A SMILES REARRANGEMENT IN THE PYRIDAZINE SERIES

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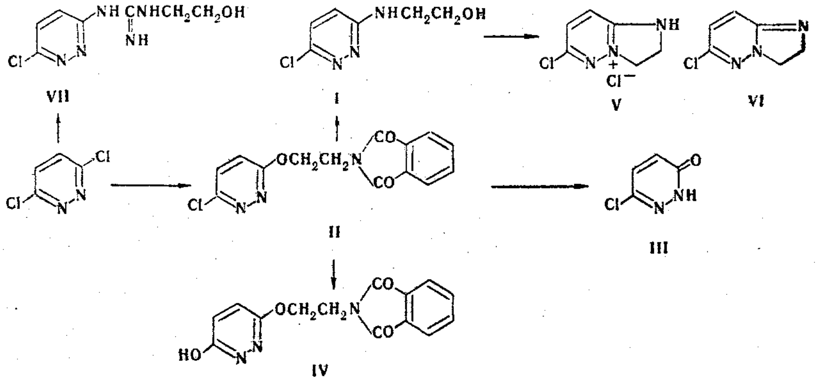
In the hydrazinolysis of 6-chloro-3-(β-phthalimidoethoxy)-pyridazine a rearrangement takes place with the formation of 6-chloro-3-(β-hydroxyethylamino)pyridazine. The action of thionyl chloride on the latter has given 6-chloro-2,3-dihydroimidazo[1,2-b]pyridazinium chloride. The reaction of β-hydroxyethylguanidine with 3,6-dichloropyridazine leads to 6-chloro-3-(β-hydroxyethylguanidino)pyridazine.

In recent years, the search for new drugs has been carried on intensively among guanidine derivatives (see, for example, [1]).

In this connection, we proposed to synthesize 3-(β-aminoethoxy)-6-chloropyridazine, which would be the key compound for a series of derivatives having biological interest by the reaction of 3,6-dichloropyridazine with the sodium derivative of 2-aminoethanol. However, instead of the expected 3-(β-aminoethoxy)-6-chloropyridazine we obtained 6-chloro-3-(β-hydroxyethylamino)pyridazine (I).



The condensation of 3,6-dichloropyridazine with N-(β-hydroxyethyl)phthalimide in the presence of potassium carbonate yielded 6-chloro-3-(β-phthalimidoethoxy)pyridazine (II), the saponification of which with dilute hydrochloric acid led to 3-chloropyridazin-6-one (III) and with dilute acetic acid to 6-hydroxy-3-(β-phthalimidoethoxy)pyridazine (IV). When compound (II) was heated with an ethanolic solution of hydrazine hydrate the saponification of the phthalimide protection was accompanied by a Smiles rearrangement with the formation of 6-chloro-3-(β-hydroxyethylamino)pyridazine (I). As is well known, the Smiles rearrangement, which is an intramolecular anionoid cleavage, takes place under the influence of bases. Apparently, a similar rearrangement takes place in the reaction of 3,6-dichloropyridazine with the sodium derivative of 2-aminoethanol.

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When compound (I) was treated with thionyl chloride, 6-chloro-2,3-dihydroimidazo[1,2-b]pyridazinium chloride (V) and 6-chloro-2,3-dihydroimidazo[1,2-b]pyridazine (VI) were isolated.

The reaction of 2-guanidinoethanol [2] with 3,6-dichloropyridazine in the presence of a sodium alkoxide formed 6-chloro-3-(β-hydroxyethylguanidino)pyridazine (VII). The latter showed no hypotensive activity.

EXPERIMENTAL

6-Chloro-3-(β-hydroxyethylamino)pyridazine (I). A. With stirring, 5.96 g (0.04 mole) of 3,6-dichloropyridazine was scattered onto a solution of the sodium alkoxide obtained from 0.96 g (0.041 g-atom) of sodium and 20 ml of 2-aminoethanol. On the following day the sodium chloride was filtered off, the aminoethanol was distilled off in vacuum, the residue was triturated with 10 ml of absolute ethanol, and 4.76 g of compound (I) was filtered off; yield 69%, mp 131-133°C (from ethanol). According to the literature [3], mp 135°C.

B. A mixture of 8.32 g (0.027 mole) of compound (II), 1.4 ml of hydrazine hydrate, and 100 ml of absolute ethanol was boiled for 2 h. The precipitate of phthalhydrazide (5.66 g) was filtered off. The filtrate was evaporated to dryness and the residue was recrystallized from a small amount of absolute ethanol, giving 2.82 g (59%) of the amino alcohol (I), mp 132-133°C (it gave no depression of the melting point with the sample obtained previously).

3-(β-Acetoxydthylamino)-6-chloropyridazine. A mixture of 1 g of the amino alcohol (I) and 20 ml of acetic anhydride was heated to 40°C and left overnight. The acetic anhydride was distilled off in vacuum to dryness, 2 ml of water was added to the residue, and 1 g of 3-(β-acetoxyethylamino)-6-chloropyridazine was filtered off; it formed colorless crystals with mp 151-153°C (from ethanol). Found: C 44.6; H 4.8; Cl 16.1; N 19.3%. $C_8H_{10}ClN_3O_2$. Calculated: C 44.6; H 4.7; Cl 16.4; N 19.5%.

