SYNTHESIS OF DERIVATIVES OF PYRAZINE-2,3-DICARBOXYLIC ACIDS AND PYRAZINE-2,3-DICARBONAMIDES FROM 2,3-DICHLOROQUINOXALINE

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The synthesis of dimethyl 2,3-dichloropyrazine-5,6-dicarboxylate from dichloroquinoxaline has been effected. The nucleophilic substitution reactions of the compound obtained have been studied.

In connection with the search for convenient methods of obtaining 2,3-diaminopyrazine and its derivatives, which are starting materials in the synthesis of imidazo[4,5-b]pyrazine and other condensed heterocyclic systems, it appeared of interest to study the oxidative cleavage of 2,3-dichloroquinoxaline (I). According to the available literature information, in the oxidation of (I) with potassium permanganate in an aqueous medium, instead of the expected 5,6-dichloropyrazine-2,3-dicarboxylic acid, the product is 5,6-dihydroxypyrazine-2,3-dicarboxylic acid (43%) [1]. The replacement of the chlorine atoms by hydroxy groups could take place either during the isolation of the reaction products, which was performed by the authors concerned with the aid of ion-exchange resins, or in the oxidation process. We have repeated the oxidation of (I) under the conditions described, but we changed the method of isolating the reaction products, as follows: the reaction solution was evaporated, the dry residue was treated with methanol, and a current of dry HCl was passed through the mixture. Under these conditions it was possible to obtain dimethyl 5,6-dichloropyrazine-2,3-dicarboxylate (II) with a yield of 49% (calculated on the I). The halogens of compound (II) readily take part in nucleophilic substitution reactions. Thus, the saponification of the ester groups in aqueous alkaline solution formed a mixture of acids which could be separated only after esterification with methanol: then dimethyl 5-chloro-6-methoxy- and 5,6-dihydroxypyrazine-2,3-dicarboxylates (III and V, respectively) were isolated. Since the esterification of a mixture of the same acids with ethanol yielded diethyl-5-chloro-6-methoxypyrazine-2,3-dicarboxylate (IV), it was concluded that the replacement of a halogen by a methoxy group took place at the stage of alkaline saponification, apparently through the methanol liberated in the reaction process. It was impossible to obtain 2,3-dichloropyrazine by heating (II) in mineral acids in water or aqueous ethanol, since under these conditions the (II) underwent far-reaching changes, evidently involving the cleavage of the ring. From the resinous mixture of reaction products formed, after esterification it was possible to isolate only compound (V) in the individual state. In an ethanolic solution of ammonia at 18-20°C, compound (II) was converted into 5-amino-6-chloropyrazine-2,3-dicarbonamide (VI) and, on heating, into 5,6-diaminopyrazine-2,3-dicarbonamide (VII). Compound (VII) did not react with orthoformic ester on heating to 145-160°C (in the absence of a catalyst or in the presence of catalytic amounts of mineral acids).

In order to aminate (II) without the simultaneous conversion of the ester groups into amide groups, we investigated the reaction of (II) with ammonia in dimethylformamide, which has previously been used successfully for the selective amination of other halogen-substituted pyrazines [2].

