IMIDAZO[1,2-a]QUINOXALINE AND ITS TRANSFORMATIONS. I

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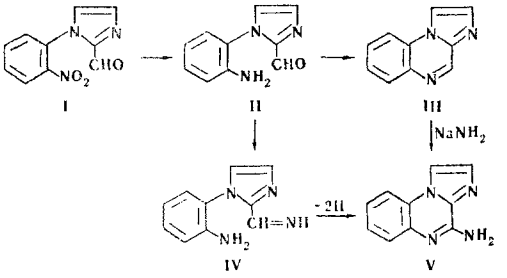
The transformations that occur during the reduction of 1-(o-nitrophenyl)-2-formylimidazole with sodium hydrosulfite in the presence of ammonia were studied. The 4-amino derivatives of imidazo[1,2-a]quinoxaline and the bisulfite derivatives of 1-(o-aminophenyl)-2-formylimidazole are formed along with the previously described imidazo[1,2-a]quinoxaline. 4-Aminoimidazo[1,2-a]quinoxaline was also obtained by alternative synthesis by amination of imidazo-[1,2-a]quinoxaline with sodium amide in dimethylaniline. The major product of the transformation is 4,4'-bisimidazo[1,2-a]quinoxalyl when the reaction is carried out in xylene.

As previously demonstrated [1], the amine (II) that is intermediately formed in the reduction of 1-(o-nitrophenyl)-2-formylimidazole with sodium hydrosulfite in ammonium hydroxide via the method in [2] undergoes cyclization to form imidazo[1,2-a]quinoxaline (III).*



A subsequent study of this reaction demonstrated that a considerable amount of the bisulfite compound of aldehyde II, which remains dissolved in the aqueous solution, is formed along with III. Acidification of this solution with hydrochloric acid and subsequent refluxing and alkalinization leads to the isolation of an additional amount of III; the yield of the latter can be raised to 90% in this way. The yield of III decreases to 50% when I is reduced with sodium hydrosulfite in the absence of ammonia.

A third product of the transformation is 4-aminoimidazo[1,2-a]quinoxaline (V). Its formation is apparently due to the cyclization of aldimine IV, which is obtained by the reduction of I in the presence of ammonia, with subsequent dehydrogenation of the transformation products. The structure of amine V was established on the basis of the IR spectrum; it was confirmed by the formation of an identical product in the amination of III in dimethylaniline. It should be noted that the expected 4-methylamino derivative is not formed when ammonia is replaced by methylamine, and only III can be isolated from the reaction mixture in a yield of ~ 50%.

* The only known representatives of this heterocyclic system are the 1,2-dihydro derivatives obtained by the isomerization of 2-aziridino-3-methoxy(oriodo)quinoxaline [3].

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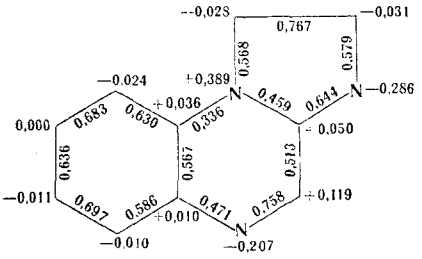
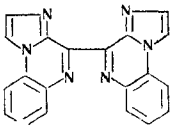
The production of V from aldimine IV also demonstrates that the amino group enters the 4 position in the amination of III. This observation is in conformity with the results of quantum-chemical calculations by the Hückel MO method, according to which the maximum effective positive charge in the imidazo[1,2-a]quinoxaline molecule is concentrated in the 4 position; attack by nucleophilic reagents should also apparently be directed there.



III



VI

A high-melting compound, to which the 4,4'-bisimidazo[1,2-a]quinoxalyl (VI) structure should be ascribed on the basis of the analytical results, IR spectrum, and molecular-weight determination, is formed in addition to V in the reaction of sodium amide with III in xylene. Similar dimerization reactions are also observed during the action of nucleophilic reagents on compounds of the benzimidazole [4] and phenanthridine [5] series.

Hydroxylation does not occur and profound destruction of III is observed when III is fused with potassium hydroxide under the conditions previously described in [6, 7].

