RESEARCHES ON IMIDAZOLES

XXVII. Imidazo [5,1-b] Thiazoles, Imidazo [5,1-b]-Thiazolines, and Imidazo [5,1-b] Thiazolid-3-Ones*

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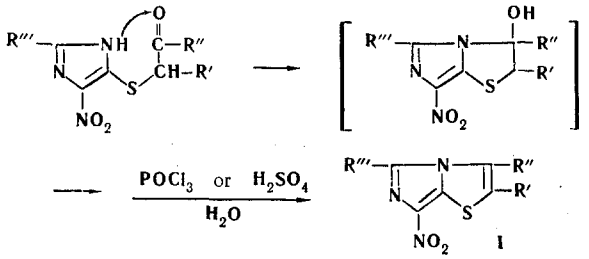
A number of derivatives of imidazo [5,1-b] thiazole, imidazo [5,1-b] thiazoline, and imidazo [5,1-b] thiazolid-3-one are synthesized by cyclizing 2-alkyl-4(5)-nitro-5(4)-formylmethyl (β-ketoalkyl-, β-hydroxyethyl-, and carboxymethyl) mercaptoimidazoles.

Previously studies have been made of the methods of synthesizing and the properties of derivatives of imidazo [2,1-b] thiazole [1–3], imidazo [2,1-b] thiazoline [4], and imidazo [2,1-b] thiazolid-3-one [5]. For the purposes of biological and chemical research it was of interest to prepare derivatives of imidazo [5,1-b] thiazole (I), imidazo [5,1-b] thiazoline (II), and imidazo [5,1-b] thiazolid-3-one (III). When the present work was begun (1962) such compounds had not been described. There were only indications that in acid solution penicillin is readily isomerized to penillic acids, 2,3,7,8-tetrahydro derivatives I [6–8]. Some synthetic penillic acids, their esters, etc., had also been prepared [9–14]. 1964 [16] saw the publication of a paper on preparation of derivatives of I by dehydrating 2-acylaminomethylthiazoles, but this was considerably later than our first brief communication [15] on the synthesis of derivatives of I, II, and III.

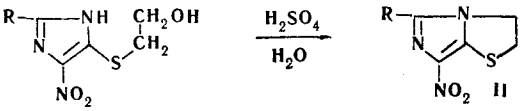
We have effected a new synthesis of I derivatives, which is also applicable to preparing derivatives of II and III [15,17]. The method is based on 4 (5)-β-keto (hydroxy-carboxy) alkylmercaptoimidazoles [18], readily cyclized by dehydrating agents to the bicyclic compounds I, II, and III.

The action of hot phosphorus oxychloride on 2-alkyl-4 (5)-nitro-5 (4)-formylmethylmercaptoimidazoles, and of concentrated sulfuric acid at 30°–40° on 2-alkyl-4 (5)-nitro-5 (4)-(β-ketoalkyl) mercaptoimidazoles, gives 5-alkyl (3,5-dialkyl, 2,3,5-trialkyl)-7-nitroimidazo [5,1-b] thiazoles (Ia-f).

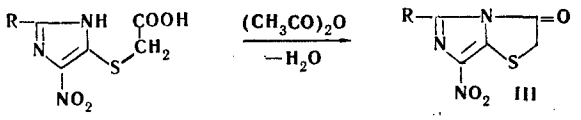
The first stage in thiazole ring closure such as occurs in preparing imidazo [2,1-b] thiazoles [2], is obviously migration of a proton from an imino group to carbonyl oxygen. Then a molecule of water is split off from the resultant intermediate 3-hydroxy derivatives II, giving derivatives I. This mechanism is supported by the structure of 4 (5)-formylmethylmercaptoimidazoles, whose IR spectra [18] indicate that they can be regarded as tautomeric 3-hydroxyimidazo [5,1-b] thiazolines.



Dehydration of 2-alkyl-4 (5)-nitro-5 (4)-(β-hydroxyethyl) mercaptoimidazoles in the presence of contrated sulfuric acid gives 5-alkyl-7-nitroimidazo [5,1-b] thiazolines (IIa,b).



The action of acetic anhydride on 2-alkyl-4 (5)-nitro-5 (4)-carboxymethylmercaptoimidazoles leads, as in the case of imidazolyl-2-mercaptoacetic acids [5], to rapid splitting out of a molecule of water to give 5-alkyl-7-nitroimidazo [5,1-b] thiazolid-3-ones (IIIa,b).



Due to the presence of the powerfully electron-accepting nitro group the bicyclic compounds prepared have very low basicities. They are soluble only in concentrated inorganic acids, and do not form hydrochlorides, sulfates, or picrates.

EXPERIMENTAL

Synthesis of the starting 2-alkyl-4(5)-nitro-5(4) formylmethyl(β-ketoalkyl-, β-hydroxyethyl-and carboxymethyl)mercaptoimidazoles has previously [18] been described.