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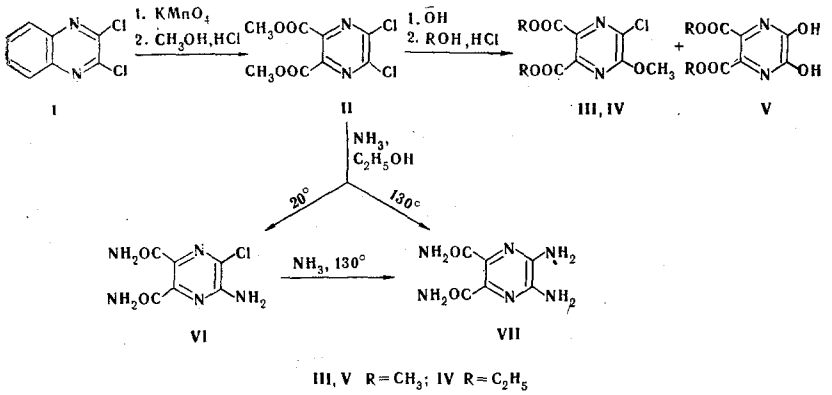
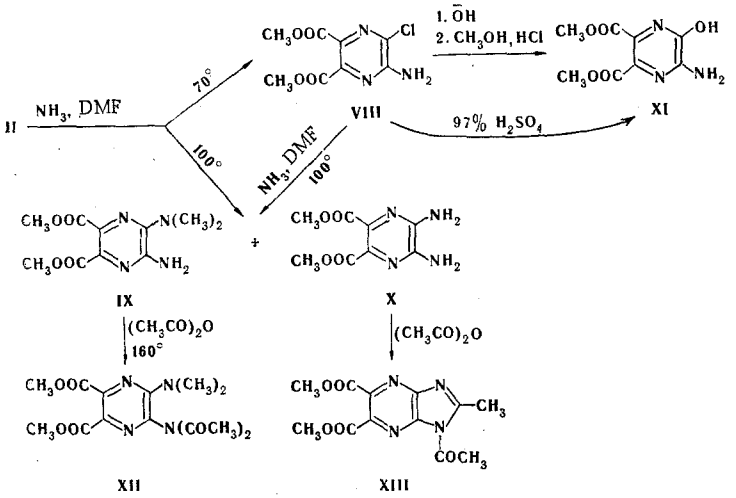


III, V R = CH_3; IV R = C_2H_5

The passage of a current of NH_3 through a solution of (II) in dimethylformamide at 70°C led to the formation of dimethyl-5-amino-6-chloropyrazine-2,3-dicarboxylate (VIII). At a higher temperature (100°C) the halogen in compound (VIII) was replaced predominantly by the dimethyl amino group, and compound (IX) was obtained; dimethyl-5,6-diaminopyrazine-2,3-dicarboxylate (X) was obtained under these conditions only in very small yield (2% of theoretical).



In compound (VIII) the halogen is comparatively easily replaced by a hydroxy group both in acid and in alkaline media; at the same time, in 97% H_2SO_4 the ester groups were not saponified, and the diester (XI) was obtained. There is information in the literature on the possibility of the formation of benzimidazoles by heating 2-amino-3-dimethylamino derivatives of benzene with acetic anhydride [3]. However, when the analogous reaction was performed with (IX), only the diacetyl derivative (XII) was obtained. Heating the diamino derivative (X) with acetic anhydride gave dimethyl 1-acetoxy-2-methylimidazo [4,5-b]pyrazine-5,6-dicarboxylate (XIII).

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer 457 instrument in paraffin oil, and the PMR spectra on a JNM-4H-100 instrument with tetramethylsilane as internal standard. Chromatography was performed on paper in the n-butanol – 5% acetic acid (1 : 1) system.

Dimethyl 5,6-Dichloropyrazine-2,3-dicarboxylate (II). With stirring, 55.35 g (350 mmoles) of $KMnO_4$ was added over 1 h to a suspension of 11.07 g (42 mmoles) of (I) in 1100 ml of water at 92-96°C, and stirring was continued at the same temperature for 1 h 30 min, by which time the $KMnO_4$ had been deoxidized. The hot solution was filtered and the precipitate of MnO_2 was washed several times with hot water, the combined aqueous extracts were evaporated, and the residue was dried. The precipitate of MnO_2 was extracted with $CHCl_3$, and after the elimination of the $CHCl_3$, 2 g of unchanged (I) was recovered. The dry residue obtained after the evaporation of the aqueous extracts was suspended in 300 ml of anhydrous methanol and, at 30-35°C, a current of dry HCl was passed in for 6 h. The reaction mixture was cooled, the precipitate was filtered off and was washed with cooled methanol, and the methanolic solutions were evaporated to