An attempt to synthesize the isomeric (with respect to III)* imidazo[5,1-a]quinoxaline (in analogy with the preparation of phenanthridine [8, 9]) by cyclization of 1-(o-formylaminophenyl)imidazole (VII) was unsuccessful. Only deformylation occurs when VII is heated with polyphosphoric acid or zinc chloride. The yield of free amine reaches 100%. The negative result is apparently due to deactivation of the imidazole ring of VII as a consequence of protonation or complexing.

EXPERIMENTAL

Imidazo[1,2-a]quinoxaline (III). A 2.17-g (10 mmole) sample of I was suspended in 15 ml of water and 3 ml of 22% ammonium hydroxide, and 6.6 g (30 mmole) of $Na_2S_2O_4 \cdot 2H_2O$ was added in portions. On completion of the spontaneous heating, the mixture was heated on a boiling-water bath for 30 min and allowed to stand overnight. The precipitate (1 g) was removed by filtration and washed with water. The filtrate, which contained the bisulfite compound of II, was refluxed with 10 ml of hydrochloric acid for 10 min, and the precipitated sulfur was removed by filtration. The filtrate was neutralized with 22% ammonium hydroxide and extracted with chloroform. Removal of the solvent by distillation gave another 0.6 g of a crystalline substance. The precipitates obtained were dissolved in chloroform, and the chloroform solution was chromatographed on aluminum oxide. The first fraction with mp 124° [1.50 g (92%)] was III, while the second fraction with mp 210° [0.05 g (3%)] was 4-aminoimidazo[1,2-a]quinoxaline (V).

4-Aminoimidazo[1,2-a]quinoxaline (V). A 0.97-g (25 mmole) sample of finely ground sodium amide in 10 ml of anhydrous dimethylaniline was added to 0.85 g (5 mmole) of III. The mixture was heated with stirring to 180° and then held at this temperature for ~ 1 h, during which 60 ml (50%) of hydrogen was evolved. The mixture was cooled, 10 ml of water was added, and the precipitate that formed after 1 h was removed by filtration, washed with petroleum ether, and extracted with hot chloroform in a Soxhlet apparatus. The yield of crude V was 0.40 g (44%). The colorless needles had mp 209-210° (from alcohol). Found: C 65.2; H 4.4; N 30.5%. $C_{10}H_8N_4$. Calculated: C 65.2; H 4.4; N 30.4%. IR spectrum: ν_{as} 3520, ν_s 3410, δ 1628 cm^{-1} (NH_2). Compound V formed an acetyl derivative with acetic anhydride. The colorless needles had mp 248° (from water).

4,4'-Bisimidazo[1,2-a]quinoxalyl (VI). A 0.85-g (5 mmole) sample of III was subjected to reaction with sodium amide in 10 ml of xylene at 150° via the method described above. Cooling of the hot chloroform solution precipitated 0.10 g (11%) of amine V. Evaporation of the filtrate and crystallization of the residue from dimethylformamide gave 0.40 g (46%) of bis derivative VI as colorless needles that were only slightly

*Ring closure should proceed at the 5 position in agreement with the results of Hückel MO calculations (see [10]).

soluble in the usual organic solvents and melted above 360°. Found: C 71.5; H 3.6; N 25.0%. M 324. $C_{20}H_{12}N_6$. Calculated: C 71.4; H 3.6; N 25.0%. M 336.

1-(o-Formylaminophenyl)imidazole (VII). This compound was obtained in 92% yield by formylation of 1-(o-aminophenyl)imidazole [10] with formic acid in benzene by the method in [11]. The colorless prisms had mp 201-202° (from water). Found: C 64.0; H 5.0; N 22.8%. $C_{10}H_9N_3O$. Calculated: C 64.2; H 4.8; N 22.5%.

Experiments on the Hydroxylation of III. No reaction occurred when III was heated to 320° with fused powdered potassium hydroxide. Violent evolution of gaseous products that burn with a smoky flame occurs above this temperature. Judging from the chromatogram, the melt contains a difficult-to-separate mixture of transformation products.

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