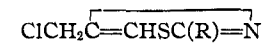
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Polymerization of 2-Methyl-4-chloromethylthiazole. XII

BY FLORENCE E. HOOPER[1] AND TREAT B. JOHNSON

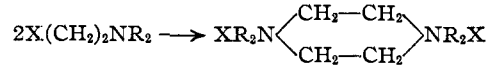
Primary halides of the thiazoles corresponding in structure to formula I are of especial interest because of their value in the synthesis of thiazole combinations difficult to obtain by other methods.[2] 2-Methyl-4-chloromethylthiazole, the first halide of this type to be described in the literature in which R represents an alkyl radical, was found to polymerize readily. This is in marked contrast to the behavior of compounds of type I where R is an aryl radical, which so far as observed in this Laboratory are entirely stable. The properties and probable structure of the polymer of 2-methyl-4-chloromethylthiazole are discussed in the present paper.



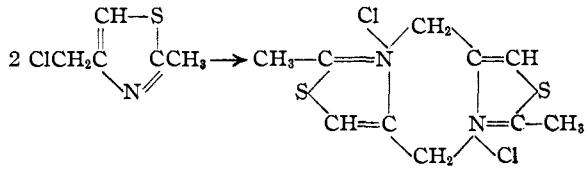
I

The original thiazole halide, a colorless oil boiling at 65–67° at 3 mm., on standing at room temperature slowly undergoes a change and is transformed into a crystalline solid. This change is greatly accelerated by heat, going practically to completion in a few hours at 115°. The purified product is a pale pink powder which dissolves in water to give a neutral solution containing ionic chlorine, and which does not melt when heated above 300°. Microanalyses showed the substance to be identical in composition with the original thiazole. Approximate molecular weight determinations by the freezing point method in glacial acetic acid indicated the presence of two formula weights per molecule. The presence of polar chlorine in contrast to the non-polar halogen of the original thiazole halide suggested that the polymerization involved the migration of halogen from carbon to nitrogen.

Knorr[3] and his co-workers have shown that ω-haloalkyl-dialkylamines, in which the number of carbon atoms between the halogen and nitrogen atoms is two, react to form piperazine quaternary salts.



Examination of formula I indicates that if the nitrogen of the ring be assumed to have the properties of an amino nitrogen a similar intermolecular addition may be expected of such compounds. The basicity of the thiazole nucleus favors such a change and the polymerization of 2-methyl-4-chloromethylthiazole to a piperazine compound may thus be represented as follows[4]

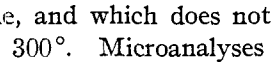


(Piperazine derivative) II

The agreement of the properties of the polymerized product with such a structure serves as evidence that this is the correct interpretation of the reaction. Since 2-aryl-4-halomethylthiazoles would be expected to have the properties of ω-haloalkyl-diarylamines their failure to polymerize is readily understood.

The quaternary salt when tested[5] was found to be practically inert both physiologically and bactericidally.

Experimental Part



2-Methyl-4-chloromethylthiazole, was obtained by a modification of the method of Suter and Johnson.[2] Equimolecular portions of *sym*-dichloroacetone and thioacetamide were dissolved separately in a minimum volume of acetone. The solutions were mixed and allowed to stand until precipitation was complete. The resulting hydrochloride, $ClCH_2COCH_2SC(CH_3)=NH\cdot HCl$, was filtered, washed with acetone, dried and converted into the thiazole as needed. A solution of this hydrochloride in absolute methyl alcohol was refluxed on the steam-bath with 20% of its weight of anhydrous zinc chloride for three to four hours. The alcohol was removed *in vacuo*, and the residue taken up with water, made alkaline with sodium bicarbonate, and filtered. The thiazole was obtained by exhaustive extraction with ether. The residual oil after ether removal was purified by distillation in a vacuum; b. p. 65–67° at 3 mm.; total yield, 75–80%.

Anal. Calcd. for C_5H_6NSCl: N, 9.49, Cl, 24.03. Found: N, 9.20, 9.19; Cl, 23.92.

(1) Metz Research Fellow in Organic Chemistry.

(2) Suter and Johnson, *Rec. trav. chim.*, **49**, 1066 (1930).

(3) Knorr, *Ber.*, **37**, 3507 (1904); Knorr, Horlein and Roth, *ibid.*, **38**, 3129 (1905).

(4) This observation is in accord with a suggestion made to one of the writers by Dr. John Aston of the Pennsylvania State College at the American Chemical Society meeting in Washington in March, 1933.

(5) We are indebted to Dr. Charles W. Hooper of the H. A. Metz Laboratories, Inc., Rensselaer, New York, for carrying out these tests.