dryness in vacuum. The residue was neutralized with an aqueous solution of $NaHCO_3$ to pH 7 and extracted with $CHCl_3$. After the distillation of the $CHCl_3$, 5.93 g (49.1%) of (II) was obtained with mp 81-82.5°C [from methanol–hexane (1:4)]. Found: C 36.5; H 2.4; Cl 26.8; N 10.7%. $C_8H_6Cl_2N_2O_4$. Calculated: C 36.2; H 2.3; Cl 26.8; N 10.6%. IR spectrum, cm^{-1}: 1745, 1727 (ester C=O groups).

Reaction of (II) with an Aqueous Solution of NaOH. A mixture of 4 g (15 mmoles) of (II) and 16 ml of a 2.5 N aqueous solution of NaOH was stirred at 18-20°C for 1 h (the temperature rose spontaneously to 50°C), and 0.22 g of unchanged (II) was filtered off. The solution was acidified to pH 1 and was evaporated, and the residue was dried over P_2O_5 and was mixed with 75 ml of anhydrous methanol, and a current of dry HCl was passed into the mixture at 30-35°C for 3 h. The undissolved matter was filtered off and the filtrate was evaporated to dryness, neutralized with $NaHCO_3$ solution to pH 7, and extracted with $CHCl_3$. The residue obtained after the distillation of the $CHCl_3$ was triturated with petroleum ether, giving 1.32 g (35.5%) of (III), mp 71.5-72.5°C (from a mixture of diethyl ether and petroleum ether). Found: C 42.1; H 3.7; Cl 13.1; N 11.0%. $C_9H_9ClN_2O_5$. Calculated: C 41.6; H 3.5; Cl 13.6; N 10.8%. IR spectrum, cm^{-1}: 1750, 1728 (ester C=O groups). PMR spectrum (in CD_3OD), ppm: 3.93 and 3.94 (protons of $COOCH_3$ groups), 4.14 (protons of an OCH_3 group).

The bicarbonate solution after extraction with chloroform was acidified to pH 1 and cooled, and 0.45 g (14%) of (V) was filtered off with mp 240-241°C (decomp., from methanol). Found: C 42.3; H 3.6; N 12.2%. $C_8H_8N_2O_6$. Calculated: C 42.1; H 3.5; N 12.3%. IR spectrum, cm^{-1}: 1674, 1715, 1734, 1775 (C=O of amide and ester groups), 3075, 3190 (NH). PMR spectrum (in CD_3OD), ppm: 3.87 (protons of $COOCH_3$ groups).

Diethyl 5-Chloro-6-methoxypyrazine-2,3-dicarboxylate (IV). The reaction of (II) with an aqueous solution of NaOH was performed as described above and, after esterfication with ethanol, compound (IV) was obtained (25%); mp 57-57.5°C (from hexane). Found: C 45.7; H 4.7; N 9.6%. $C_{11}H_{13}ClN_2O_5$. Calculated: C 45.8; H 4.5; N 9.7%.

Dimethyl 5-Amino-6-chloropyrazine-2,3-dicarboxylate (VIII). A current of NH_3 was passed into a solution of 7 g (26 mmoles) of (II) in 42 ml of dimethylformamide for 30 min (slow spontaneous rise in the temperature to 70°C). The reaction mixture was cooled to 20°C, the precipitate of NH_4Cl was filtered off, and the solution was evaporated in vacuum to 1/3 of its original volume. The residue was treated with water and ice, giving 6 g (93%) of (VIII) with mp 127-128°C (from a mixture of ether and methanol). Found: Cl 14.1; N 16.9%. $C_8H_8ClN_3O_4$. Calculated: Cl 14.4; N 17.1%. IR spectrum, cm^{-1}: 3470, 3300, 3155 (NH_2); 1738, 1717 (ester C=O groups); 1632 (δ_{NH_2}). PMR spectrum (in $CDCl_3$), ppm: 3.95, 3.98 (protons of $COOCH_3$ groups); 6.09 (protons of an NH_2 group).

