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[1] AND TREAT B. JOHNSON

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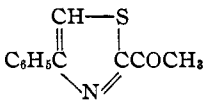
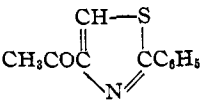
So far as the authors are aware, no thiazole ketones have hitherto been described in the chemical literature. Several of the aryl substituted ketone constructions, for example, as represented by the type formulas I and II, have assumed considerable importance in our thiazole researches because they promise 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.



I



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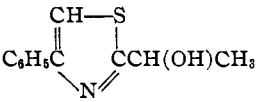
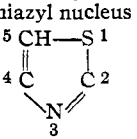


III

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.[2] 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, $C_6H_5T^*COCH_2Br$.

T* is the thiazyl nucleus



[1] Metz Research Fellow in Organic Chemistry, 1929–1930.

[2] Olin and Johnson, *Rec. trav. chim.*, **50**, 72 (1931).

Experimental Part

Benzoate of 4-Phenylthiazole-2-α-ethanol, $C_6H_5TCH(CH_3)OCOC_6H_5$.—Fifty-three grams of benzoyl lactic-thioamide[2] and 50 g. of bromo-acetophenone are dissolved in 150 cc. of alcohol and the solution heated on a steam-bath for one and one-half hours. Part of the alcohol is then allowed to evaporate and the mixture is made alkaline by the addition of dilute sodium hydroxide solution. The benzoyl thiazole separates as an oil and is extracted by ether and dried over sodium sulfate. The ester was purified by distillation and boiled at 252–254° at 14 mm. Thirty-five grams of a viscous oil was obtained which showed no signs of crystallizing on standing. The thiazole is very feebly basic and possesses a characteristic thiazole odor.

Anal. Calcd. for $C_{18}H_{15}O_2NS$: N, 4.53. Found: N, 4.55, 4.59.

4-Phenylthiazole-2-α-ethanol. III.—This alcohol is prepared by digesting its corresponding benzoate (above) in alcohol with potassium hydroxide. From 28 g. of the benzoate we obtained 17 g. of the alcohol boiling at 191–194° at 16 mm. It was obtained as an amber-colored viscous oil which solidified on standing. It crystallized from chloroform in the form of large, yellow cubical crystals which melted at 76°. The alcohol is very soluble in all the common organic solvents except petroleum ether, and is insoluble in cold water. Attempts to dehydrate the alcohol by the action of phosphorus pentoxide were unsuccessful. Fifteen grams was digested in benzene with 20 g. of phosphorus pentoxide for fifteen hours without change.

Anal. Calcd. for $C_{11}H_{11}ONS$: N, 6.83; S, 15.61; C, 64.39; H, 5.36. Found: N, 6.80, 6.83; S, 15.54; C, 64.20; H, 5.21.

4-Phenyl-2-acetothiazole. I.—Ten grams of the alcohol III is dissolved in 100 cc. of acetic acid and to the solution is added 8 g. of sodium dichromate dissolved in 10 cc. of water. After heating this mixture on a steam-bath for one hour, it is poured upon crushed ice, when there is an immediate precipitation of the crude ketone in crystalline condition. It was purified by crystallization from hot dilute alcohol and separated in the form of yellow needles melting at 78–79°. The yield was 9 g. A mixture of this ketone and the alcohol III melted at 55–60°. The ketone is much less soluble in the common organic solvents than the alcohol III.

Anal. Calcd. for $C_{11}H_9ONS$: N, 6.89; C, 65.00; H, 4.43. Found: N, 6.75, 6.81; C, 64.91; H, 4.30.

Phenylhydrazone.—Crystallizes in yellow needles melting at 208–209°.

4-Phenyl-2-bromoacetothiazole, $C_6H_5TCOCH_2Br$.—Forty-three grams of the above ketone dissolved in 300 cc. of hot carbon tetrachloride was combined with 34 g. of bromine. There was an immediate reaction with evolution of hydrobromic acid and separation of the hydrobromide of the thiazole. After cooling the mixture and decanting the carbon tetrachloride, the reaction product was triturated with an aqueous solution of potassium hydroxide and the ketone bromide extracted with ether. On evaporating the ether a semi-solid residue was left which dissolved in hot alcohol. On cooling the alcohol solution the above bromide separated in the form of buff-colored needles melting at 106–107°. When the compound was warmed in dilute alkaline solution or with an amine (methylamine), it readily lost its bromine, indicating that the halogen occupies a reactive position in the methyl radical of the ketone group.

Anal. Calcd. for $C_{11}H_8ONSBr$: N, 4.97; Br, 28.3. Found: N, 5.05, 5.07. Br, 27.8.

Summary

1. Benzoyl lactic-thioamide interacts with bromoacetophenone to form the benzoate of 4-phenylthiazole-2-α-ethanol. The corresponding alcohol is obtained by saponification of this ester.

2. 2-Phenylthiazole-2-α-ethanol is oxidized practically quantitatively to the ketone, 4-phenyl-2-acetothiazole, by the action of chromic acid in acetic acid solution.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

SYNTHESIS OF SOME NEW THIAZOLE AMINES CONTAINING THE CATECHOL GROUP. X

BY JOHN F. OLIN[1] AND TREAT B. JOHNSON

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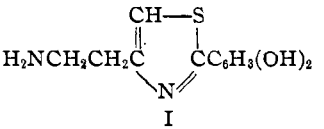
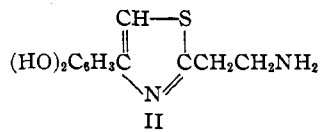
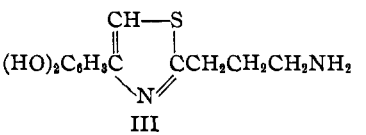
In the first paper of this series Johnson and Gatewood[2] reported the use of chloroacetocatechol as a reagent for thiazole syntheses, and described several thiazoles containing the catechol group in position 4 of the thiazole ring. Suter and Johnson[3] continued the work and described several thiazoles containing the catechol group in both positions 2 and 4 of the thiazole ring. The next contribution to the chemistry of these catechol derivatives was a paper by Hinegardner and Johnson,[4] who described a method of preparing the new thiazole amine represented by formula I.



I



II



III

This was found to be a potent substance physiologically, and, therefore, it was decided to synthesize its isomer represented by formula II in which the positions of the aliphatic amine and catechol groups in the thiazole nucleus are reversed. It became very important to determine which one of these two amines would be the most active substance when submitted to a comparative pharmacological study. In this paper is described the synthesis of this new thiazole amine II and also its next higher homolog, or the propyl derivative represented by formula III.

Our method of synthesis involved first the preparation of cyanethyl- and cyanpropylphthalimide, second, their conversion into their corresponding thioamides and third, interaction of these respective thioamides with

[1] Metz Research Fellow in Organic Chemistry, 1929–1930.

[2] Johnson and Gatewood, THIS JOURNAL, 51, 1815 (1929); U. S. Patent No. 1,743,083 (1930).

[3] Suter and Johnson, THIS JOURNAL, 52, 1685 (1930).

[4] Hinegardner and Johnson, Paper VI of this series, *ibid.*, 52, 4141 (1930).