an aromatic aldehyde and is converted quantitatively into its aldoïn by digestion in alcohol solution in the presence of potassium cyanide. The compound crystallizes from boiling alcohol as yellow needles which turn red on heating and melt at 256°. The compound is insoluble in dilute acids and alkalis and belongs to a new class of compounds corresponding to the benzoïns in the benzene series.

*Anal.* Calcd. for  $C_{22}H_{14}O_2N_2S$ : N, 7.40. Found: N, 7.40, 7.42.

### Summary

1. Methods of synthesizing 4-phenylthiazole-2-methanol and 4-phenylthiazole-2-aldehyde have been described.

2. This alcohol and the aldehyde are the first representatives of their types to be described in the thiazole series.

3. Several derivatives of the thiazole methanol have also been described.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

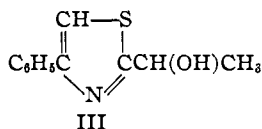
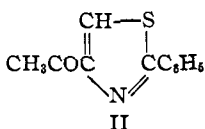
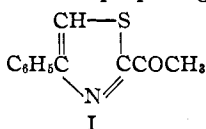
## SYNTHESIS OF 4-PHENYL-2-ACETOTHIAZOLE. IX

BY JOHN F. OLIN<sup>1</sup> AND TREAT B. JOHNSON

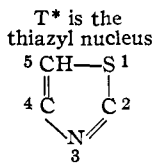
RECEIVED DECEMBER 8, 1930

PUBLISHED APRIL 6, 1931

So far as the authors are aware, no thiazole ketones have hitherto been described in the chemical literature. Several of the aryl substituted ketone constructions, for example, as represented by the type formulas I and II, have assumed considerable importance in our thiazole researches because they promise to serve as practical starting points for the synthesis of some new types of amino alcohols possessing physiological interest. Such ketone combinations being available, it should then be possible, theoretically, to transform them by an established technique into bridged thiazole amino alcohols having pharmacological properties similar to those of compounds of the adrenaline type. In this paper we now describe a method for preparing the thiazole ketone I.



The ketone I is easily obtained by oxidation of the thiazole ethanol, III. The latter is a new alcohol which can be prepared easily in quantity by application of a normal thiazole synthesis with bromoacetophenone and the benzoate of lactic-thioamide, which has recently been described by Olin and Johnson.<sup>2</sup> The resulting benzoyl derivative is easily transformed into the alcohol III by the action of alkali. This is the first secondary alcohol of this type to be described in the thiazole series. It is a stable compound and can be oxidized smoothly to the ketone I without destruction of the thiazole ring. This change is accomplished by means of chromic acid in acetic acid solution. The ketone I may be considered as a bridged thiazole ketone corresponding to acetophenone, in which the aryl group is separated from the acetyl radical by the thiazyl nucleus. The ketone exhibits many of the properties of acetophenone and is attacked by bromine in a similar manner with formation of the bromide,  $\text{C}_6\text{H}_5\text{T}^*\text{COCH}_2\text{Br}$ .



<sup>1</sup> Metz Research Fellow in Organic Chemistry, 1929-1930.

<sup>2</sup> Olin and Johnson, *Rec. trav. chim.*, 50, 72 (1931).