Dimethyl 5-Amino-6-dimethylaminopyrazine-2,3-dicarboxylate (IX) and Dimethyl 5,6-Diaminopyrazine-2,3-dicarboxylate (X). A current of NH_3 was passed into a solution of 3 g (12 mmoles) of (VIII) in 18 ml of dimethylformamide at 100-105°C for 7 h. The solvent was distilled off in vacuum, the residue was treated with water, and the precipitate was filtered off and, after drying, was extracted with ether in a Soxhlet apparatus. The ethereal extract yielded 2.54 g (82%) of (IX) with mp 181.5-182.5°C (from methanol). Found: C 47.3; H 5.7; N 21.6%. $C_{10}H_{14}N_4O_4$. Calculated: C 47.3; H 5.6; N 22.0%. IR spectrum, cm^{-1}: 3370, 3315, 3220 (NH_2); 1728, 1718 (ester C=O groups); 1632 (δ_{NH_2}). PMR spectrum (in $CDCl_3$): 3.90 ($COOCH_3$ protons); 5.37 (protons of an NH_2 group); 2.94 [protons of an $N(CH_3)_2$ group].

The ether-insoluble residue was crystallized from methanol, giving 0.5 g (2%) of (X) with mp 268.5-269.5°C (decomp.). Found: C 42.0; H 4.4; N 24.7%. $C_8H_{10}N_4O_4$. Calculated: C 42.4; H 4.5; N 24.7%. IR spectrum, cm^{-1}: 3480, 3420, 3305, 3175 (NH_2); 1703 (ester C=O groups); 1630 (δ_{NH_2}). PMR spectrum (in DMSO), ppm: 3.79 (protons of $COOCH_3$ groups); 6.83 (protons of an NH_2 group).

Dimethyl 5-Amino-6-hydroxypyrazine-2,3-dicarboxylate (XI). A mixture of 1 g (4.1 mmoles) of (VIII) and 1.8 ml of H_2SO_4 (d 1.84) was stirred at 40-42°C for 40 min. The reaction solution was poured onto ice, a 2.5 N solution of NaOH was added with cooling to give pH 3, and 0.9 g (97%) of (XI) was filtered off; mp 238.5-239.5°C (decomp., from water). Found: C 42.1; H 4.0; N 17.9%. $C_8H_9N_3O_5$. Calculated: C 42.3; H 4.0; N 18.5%. IR spectrum, cm^{-1}: 3430, 3270, 3160, 3130, 3050 (NH_2, NH); 1732, 1715 (ester C=O groups); 1678, 1640 ($\nu_{C=O}$ of an amide, δ_{NH_2}).

Reaction of (VIII) with an Aqueous Solution of NaOH. A mixture of 4 g (16 mmoles) of (VIII) and 16 ml of a 2.5 N aqueous solution of NaOH was stirred at 18-20°C for 1 h 30 min. Then the reaction mixture was brought to pH 1 and cooled, and the precipitate that deposited, after being dried over P_2O_5, was dissolved in 45 ml of anhydrous methanol. A current of dry HCl was passed into the resulting solution at 30-35°C for 2 h. The solvent was distilled off in vacuum, the residue was neutralized with $NaHCO_3$ solution to

pH 7, and the unchanged (VIII) (3 g) was extracted with chloroform. The bicarbonate solution was treated with a 2.5 N solution of HCl to pH 1, and then with NaCl to saturation, and was extracted with $CHCl_3$. Elimination of the solvent yielded 0.46 g (12.4%) of (XI), which was identical with the substance obtained above according to its melting point and R_f value (0.36, dark violet spot).

