SYNTHESIS OF CONDENSED AZAHETEROCYCLES DERIVED FROM 2,3-DICHLOROPYRAZINE

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A study was carried out on the reaction of 2,3-dichloropyrazine with compounds containing an activated methylene group. The reaction course and structure of the final products are a function of the nucleophile.

The pyrazine ring is found in many physiologically active compounds, including natural products such as pteridines, folic acid, riboflavin, and alloxanthine and synthetic drugs including diuretics [1] and anti-cancer and anti-inflammatory drugs [2]. In this regard, we have attempted to develop new methods of synthesis for pyrazine derivatives, in particular, condensed heterocyclic systems.

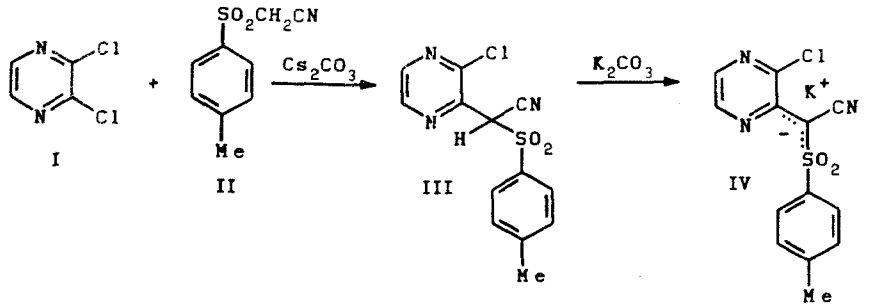
The nucleophilic substitution of halogen atoms in 2,3-dichloroquinoxaline was studied in our previous work [3-5]. In the present work, we studied the reaction of 2,3-dichloropyrazine I with various compounds containing an activated methylene group. We should note that the nucleophilic substitution of a halogen atom by carbanions in 2,3-dichloropyrazine has not yet been studied.

The reaction of dichloropyrazine I with tosylacetonitrile II in DMSO in the presence of cesium carbonate, used to generate the carbanion, features nucleophilic substitution of one chlorine atom, leading to α-tosyl-[2-(3-chloro)pyrazinyl]acetonitrile III (see Table 1).

The presence of three electron-withdrawing substituents at the sp^3-hybridized carbon atom accounts for the high CH-acidity of the remaining proton. In particular, this leads to the dissolution of III in aqueous potassium carbonate with the formation of mesomerically stabilized potassium salt IV [3].

The polyfunctional nature of product III opens definite synthetic possibilities. We studied the reaction of III with simple heterocycles, namely, 1-alkylimidazoles and pyridine.

Heating III with 1-methylimidazole in DMF at reflux leads to 4-amino-5-tosylimidazo[1′,2′:1,6]pyrido[2,3-b]pyrazine (V), accompanied by demethylation of the imidazole system.



(see remainder of the scheme in the middle of the next page)

According to this mechanism, quaternary imidazolium salt A is formed in the first reaction step. Ylid B is formed in the presence of excess 1-methylimidazole in the reaction medium, which acts as a base. (Quaternary azole salts have a high tendency to form such ylid species [6].) Subsequent nucleophilic addition to the nitrile group accompanied by demethylation of the imidazolium ring and terminating in imine—amine isomerization of the product leads to V.

