UDC 547.78+542.95

SYNTHESIS OF DERIVATIVES OF IMIDAZO [5, 1-b] THIAZOLE AND IMIDAZO [5, 1-b] THIAZOLINE

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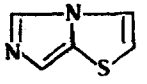
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2 pp. 313-314, 1965

The isomerization of penicillins to penillic acids, 2, 3, 7, 8-tetrahydro derivatives of imidazo[5, 1-b]thiazole (I), is known. Certain penillic acids and their esters have been prepared synthetically [1, 3]. Derivatives of imidazo[5, 1-b] thiazole and imidazo [5, 1-b] thiazoline have now been synthesized with a view to studying their chemical and biological properties. Reaction of the ammonium salt of 2-methyl-4(5)-nitro-5(4)mercaptoimidazole [4] with hydrated dimeric chloroacetaldehyde, chloroacetone, ethylene chlorhydrin, and chloroacetic acid in aqueous or aqueous-alcoholic solution gives the sulfides II-V. Yields 70-95%. Dehydrating agents ($POCl_3$ with II, conc. H_2SO_4 with III and IV, $(CH_3CO)_2O$ with V) give the bicyclic compounds VI-IX in 50-93% yields.



I

2-Methyl-4(5)-nitro-5(4)-formylmethylmercaptoimidazole (II). Decomposes 198-202° (from glacial acetic acid). Found: C 35.81; H 3.42; N 20.51; S 15.94%. Calculated for $C_6H_7N_3O_3S$: C 35.82; H 3.51; N 20.88; S 15.94%.

2-Methyl-4(5)-nitro-5(4)-acetonylmercaptoimidazole (III). Mp 110-111° (from alcohol). Found: C 39.18; H 4.26; N 19.47; S 14.72%. Calculated for $C_7H_9N_3O_3S$: C 39.06; H 4.22; N 19.53; S 14.90%.

2-Methyl-4(5)-nitro-5(4)-hydroxyethylmercaptoimidazole (IV). Mp 191-192° (from water). Found: C 35.44; H 4.48; N 20.40; S 15.87%. Calculated for $C_6H_9N_3O_3S$: C 35.46; H 4.46; N 20.68; S 15.78%.

2-Methyl-4(5)-nitro-5(4)-carboxymethylmercaptoimidazole (V). Mp 204-204.5° (decomp., from water). Found: C 33.03; H 3.23; N 19.06; S 14.78%. Calculated for $C_6H_7N_3O_4S$: C 33.18; H 3.25; N 19.36; S 14.76%.

5-Methyl-7 nitroimidazo[5, 1-b]thiazole (VI). Mp 311-312° (decomp., from glacial acetic acid). 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%.

3, 5-Dimethyl-7-nitroimidazo[5, 1-b]thiazole (VII). Mp 275-276° (from alcohol). 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%.

5-Methyl-7-nitroimidazo[5, 1-b]thiazoline (VIII). Mp 214-215° (decomp., from alcohol). 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-Methyl-7-nitroimidazo[5, 1-b]thiazolid-3-one (IX). Mp 205-205.5° (decomp., from glacial CH_3COOH). 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%.

The paper was read at the 1962 All-Union Conference on the Chemistry of 5-Membered Nitrogen Ring Compounds [5]. After the present work was finished, a paper [6] appeared describing synthesis of certain derivatives of I by cyclizing 2-acylaminomethylthiazoles.

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12 November 1964

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UDC 547.79+542.95

BEHAVIOR OF 4- AND 5-AMINOBENZ-2,1,3-THIADIAZOLES UNDER HERZ AND SKRAUP REACTION CONDITIONS

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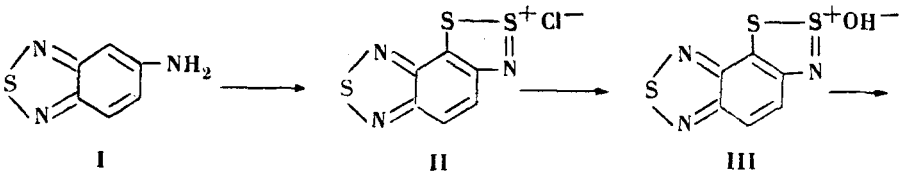
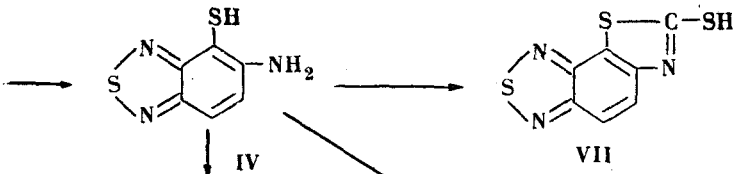
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2, pp. 314-315, 1965

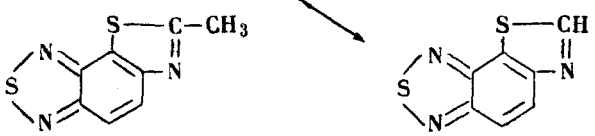
Like aromatic amines, 5-aminobenz-2, 1, 3-thiadiazole (I) reacts with sulfur chloride to give thiazothionium [5, 4-e]benz-2, 1, 3-thiadiazole chloride (II), which, on treatment with water, gives the hydrate (III), mp 142-143° (from alcohol). Degradation of III with alcoholic alkali gives 5-amino-4-mercaptobenz-2, 1, 3-thiadiazole (IV), and the latter, treated with acetic anhydride, ethyl orthoformate, or carbon disulfide, gives 2-methylthiazolo[5, 4-e]benz-2, 1, -3-thiadiazole (V), mp 137-139° (from alcohol), thiazolo[5, 4-e]benz-2, 1, 3-thiadiazole (VI), mp 98-100° (from 50% alcohol), and 2-mercaptothiazolo[5, 4-e]benz-2, 1, 3-thiazole (VII), mp 260-262° (decomp.), respectively.



I II III

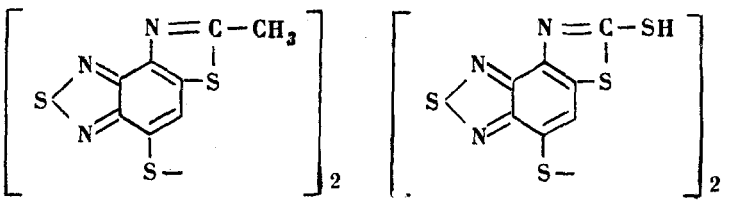


IV VII



V VI

When the above reactions are carried out with 4-aminobenz-2, 1, 3-thiadiazole (VIII), the end products, judging by the analytical data and certain properties, are 2-methylthiazolo[4, 5-e]benz-2, 1, 3-thiadiazolyl-7-disulfide (IX), mp 266-270°, and 2-mercaptothiazolo[4, 5-e]benz-2, 1, 3-thiadiazolyl-7-disulfide (X), mp 285-290°. The structures of the intermediates from which compounds IX and X are formed, are being investigated.



IX X

Reaction of 4-amino-(VIII) or 5-aminobenz-2, 1, 3-thiadiazoles (I) with glycerol, sulfuric and arsenic acids gives quinolino[7, 8-d]-2, 1, 3-thiadiazole (XI), mp 139-140° (from petrol ether), and quinolino[6, 7-d]2, 1, 3-thiadiazole (XII), mp 112-113° (from alcohol), respectively.