5-Methyl-7-nitroimidazo [5, 1-b] thiazole (Ia). A solution of 0.5 g (25 mmole) 2-methyl-4(5)nitro-5(4)formylmethylmercaptoimidazole in 15 ml $POCl_3$ was refluxed for 5 hr, the solvent vacuum-distilled off, 20 ml water added to the residue, the dark brown precipitate filtered off, washed with water, and dried. Yield 0.25 g (55%), greenish-yellow crystals, mp 311–312° (decomp, ex EtOH and then from AcOH), only slightly soluble in most organic solvents, insoluble in water. Found: C 39.58; H 2.81; N 22.95; S 17.46%. Calculated for $C_6H_5N_3O_2S$: C 39.34; H 2.75; N 22.94; S 17.50%.

5-Ethyl-7-nitroimidazo [5, 1-b] thiazole (Ib). Prepared similarly by dehydrating 2-ethyl-4(5)-nitro-5(4)-formylmethylmercaptoimidazole. Yield 86.2%, mp 236–237° (decomp, ex EtOH). Greenish-yellow crystals, soluble in hot EtOH, acetone, and water, insoluble in petrol

*For Part XXVI see [18].

ether. Found: C 42.77; H 3.85; N 21.20; S 16.39%. Calculated for $C_7H_7N_3O_2S$: C 42.63; H 3.58; N 21.31; S 16.26%.

3, 5-Dimethyl-7-nitroimidazo [5, 1-b] thiazole (Ic). A solution of 0.33 g (2 mmole) 2-methyl 4(5) nitro-5(4)-acetonylmercaptoimidazole in 4 ml concentrated H_2SO_4 was heated for 1 hr at 30–42° (in a bath), then poured into cold water (30 ml), neutralized with 20% aqueous NaOH, and brought to pH 7 with aqueous $NaHCO_3$, using a universal indicator. The precipitate was filtered off, washed with water, and dried, yield 0.25 g (85.5%), mp 275.276° (decomp, ex EtOH). Yellow needles, slightly soluble in EtOH, insoluble in water and petrol ether. Found: C 42.83; H 3.70; N 21.34; S 15.92%. Calculated for $C_7H_7N_3O_2S$: C 42.63; H 3.58; N 21.31; S 16.26%.

3-Methyl-5-ethyl-7-nitroimidazo [5, 1-b] thiazole (Id). Prepared by dehydrating 2-ethyl-4(5)-nitro-5(4)-acetonylmercaptoimidazole [0.85 g (3.7 mmole) in 5 ml conc H_2SO_4], as described above. Yield 26%, mp 239–240° (decomp, ex AcOH). Greenish-yellow needles, soluble in hot EtOH and hot water, insoluble in petrol ether. Found: C 45.62; H 4.46; N 19.53; S 16.31%. Calculated for $C_8H_9N_3O_2S$: C 45.49; H 4.29; N 19.89; S 15.18%.

2, 3, 5-Trimethyl-7-nitroimidazo [5, 1-b] thiazole (Ie). Prepared by dehydrating 2-methyl-4(5)nitro-5(4)-(α-methylacetonyl)mercaptoimidazole, in the way described for compound III. Yield 92.7%. Greenish-yellow needles, mp 237.239° (decomp, ex EtOH), soluble on heating with acetone, EtOH, dichloroethane, but insoluble in water and petrol ether. Found: C 45.42; H 4.36; N 20.14; S 15.04%. Calculated for $C_8H_9N_3O_2S$: C 45.48; H 4.29; N 19.83; S 15.18%.

2, 3-Dimethyl-5-ethyl-7-nitroimidazo [5, 1-b] thiazole (If). Prepared by dehydrating 2-ethyl-4(5)-nitro-5(4)-(α-methylacetonyl)mercaptoimidazole in the way previously described. Yield 35.3%. Greenish-yellow needles mp 166.5–167° (ex 40% aqueous EtOH), readily soluble in most organic solvents and in hot water, insoluble in ether and petrol ether. Found: C 48.13; H 4.90; N 18.81; S 14.02%. Calculated for $C_9H_{11}N_3O_2S$: C 47.99; H 4.92; N 18.66; S 14.23%.

5-Methyl-7-nitroimidazo [5, 1-b] thiazoline (IIa). A solution of 0.6 g (3 mmole) 2-methyl-4(5)-nitro-5(4)-(β-hydroxyethyl)mercaptoimidaxole in 8 ml conc H_2SO_4 was held at 30–40° (in a bath) for 1 hr, poured into water, neutralized with 40% NaOH, the solution being finally brought to pH 7 (universal indicator) using an aqueous $NaHCO_3$ solution. The products were evaporated to dryness on a water-bath, the residue powdered, then repeatedly extracted with boiling EtOH. The solution was filtered, the EtOH vacuum-distilled off, and the residue recrystallized from EtOH. Yield 0.35 g (64%), yellow crystals, mp 218–218.5°, soluble in acetone, dichloroethane, and water (hot), insoluble in benzene and petrol ether. Found: C 39.15; H 3.94; N 22.75; S 16.83%. Calculated for $C_6H_7N_3O_2S$: C 38.91; H 3.81; N 22.69; S 17.31%.