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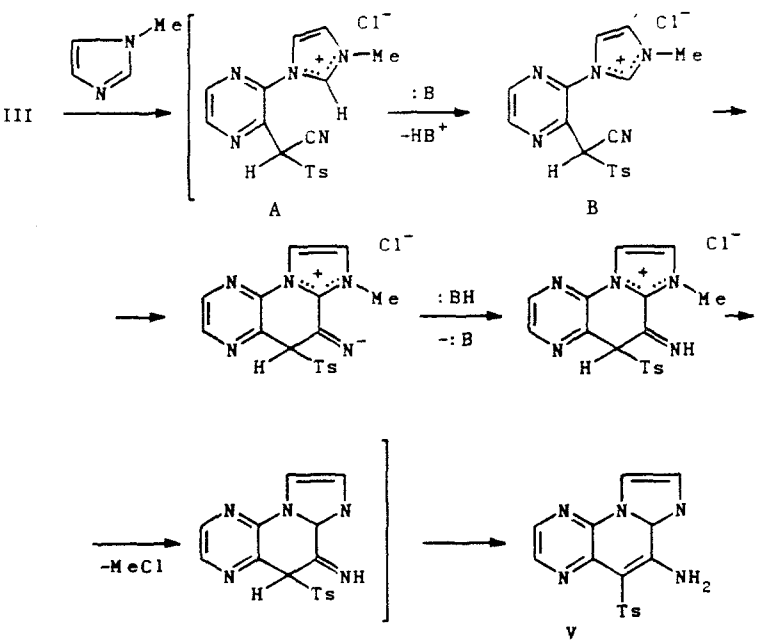
TABLE 1. Characteristics of III and V-VIII

Compound	Chemical formula	Mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (coupling constant, J, Hz)**	Yield, %
III	$C_{13}H_{10}ClN_3O_2S$	126*	2260 (CN)	2,51 (3H, s, CH_3); 5,92 (1H, s, CH_3); 7,42 (2H, d, J = 10.0; 2 CH-benzene) 7,75 (2H, d, J = 10.0; 2 CH-benzene) 8,49...8,54 (2H, m 2 CH-pyrazine)	48
V	$C_{16}H_{13}N_5O_2S$	297	3480 (NH_2, *as*); 3360 (NH_2, *s*)	2,35 (3H, s, CH_3); 7,34 (2H, d, J = 9,8; 2 CH-benzene) 7,74 (1H, d, J = 1,3; 2-H); 7,97 (2H, d, J = 9,8; 2 CH-benzene) 8,33 (1H, d, J = 2,2; 8-H); 8,53 (1H, d, J = 1,3; 1-H); 8,57 (1H, d, J = 2,2; 7-H); 8,21 (2H, br.s NH)	89
VI	$C_{11}H_6N_4$	213	2215 (CN)	7,69 (1H, t, 7-H); 8,14...8,47 (2H, m, 2-H and 4-H); 8,80 (1H, d, J = 2,4, 2-H); 8,99 (1H, d, J = 2,4, 3-H); 9,43 (1H, d, J = 7,0; 6-H)	66 (A) 52 (B)
VII	$C_{15}H_8N_4$	264	2212 (CN)	7,15 (1H, d, J = 9,0; 6-H); 8,0...8,19 (3H, m, 2-H, 3-H, 4-H); 8,56 (1H, d, J = 9,0; 5-H); 8,83 (1H, d, J = 2,4; 10-H); 9,20 (1H, d, J = 2,4; 9-H); 10,07 (1H, d, J = 8,8; 1-H)	70
VIII	$C_{15}H_{11}N_3O_2S$	234	1337 (SO_2, *as*) 1154 (SO_2, *s*)	3,46 (3H, s, CH_3); 7,62...8,38 (5H, m, 2-H...6-H); 8,73 (1H, d, J = 2,3; 10-H); 8,93 (1H, d, J = 2,3; 9-H); 9,90 (1H, d, J = 8,0; 1-H)	41

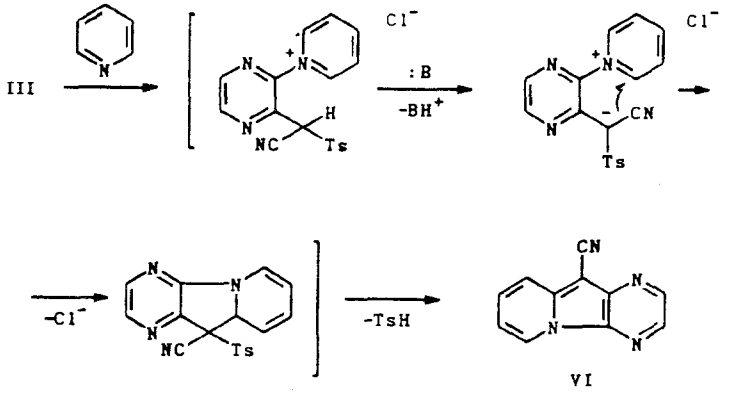
*Crystallization solvents: ethanol for III, DMF for V, toluene for VI and VIII, and propanol for VII.