The Polymerization of 2-Methyl-4-chloromethylthiazole.—The thiazole was polymerized by allowing it to stand at room temperature and also by heating at 75, 90 and 110–115°. The products so far as observed were identical in all cases. The highest temperature was found preferable since the reaction went more nearly to completion and proceeded at a more rapid rate. The polymerized product was freed from unchanged thiazole by sucking dry on a Buchner funnel and by washing with ether. The product was purified by recrystallization from hot absolute alcohol followed by precipitations from absolute methyl alcohol with ether and with ethyl acetate, and was dried over phosphorus pentoxide in a vacuum desiccator.

Anal. Calcd. for C_5H_6NSCl: C, 40.65; H, 4.10; N, 9.49; S, 21.72; Cl, 24.03. Found: C, 40.51; H, 4.36; N, 9.21; S, 21.52, 21.70; Cl, 23.92.

Molecular weight determinations (freezing point depression in glacial acetic acid). Calcd. for $(C_5H_6NSCl)_2$: mol. wt., 295. Found: mol. wt., 315, 278.

Summary

1. 2-Methyl-4-chloromethylthiazole has been prepared and has been found to readily polymerize to form a bimolecular product.

2. It has been concluded that this polymerization is analogous to the transformation of ω-haloethyl dialkylamines into cyclic quaternary salts, and that the polymerization product may be represented structurally as a piperazine derivative.

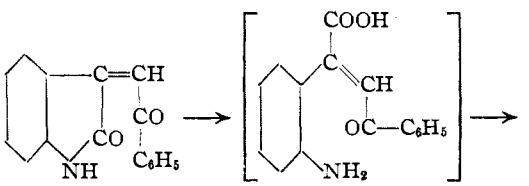
NEW HAVEN, CONN. RECEIVED NOVEMBER 1, 1933

[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

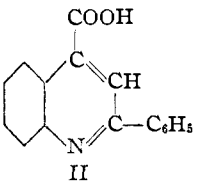
A Synthesis of Cinchophens from Phenacylideneoxindoles[1]

BY R. N. DUPUIS AND H. G. LINDWALL

It has been reported[2] that 3-phenacylideneoxindole (I) cannot be converted successfully to cinchophen (II) under the conditions of the Pfitzinger[3] reaction (33% aqueous alcoholic potassium hydroxide). It has been found, however, that if compound I is warmed with aqueous-alcoholic hydrochloric acid, rearrangement takes place with the formation of cinchophen.



I



II

The rearrangement evidently involves hydrolytic opening of the oxindole ring at the amidic linkage followed by reaction of the primary amino group with the carbonyl. This reaction has been applied also to the formation of certain cinchophen derivatives, as indicated in the Experimental Part. While better yields are obtained when hydrochloric acid is used, sulfuric acid of the same concentration may be substituted.

The method is being studied further particularly from the point of view of synthesis of amino and 3,4-dihydroquinoline derivatives. It suggests itself as a means of synthesis of alkali-sensitive quinoline derivatives from isatin, avoiding strenuous alkali treatment.

Experimental Part

Rearrangement of 3-Phenacylidene-oxindole (I) to Cinchophen (II).—A mixture of 2 g. of I (crude), 20 cc. of 95% ethyl alcohol, and 20 cc. of concd. hydrochloric acid was heated under reflux for two hours at 120°. A dense precipitate was formed upon cooling. This material was dissolved in alkali and reprecipitated with acid. The product at this stage is already in a high state of purity. Crystallization from alcohol yielded a product which was identified as 2-phenylcinchoninic acid (cinchophen), by melting point (210–212° corr.) and melting point mixed with a known sample. The identity of cinchophen was confirmed by decarboxylation to form 2-phenylquinoline (m. p. 83–84.5°). This general procedure was followed in the preparation of the para-substituted cinchophens listed in Table I.

4′-Methyl-2-phenylcinchoninic acid[4] was identified by its melting point, mixed with a known sample. Preparation from it of 2-(*p*-tolyl)-quinoline by decarboxylation was confirmation of identity.

4′-Bromo-2-phenylcinchoninic acid[5] was identified in the same way.

(1) Presented in part at the Chicago Meeting of the American Chemical Society, September, 1933.

(2) Lindwall and Maclennan, THIS JOURNAL, **54**, 4739 (1932).

(3) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 583 (1888); **56**, 283(1897).

(4) Von Braun and Brauns, *Ber.*, **60**, 1255 (1927).

(5) Lindwall, Bandes and Weinberg, THIS JOURNAL, **53**, 317 (1931).