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Novel Methods of Formation of Imidazo[2,1-*b*]thiazole

by

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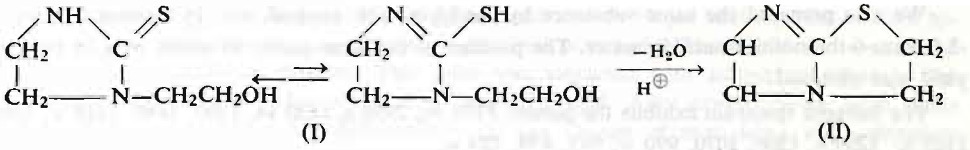
The imidazo[2,1-*b*]thiazole system [1] is relatively little known. For the first time it has been described by Stephen and Wilson [2] as both the simple and condensed with benzene ring. It was of particular interest since Todd, Bergel and coworkers [3] have found that Thiochrom, a product of oxidation of vitamin B_1, is a pyrimidine derivative condensed with the discussed ring system [4].

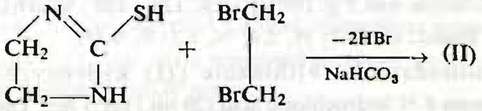
The simple imidazo[2,1-*b*]thiazole derivatives have been obtained by a number of authors [5]—[7].

Now, we are describing the preparation of the parent substance of the system in question starting form 1-β-hydroxyethylimidazolidine-2-thione (I) [8]. When boiled with 2—6 N aqueous solution of mineral acid it yielded imidazo[2,1-*b*]thiazole (II)*).



The reaction of (I) to yield (II) occurs through a strongly electron donating thiol group which attacks the hydroxylic group, followed by the loss of a molecule of water and the ring closure.

Our another method of preparation of (II) substantiated its structure. This was done by heating ethylenethiourea (III) [9] with ethylene 1,2-dibromide in the presence of a basic agent:



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*) We also suggest another naming based on A. Baeyer method, *viz.* 2-thia-5,8-diazabicyklo[3.3.0] octene-8 which seems to be more lucid. However, in view of the fact that the Ring Index nomenclature is generally accepted we will use it here.

Product (II) is stable both in form of salts of mineral acids or of picric acid and as the free base. It is not decomposed by alkali at room temperature, but can be hydrolyzed when boiled with aqueous sodium hydroxide to recover (I). Benzoylation of (II) according to the method of Schotten-Baumann gives dibenzoyl derivative of (I).

The infrared absorption spectra confirmed the structure (II). Very strong bands at 3270, 2950, and 1070 cm.$^{-1}$ in the spectrum of (I) correspond to O—H stretching, N—H stretching and O—H bending vibrations, respectively. They disappear in the spectrum of (II). Instead, a new very strong band at 1605 cm.$^{-1}$ appeared indicating the presence of a C=N bond.

Our present work was reported at the Annual Meeting of the Polish Chemical Society, June 1967, the abstract of which has already been published [10].

By the end of this same year an extensive paper appeared by Dorn and Welfle [11] describing, among numerous substances, the preparation of (II) from the respective nitrogen mustard and isothiocyanic acid.

The properties of our compound and its salts are identical with those described by Dorn and Welfle.

Experimental

1-β-Hydroxyethylimidazolidine-2-thione (I). (I) was prepared according to McKay and Vavasour [8]. The product was crystallized from water, m.p. 142—143° in 85 per cent yield (reported m.p. 136.5—137.5°, yield 86.3% [8]).

We also prepared the same substance by modifying the method, *viz.* by boiling 1-hydroxy--3,6-diaza-6-thionothiolic acid in water. The product of the same purity as above in a 88 per cent yield was obtained.

The infrared spectrum exhibits the bands: 3270 vs, 2950 s, 1530 vs, 1500, 1480, 1410 w, 1380, 1325 s, 1290 s, 1200, 1070, 990 w, 945, 870, 720 w.

N-nitrozo derivative of (I). The product (I) (0.7 g.) dissolved in 20 ml. 0.1 N hydrochloric acid was reacted at 0° with sodium nitrite (0.7 g) added in small portions. The *N*-nitroso derivative, i.e. 1-β-hydroxyethyl-3-nitrosoimidazolidine-2-thione precipitated, after crystallization from water (yield 0.4 g., 47%), m.p. 127—128°. $C_5H_9N_3O_2S$ requires: N, 24.0; found: N, 23.2%.