**The spectra for III were taken in $CDCl_3$, for V in DMSO-d_6, and for VI-VIII in CF_3CO_2D.



:B —1-methylinidazole

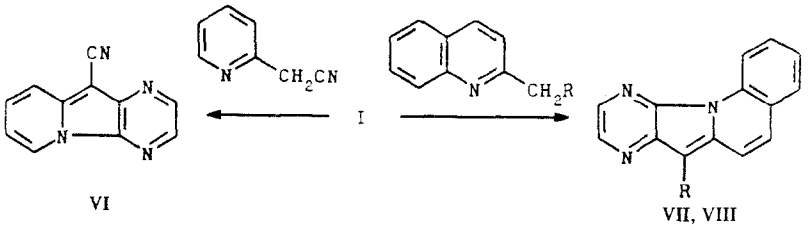
The signal for the amino group protons in the PMR spectrum taken for a solution in DMSO-d_6 appears at 8.21 ppm. This signal disappears upon treatment of the sample with D_2O. The doublet corresponding to 1-H in V is found at 8.53 ppm, while the coupled doublet, corresponding to 2-H, is found at 7.74 ppm. The paramagnetic shift of the signal for 1-H is attributed to the location of this proton in the region of the deshielding effect of the unshared electron pair of $N_{(9)}$, which lies close to this proton. A similar effect is possible only for a rigid cyclic structure, which is additional evidence for proposed structure V.



: B —pyridine

When the reaction is carried out with 1-benzyl- or 1-ethylimidazole, the same reaction product, namely 4-amino-5-tosylimidazo[1′,2′:1,6]pyrido[2,3-b]pyrazine, is formed. The rate of the reaction with 1-benzylimidazole is approximately equal to the rate with 1-methylimidazole. On the other hand, the loss of the ethyl group is slower by a factor of 4-5 as seen by monitoring the reaction by thin-layer chromatography. This corresponds to the reported chemical behavior of quaternary imidazolium salts [7]. The similar nature of all the cyclic compounds obtained was indicated by the identical pattern in the fingerprint regions in their IR spectra, lack of depression in the melting point of mixed samples, and complete agreement of all other spectral and physical indices.

The reaction of α-tosyl-[2-(3-chloro)pyrazinyl]acetonitrile III with pyridine proceeds differently. Heating III in pyridine at reflux leads to 10-cyanopyrazino[2,3-b]indolizine VI in good yield.



VII R = CN; VIII R = SO_2CH_3

The first reaction step, as in the case of the reaction with 1-methylimidazole, apparently gives a quaternary salt, which facilitates deprotonation of the electron-deficient sp^3-hybridized carbon atom by the action of excess pyridine. The carbanion attacks the α-carbon atom of the pyridine ring. The elimination of p-toluenesulfinic acid completes the formation of heteroaromatic system VI.

The nitrile group in the IR spectrum of product VI appears as a strong band at 2215 cm^{-1}. The most characteristic feature of the PMR spectrum taken in DMSO-d_6 is a one-proton downfield doublet at 9.43 ppm, corresponding to 4-H in VI. The reason for the paramagnetic shift of this signal is analogous to that for the signal of 1-H in the PMR spectrum of V, namely, the effect of the close-lying $N_{(3)}$ atom with an unshared electron pair.