6-Chloro-3-(N-hydroxyethyl-N-nitrosoamino)pyridazine. A saturated solution of sodium nitrite was added to a solution of 1 g of the amino alcohol (I) in 45 ml of 0.5 N hydrochloric acid until a reaction was given with starch–iodide paper. The precipitate was filtered off and washed with water. Colorless crystals with mp 104-105.5°C (from ethanol). Found: C 35.8; H 3.6; Cl 17.0; N 27.6%. $C_6H_7ClN_4O_2$. Calculated: C 35.6; H 3.5; Cl 17.5; N 27.7%.

3-(N-Acetoxyethyl-N-nitrosoamino)-6-chloropyridazine. This was obtained in a similar manner to the preceding compound from 3-(β-acetoxyethylamino)-6-chloropyridazine. Colorless crystals with mp 73.5-74.5°C (from absolute ethanol). Found: C 39.2; H 3.8; Cl 14.1; N 22.9%. $C_8H_9ClN_4O_3$. Calculated: C 39.3; H 3.7; Cl 14.5; N 22.9%.

6-Chloro-3-(β-phthalimidoethoxy)pyridazine (II). A mixture of 12.3 g (0.083 mole) of dichloropyridazine, 16.51 g (0.086 mole) of β-hydroxyethylphthalimide [4], and 11.5 g of calcined potassium carbonate was heated at 140°C for 2 h. After cooling, the reaction mixture was crystallized from absolute ethanol. This gave 9.86 g (39%) of (II) in the form of colorless crystals with mp 168.5-170°C. Found: C 55.4; H 3.4; Cl 11.4; N 13.8%. $C_{14}H_{10}ClN_3O_3$. Calculated: C 55.4; H 3.2; Cl 11.7; N 13.8%.

6-Chloro-2,3-dihydropyridazin-3-one (III). A mixture of 1 g of compound (II) and 30 ml of dilute (1 : 1) hydrochloric acid was boiled for 3 h and cooled, and 0.38 g of phthalic acid was filtered off. The aqueous layer was evaporated to dryness in vacuum, a small amount of water was added, the phthalic acid that had deposited was filtered off, and the filtrate was treated with aqueous ammonia to pH 7.5-8. The (III) that separated out was filtered off. Colorless needles with mp 146-148°C (from absolute ethanol). Found: C 36.4; H 2.2; N 22.0%. $C_4H_3ClN_2O$. Calculated: C 36.8; H 2.7; N 21.5%.

3-Hydroxy-6-(β-phthalimidoethoxy)pyridazine (IV). A mixture of 1 g of compound (II) and 30 ml of 50% acetic acid was boiled for 10 h. Then the solution was evaporated to dryness, the residue was neutralized with ammonia, and 0.58 g of (IV) was filtered off. Colorless crystals with mp 239-241°C (from absolute ethanol). Found: C 58.9; H 3.8; N 14.9%. $C_{14}H_{11}N_3O_4$. Calculated: C 58.9; H 3.9; N 14.7%.

6-Chloro-2,3-dihydroimidazo[1,2-b]pyridazinium Chloride (V). Thionyl chloride (2.8 ml) was gradually added to a solution of 2.84 g (0.02 mole) of (I) in 240 ml of dry dichloroethane. The reaction mixture was evaporated to dryness. The residue was treated with 20 ml of water, and, with cooling, the mixture was made alkaline with aqueous ammonia. The precipitate was filtered off and washed with water, to give 2.2 g (58%) of the chloride (V). Colorless crystals with mp 235-236°C (decomp., from absolute ethanol). Found: C 37.5; H 3.8; Cl 36.7; Cl^- 18.2; N 21.2%. $C_6H_7Cl_2N_3$. Calculated: C 37.5; H 3.7; Cl 36.9; Cl^- 18.2; N 21.9%.

The aqueous solution was extracted with ether, the extract was dried with calcined magnesium sulfate, and the ether was distilled off, giving 0.5 g of the imidazopyridine (IV) in the form of yellow plates with mp 116-117°C. According to the literature [5], mp 113-115°C.

Hydrochloride of 6-Chloro-3-(β-hydroxyethylguanidino)pyridazine (VII). To a solution of the sodium ethoxide obtained from 0.2 g of sodium and 7 ml of absolute ethanol was added 1.33 g of β-hydroxyethylguanidine hemisulfate, the mixture was triturated, and after 30 min it was filtered. The filtrate was treated with 1.3 g of dichloropyridazine; the resulting precipitate was filtered off. The addition of absolute ether to the solution yielded a gradually crystallizing precipitate of (VII); weight 1 g, colorless crystals with mp 186-187°C. Found: C 33.5; H 4.3; N 27.8%. $C_7H_{10}ClN_5O_2 \cdot HCl$. Calculated: C 33.4; H 4.4; N 27.7%.

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