5-Amino-6-chloropyrazine-2,3-dicarbonamide (VI). A. A mixture of 1.5 g (5.7 mmoles) of (II) and 15 ml of an ethanolic solution of NH_3 (15.8%) was kept at 18-20°C for four days. The precipitate of (VI) was filtered off; 1.13 g (93%), mp 227-228°C (decomp., from water). Found: Cl 15.9; N 32.4%. $C_6H_6ClN_5O_2$. Calculated: Cl 16.4; N 32.5%. IR spectrum, cm^{-1}: 3460, 3335, 3150 (NH_2); 1688, 1650 ($\nu_{C=O}$ of an amide, δ_{NH_2}).

B. In a similar manner to the preceding case, 1.5 g (6.1 mmoles) of (VIII) gave 0.85 g (64.5%) of (VI) identical with that obtained above.

5,6-Diaminopyrazine-2,3-dicarbonamide (VII). A. A catalytic amount of Cu was added to 3.89 g (16 mmoles) of (VIII) in 47 ml of ethanolic NH_3 (15.8%), and the mixture was heated in an autoclave at 135-140°C for 33 h. After cooling, the precipitate was filtered off and it was treated with a small amount of water; this gave 1.52 g (49%) of (VII), not melting below 300°C (from 40% methanol). Found: C 37.0; H 4.2%. $C_6H_8N_6O_2$. Calculated: C 36.8; H 4.1%. IR spectrum, cm^{-1}: 3445, 3415, 3200, 3165, 3120 (NH_2); 1675, 1652 ($\nu_{C=O}$ of an amide, δ_{NH_2}).

B. Under similar conditions, 4 g (15 mmoles) of (II) yielded 2.63 g (88%) of (VII).

5-Amino-6-dimethylaminopyrazine-2,3-dicarbonamide (XIV). A mixture of 1 g (3.9 mmoles) of (IX) and 60 ml of a 15.8% ethanolic solution of NH_3 was kept at 18-20°C for 20 days. This gave 0.6 g (68%) of (XIV), mp 230-231°C (decomp., from aqueous methanol). Found: C 42.9; H 5.3%, $C_8H_{12}N_6O_2$. Calculated: C 42.8; H 5.4%. IR spectrum, cm^{-1}: 3460, 3365, 3345, 3200 (NH_2); 1688, 1655 ($\nu_{C=O}$ of an amide and δ_{NH_2}).

Dimethyl 5-Diacetylamino-6-dimethylamino-2,3-dicarboxylate (XII). A solution of 0.5 g (2 mmoles of (IX) in 5 ml of acetic anhydride was heated at 160°C in an autoclave for 2 h. Then the reaction solution was filtered, the acetic anhydride was distilled off in vacuum, and the residue was triturated with ether, after which 0.5 g (75%) of (XII) was filtered off; mp 139-139.5°C (from a mixture of ether and methanol). Found: C 49.9; H 5.4; N 16.3%. $C_{14}H_{18}N_4O_6$. Calculated: C 49.7; H 5.3; N 16.5%. IR spectrum, cm^{-1}: 1758, 1722, 1705 (ester and amide $\nu_{C=O}$).

Dimethyl 1-Acetyl-2-methylimidazo[4,5-b]pyrazine-5,6-dicarboxylate (XIII). A solution of 0.3 g (1.3 mmoles) of (X) in 3 ml of acetic anhydride was boiled for 1 h. The acetic anhydride was distilled off in vacuum, the residue was triturated with ether, the mixture was cooled, and 0.3 g (77.5%) of (III) was filtered off; mp 186-187°C (from ethanol). Found: C 50.0; H 4.2; N 18.8%. $C_{12}H_{12}N_4O_5$. Calculated: C 49.4; H 4.1; N 19.1%. IR spectrum, cm^{-1}: 1750, 1725 (C=O). PMR spectrum (in $CDCl_3$), ppm: 3.12, 3.02 (protons of $COCH_3$ and 2-CH_3 groups); 4.05, 4.03 (protons of $COOCH_3$ groups).

LITERATURE CITED

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