The benzo-fused analog of pyridine, namely, quinoline, does not react with III. The major reason for this failure of quinoline, in our view, is the significant steric hindrance created by 8-H in the formation of the quaternary quinolinium salt.

Hetarylacetonitriles in the presence of base are known to form ambident carbanions, capable of nucleophilic substitution of the a halogen atom [8, 9]. The reaction of dichloropyrazine I with 2-pyridylacetonitrile gives consecutive nucleophilic substitution of both chlorine atoms resulting in 10-cyanopyrazino[2,3-b]indolizine (VI) described above.

Indolizine VI and the product synthesized from 2-cyanomethylpyridine were shown to be identical by the lack of a depression in the melting point of their mixture and coincidence of all spectral indices.

The reaction of dichloropyrazine I and 2-cyanomethylquinoline proceeds analogously to give the analogous cyclic product VII. The replacement of the nitrile group in 2-cyanomethylquinoline by a sulfonylmethyl group does not lead to a fundamental change in the reaction course. 7-Methylsulfonylpyrazino[2′,3′:4,5]pyrrolo[1,2-a]quinoline VIII is formed smoothly and in high yield (see Table 1).

We were unable to isolate the proposed products of the primary hetarylation of the cyanomethylazaheterocycles at the methylene group. This probably is the consequence of the high lability of the remaining chlorine atom, which is readily replaced upon the action of the nitrogen atom of the heterocyclic system, which is an efficient nucleophile.

The nucleophilic substitution of chlorine in 2,3-dichloropyrazine proceeds more slowly by a factor of 8-10 than for previously studied 2,3-dichloroquinoxaline [3-5]. This discrepancy corresponds to the reported activity of halogens in mononuclear azines and their benzo-fused analogs (compare the lability of the chlorine atom in 2-chloropyrazine and 2-chloroquinoline [10]).

EXPERIMENTAL

The IR spectra were taken on a Pye-Unicam SP3-300 spectrometer for KBr pellets. The PMR spectra were taken on a Bruker WP-100 spectrometer at 100 MHz with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with 10:3 toluene—2-propanol as the eluent.

The elemental analysis data were in accord with the calculated values.

α-Tosyl[2-(3-chloro)pyrazinyl]acetonitrile (III). A sample of 0.75 g (5 mmoles) 2,3-dichloropyrazine was dissolved in 30 ml dry DMSO and 0.97 g (5 mmoles) tosylacetonitrile II and 1.68 g (5 mmoles) roasted cesium carbonate were added. The mixture was stirred for 6 h at 60°C. The solvent was evaporated in vacuum and 30 ml water and 3 g activated charcoal were added to the residue. The mixture was stirred for 3 h at room temperature. The precipitate was filtered off and the mother liquid was acidified by the addition of 3 ml acetic acid. The precipitate formed was filtered off, dried, and crystallized to give 0.74 g III.

4-Amino-5-tosylimidazo[1′,2′:1,6]pyrido[2,3-d]pyrazine (V). A sample of 0.62 g (2 mmoles) III was dissolved in 20 ml DMF and 0.32 ml (4 mmoles) 1-methylimidazole was added. The solution obtained was heated at reflux for 12 h. The solvent was evaporated in vacuum and 20 ml water was added to the residue. The residue was filtered off, dried, and crystallized to give 0.61 g V.

10-Cyanopyrazino[2,3-b]indolizine (VI). A. A sample of 0.62 g (2 mmoles) III was dissolved in 10 ml dry pyridine. The solution was heated at reflux for 16 h. The excess solvent was distilled off in vacuum and 10 ml water was added to the residue. The precipitate was filtered off, dried, and crystallized to give 0.25 g VI.