5-Ethyl-7-nitroimidazo [5, 1-b] thiazoline (IIb). Prepared by the procedure described for compound IIa, by dehydrating 2-ethyl-4(5)-nitro-5(4)-(β-hydroxyethyl)mercaptoimidazole. Yield 42.5%, yellow crystals mp 189–190° (ex EtOH), readily soluble in most organic solvents and hot water, insoluble in benzene, ether, and petrol ether. Found: C 42.46; H 4.52; N 20.94; S 16.48%. Calculated for $C_7H_9N_3O_2S$: C 42.21; H 4.55; N 21.09; S 16.09%.

5-Methyl-7-nitroimidazo [5, 1-b] thiazolid-3-one (IIIa). 1.09 g (5 mmole) 2-methyl-4(5)nitro-5(4)-carboxymethylmercaptoimidazole was boiled in 17 ml Ac_2O for 5–7 min, the brown solution cooled, the precipitate filtered off, washed with acetone, then with ether, and dried. Yield 0.8 g (88.8%), mp 205–205.5° (decomp, ex AcOH). Yellow leaflets, very slightly soluble in EtOH and most organic solvents, insoluble in water. Mixed mp with starting acid (mp 204–204.5°) 192–193° (decomp). The IR spectrum had an absorption band at 1780 cm^{-1} (ν CO). Found: C 36.24; H 2.53; N 20.60; S 16.17%. Calculated for $C_6H_5N_3O_3S$: C 36.18; H 2.53; N 21.10; S 16.10%.

5-Ethyl-7-nitroimidazo [5, 1-b] thiazolid-3-one (IIIb). 0.5 g (2.2 mmole) 2-ethyl-4(5)-nitro-5(4) carboxymethylmercaptoimidazole in 2 ml Ac_2O was refluxed for 3 min, the solution cooled, 5 ml ether added, the precipitate filtered off, washed with ether, and dried, yield 0.38 g, 82.5%), mp 162–163° (decomp, ex 50% aqueous EtOH). Yellow crystals, readily soluble in EtOH, acetone, and hot water, insoluble in petrol ether. The IR spectrum has an absorption band at 1780 cm^{-1} (ν CO). Found: C 39.39; H 3.08; N 20.07; S 15.12%. Calculated for $C_7H_7N_3O_3S$: C 39.43; H 3.31; N 19.71; S 15.04%.

REFERENCES

1. P. M. Kochergin and M. N. Shchukina, ZhOKh, **26**, 458, 1723, 1956.
2. P. M. Kochergin and M. N. Shchukina, ZhOKh, **26**, 2905, 1956.
3. P. M. Kochergin, ZhOKh, **26**, 2493, 2916, 1956; **30**, 1529, 1960.
4. Yu. V. Markova, K. K. Kuz'micheva, E. M. Peresleni, and M. N. Shchukina, KhGS [Chemistry of Heterocyclic Compounds], (in press).
5. P. M. Kochergin, ZhOKh, **31**, 3267, 1961.
6. Chemistry of Penicillin, Princeton, 1949.
7. M. M. Shemyakin, L. S. Khokhlov, M. S. Kolosov, L. D. Bergel'son, and V. K. Antonov, Chemistry of Antibiotics [in Russian], Moscow, **2**, Chapter XI, 1961.
8. W. L. Mosby, "Heterocyclic systems with bridgehead nitrogen atoms," N. Y., Lond., 1, p. 151–156, 1961.
9. R. W. Holly, F. A. Carpenter, H. Livermore, and V. du Vigneaud, Science, 108, 136, 1948.
10. F. A. Carpenter, R. A. Turner and V. du Vigneaud, J. Biol. Chem., **176**, 893, 1948.
11. H. E. Stavely, J. Am. Chem. Soc., **73**, 3450, 1951.
12. J. C. Sheehan and M. Tishler, U. S. patent no. 2492243; C. A. 44, 8376, 1950.
13. I. M. Heilbron A. H. Cook and J. A. Elvidge, British Patent no. 600245; C.A. **42**, 8214, 1948.
14. R. N. Hurd and G. De La Mater, Chem. Rev., **61**, 63, 1961.
15. P. M. Kochergin and A. M. Tsyganova, collection: Chemistry of 5-Membered Nitrogen Rings [in Russian], Rostov University Press, **13**, 1962.
16. T. Pyl, O. Sietz and K. Staege, Ann., **679**, 144, 1964.
17. P. M. Kochergin and A. M. Tsyganova, KhGS [Chemistry of Heterocyclic Compounds], **1**, 313, 1965.
18. P. M. Kochergin, A. M. Tsyganova, L. M. Viktorova, and E. M. Peresleni, KhGS (in press).

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