MERCURATION OF THIAZOLE DERIVATIVES

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Conditions have been found for the mercuration of alkyl- and aryl- thiazoles. Mercuration takes place in position 5 of the ring, if it is free, and does not depend on the nature of the substituent in position 2. The possibility of the mercuration of a trisubstituted thiazole has been shown for the first time. When a phenyl radical is present in position 2, the mercury ion enters the para position of the phenyl nucleus.

Electrophilic substitution in the thiazole series is known, and takes place differently according to the position of the substituent and its nature [1–3]. The mercuration reaction has not been described in the literature for alkyl- and arylthiazoles.

A paper [4] exists on the mercuration of 1,3-oxazole derivatives, the chemical properties of which are similar to those of thiazole derivatives [5]. We have been able to show that there are some differences in mercuration, for example, in a trisubstituted thiazole with a phenyl radical in position 2, the mercury atom may enter the phenyl nucleus, which was not found for the oxazole derivatives.

The mercuration of the thiazole homologs was carried out by heating them with mercuric acetate in acetic acid. 2,4-Dimethylthiazole (I) [6], 4-methyl-2-phenylthiazole (II) [7], and 4,5-dimethyl-2-phenylthiazole (III) [8] were subjected to mercuration. The choice of these thiazoles was due to the fact that in I position 5 is free and mercuration can take place only at this position. In II, the mercury atom can enter either position 5 or the phenyl radical. In III all the positions of the ring are occupied and either the mercuration reaction will not take place, or the mercury atom will occupy a position in the phenyl nucleus. To show the structure of the mercury derivatives obtained, they were converted into the corresponding bromides by treatment with bromine in carbon tetrachloride. The bromides obtained from the mercury derivatives proved to be identical with the substances obtained by the direct promination of the substituted thiazoles or by independent synthesis.

In the mercuration of I and II, the mercury atom entered position 5. When position 5 in the thiazole ring is free mercuration takes place in this position regardless of the nature of the substituent in position 2. In compound III, the mercury atom occupied the para position of the phenyl ring, as was shown by the identity of the bromides obtained from the mercury derivative and by independent synthesis of the previously unreported 2-(p-bromphenyl)-4,5-dimethylthiazole (IX). It was impossible to obtain IX by the direct bromination of III.

The thiazole homologs are stable to the action of mineral acids. On being boiled with concentrated hydrochloric acid, the mercury-substituted thiazoles are hydrolyzed to the initial thiazoles, and they are unstable to the action of hydrogen sulfide.

EXPERIMENTAL

2,4-Dimethyl-5-acetylmercurithiazole (IV). To 3 g (0.026 mole) of I was added 8.5 g (0.026 mole) of mercuric acetate in 50 ml of glacial acetic acid, and with constant stirring the mixture was heated in a water bath at 60–70° C for 12 hr. A very small amount of IV deposited. The precipitate was filtered off, and the filtrate, on long standing (6 days) deposited a further precipitate of IV. Yield 2.9 g (30%). The product obtained is sparingly soluble in organic solvents, and it crystallizes from glacial acetic acid in the form of white plates with mp 250° C (decomp). Found, %: N 3.6; Hg 53.5; S 8.8. Calculated for $C_7H_9NO_2HgS$, %: N 3.8; Hg 54.0; S 8.6.

Hydrolysis of IV. A mixture of 0.4 g (0.0035 mole) of IV and 4 ml of conc HCl was heated at 100° C for 20 min. The cooled solution was filtered from the inorganic salts, and the filtrate was made alkaline with ammonia and extracted with ether; distillation of the latter yielded an oil from which a picrate was obtained with mp 135° C, giving no depression with the picrate of I.

Bromination of IV. To 0.6 g (0.0053)mole) of IV in 5 ml of CCl_4 was added 0.28 g (0.0017 mole) of bromine, and the mixture was heated in a water bath for 1 hr. The CCl_4 was distilled off, and the residual oil gave a picrate with mp 103° C. According to the literature [9], this corresponds to the picrate of 5-bromo-2,4-dimethylthiazole.

5-Acetylmercuri-4-methyl-2-phenylthiazole (V). A mixture of 3.5 g (0.02 mole) of II and 6.4 g (0.02 mole) of mercuric acetate in 50 ml of glacial acetic acid was heated at 60–70° C with stirring for 1 hr 30 min. Yield 5.8 g (67.5%). The crystals obtained formed lustrous gray-white leaflets with mp 186–187° C (from chloroform), readily soluble in acetone. Found, %: N 3.2; Hg 46.0; S 7.5. Calculated for $C_{12}H_{11}NO_2HgS$, %: N 3.2; Hg 46.2; S 7.4. The product isolated from the hydrolysis of V yielded a picrate mp 129–130° C giving no depression with the picture of II. The bromination of V yielded crystals with mp 56–57° C, picrate with mp 131–132° C. Mixtures with VII and VIII, respectively, gave no depression of the melting points.

5-Bromo-4-methyl-2-phenylthiazole (VII). To 1 g (0.0058 mole) of II in 3 ml of glacial acetic acid was added 0.3 ml of bromine. The temperature rose and the hydrobromide precipitated. This was left at room temperature for 12 hr and then decomposed with ammonia. Crystals of VII were formed with mp 57–58° C (from ethanol) [10]; the picrate of 5-bromo-4-methyl-2-phenylthiazole (VIII) had mp 131–132° C.

4,5-Dimethyl-2-(p-acetylmercuriphenyl)thiazole (VI). A solution of 3.8 g (0.02 mole) of III in 50 ml of glacial acetic acid was mixed with 6.4 g (0.02 mole) of mercuric acetate and, with constant stirring, the mixture was heated at 90–95° C for 8 hr. The yield was 0.8 g (9%). Yellowish crystals with mp 230–232° C (decomp, from glacial acetic acid). Found, %: N 3.0; Hg 44.2; S 7.0. Calculated for $C_{13}H_{13}NO_2HgS$, %: N 3.1; Hg 44.7; S 7.2. The bromination of VI yielded crystals with mp 105° C; picrate with mp 205–206° C (decomp). A mixture with the IX obtained by independent synthesis, and also a mixture of the picrates, gave no depression of the melting points.

2-(p-Bromophenyl)-4,5-dimethylthiazole (IX). A) A solution of 20 g (0.1 mole) of p-bromobenzamide in 30 ml of toluene was mixed with 4.4 g (0.02 mole) of phosphorus pentasulfide and the mixture was boiled for 1 hr. This gave 2.6 g (60%) of p-bromothiobenzamide with mp 140° C (from ethanol: mp 145° C) [11].

B) With constant stirring, 1.1 g (0.01 mole) of α-chloroethyl methyl ketone in 10 ml of ethanol was added to 2.2 g (0.01 mole) of p-bromoethiobenzamide in 10 ml of ethanol. The reaction was accompanied by the evolution of heat. When the spontaneous heating of the mixture had ceased, it was heated in a water bath for 1 hr 30 min. The reaction mixture was diluted with water, made alkaline with caustic soda, and extracted with ether. The ethereal extract was dried over Na_2SO_4. Distillation of the ether yielded 1.4 g (50%) of white crystals of IX; mp 106–107° C (from ethanol) readily soluble in benzene and acetone. Found, %: C 49.0; H 3.7; N 5.1; S 11.8. Calculated for $C_{11}H_{10}NBrS$, %: C 49.2; H 3.7; N 5.2; S 11.9.

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