Di(*N*, *O*-benzoyl)derivative of (I). Substance (I) (1.5 g., 0.01 mol.) was dissolved in 40 ml. aqueous (10%) sodium hydroxide. Benzoyl chloride (3 g., 0.022 mole) was added dropwise on shaking. The precipitated product was crystallized from benzene. The yield of 1-β-benzoyloxyethyl--3-benzoylimidazolidine-2-thione was 3 g. (80%), m.p. 125—126°. $C_{19}H_{18}N_2O_3S$ requires: C, 64.4; H, 5.1; N, 7.9; S, 9.1%; found: C, 64.7; H, 5.4; N, 8.1; S, 9.3%.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (II) hydroxychloride. Substance (I) (1.5 g.) was boiled in aqueous 6 N hydrochloric acid (20 ml.) for 3 hrs. The solution was evaporated to dryness under reduced pressure. The oily residue was allowed to crystallize. The hydrochloride of (II) was purified by crystallization from ethanol. The compound is soluble in water, insoluble in acetone and ether. The yield was 1.2 g (90%), m.p. 185—186°. $C_5H_8N_2S.HCl$ requires: C, 36.5; H, 5.5; Cl, 21.5; N, 17.0; S, 19.5%; found: C, 36.2; H, 5.6; Cl, 21.9; N, 17.0; S, 19.6%.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (II) hydrobromide. 2,3,5,6,-Tetrahydroimidazo[2,1-*b*] thiazole (II) hydrobromide was prepared as the hydrochloride by using (I) (1.5 g) and aqueous 2 N hydrobromic acid (20 ml.). The solution was evaporated under reduced pressure to *c.* 5 ml., and acetone was added to precipitate the hydrobromide. It was crystallized from ethanol. The substance is soluble in water, insoluble in acetone and ether. The yield was 1.8 g. (85%), m.p. 182—183°. $C_5H_8N_2S.HBr$ requires: C, 28.7; H, 4.3; Br, 38.2; N, 13.4; 5, 15.3%; found: C, 28.4; H, 4.0; Br, 38.0; N, 13.4; S, 14.9%.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (II) picrate. Hydrochloride of (II) (1.6 g.) was dissolved in water (5 ml.) and 5 per cent solution of picric acid in ethanol (70 ml.) was added. Picrate of (II) precipitated. It was crystallized from water. It is soluble in ethanol and in benzene. The yield was 2.3 g . (70%), m.p. 181—182°. ([11] 175—177°). $C_5H_8N_2S.C_6H_3N_3O_7$ requires: C, 37.0; H, 3.1; N, 19.6: S, 8.8%; found: C, 37.3; H, 3.3; N, 20.0; S, 9.5%.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (II). Hydrochloride of (II) (8.2 g.) was dissolved in 40-% sodium hydroxide (10 ml.). Two liquid layers were formed. The upper layer of free base (II) was dried over solid sodium hydroxide and purified by distillation under reduced pressure b.p. 70°/0.015. The product (II) (5.2 g.) crystallized on standing, m.p. 27—29°. ([11] 26—28°). The substance is soluble in water and in ethanol. The yield was 80 per cent.

The infrared spectrum exhibits the bands: 2930, 2820, 1605 vs., 1485 w, 1445 w, 1380, 1315, 1300, 1270 w 1240, 1190 s, 1160 s, 1080 w, 1035 w, 1015, 975, 960 w, 940 vw, 880 w, 775 w, 690 w, 660.

$C_5H_8N_2$ Srequires: C, 46.8; H, 6.3; N, 21.8; S, 25.0%; found: C, 46.7; H, 6.1; N, 21.5; S, 25.3%.

MW, 128.2 — MW (cryometry) in benzene 135, in dioxane 132.

Benzoylation of (II). Substance (II) (1.3 g.), 0.01 mol. was dissolved in 10 per cent aqueous solution of sodium hydroxide (10 ml.) and benzoyl chloride (3 g., 0.02 ml.) was added dropwise on shaking. The benzoylated product was crystallized from benzene. It gave m.p. 125—126° and proved to be identical with the described above product of benzoylation of (I), i.e. 1-β-benzoxyethyl-3-benzoylimidazolidine-2-thione. No change of m.p. was found when two substances were mixed. The yield was 1.0 g. (30%).

Hydrolysis of (II). Substance (II) (1.3 g.) was boiled with 10 per cent aqueous sodium hydroxide (20 ml.). The resulting solution was neutralized with hydrochloric acid and evaporated under reduced pressure to dryness. The solid was extracted with anhydrous ethanol. The solution was evaporated and the crystalline product collected. After crystallization from water m.p. 142—143° and proved to be identical with (I) (no change of m.p. when two substances mixed).

Preparation of 2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (II) from ethylenethiourea (III) and ethylene-1,2-dibromide. Ethylenethiourea [9] (5 g., 0.05 mol.) was mixed with sodium hydrogen carbonate (4.2 g., 0.005 mol.), methanol (50 mol.), ethylene 1,2-dibromide (9.4 g., 0.05 mole). and boiled for 2 hrs. The reaction mixture was cooled to 15°, filtered off from the solids and the clear solution was evaporated to 5 ml. Conc. hydrochloric acid (5 ml.) was added and the solution was evaporated under reduced pressure until the crystalline precipitate appeared. All was left overnight and the product, m.p. 185—186°, collected. It proved to be identical with (II) prepared previously. No depression of m.p. occurred when two substances were mixed. Both substances showed identical infrared absorption spectra.

Infrared absorption spectra were examined as Nujol mulls on a Unicam SP. 200 spectrophotometer with the sodium-chloride optics.

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