B. A sample of 1.49 g (10 mmoles) 2,3-dichloropyrazine was dissolved in 30 ml DMF and 1.18 g (10 mmoles) 2-pyridylacetonitrile and 1.38 g (20 mmoles) roasted potassium carbonate were added. The mixture was heated at reflux for 6 h, adding 0.96 g (10 mmoles) sodium tert-butylate every 2 h. The solvent was evaporated in vacuum and 30 ml water and 5 ml acetic acid were added to the residue. The precipitate was filtered off, dried, and crystallized to give 0.95 g VI.

7-Cyanopyrazino[2′,3′:4,5]pyrrolo[1,2-a]quinoline (VII) was synthesized analogously to VI (Method B) from 2,3-dichloropyrazine and 2-cyanomethylquinoline.

7-Methylsulfonylpyrazino[2′,3′:4,5]pyrrolo[1,2-a]quinoline (VIII). A sample of 1.49 g (10 mmoles) 2,3-dichloropyrazine was dissolved in 30 ml dry pyridine and, then, 2.2 g (10 mmoles) 2-methylsulfonylquinoline and 1.92 g (20 mmoles) sodium tert-butylate were added. The mixture was heated on a steam bath for 8 h, adding 0.96 g fresh sodium tert-butylate every 2 h. Pyridine was evaporated in vacuum and 30 ml water and 5 ml acetic acid were added to the residue. The precipitate was filtered off, dried, and subjected to chromatography on a column packed with silica gel L40-100 with chloroform as the eluent. The fraction giving a yellow-blue fluorescence when irradiated with ultraviolet light was collected. Chloroform was evaporated in vacuum and the residue was crystallized. The yield of VIII was 1.22 g.

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SYNTHESIS OF PYRROLO[1,2-a]QUINOXALINE DERIVATIVES BY THE REACTION OF 2-HYDROXY-1,5-DIKETONES WITH o-PHENYLENEDIAMINE

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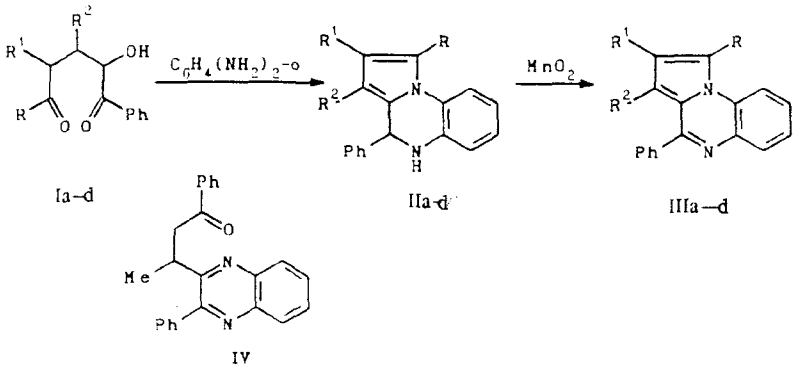
The reaction of 2-hydroxy-1,5-diketones with o-phenylenediamine leads to the formation of 4,5-dihydropyrrolo[1,2-a]quinoxaline derivatives, which are dehydrogenated by the action of MnO_2 to give the corresponding pyrrolo[1,2-a]quinoxaline derivatives.

Methods have been reported for the synthesis of derivatives of pyrrolo[1,2-a]quinoxaline from derivatives of pyrrole [1, 2] and quinoxaline [3, 4] and also by the reaction of o-phenylenediamine with several polyfunctional compounds, in particular, with α-ketoglutarate esters [5]. We have found a simple method for the synthesis of pyrrolo[1,2-a]quinoxalines by the reaction of relatively available 2-hydroxy-1,5-diketones (Ia)-(d) [6, 7] with o-phenylenediamine upon heating in 2:1 ethanol—acetic acid at reflux.



I — III a R = R_2 = Ph, b R = Ph, R^1 = H, R^2 = Me; c R = Ph, R^1 = R^2 = H; d R + R^1 = $(CH_2)_4$, R_2 = Ph

The initial products of the reaction are derivatives of 4,5-dihydropyrrolo[1,2-a]quinoxaline (IIa)-(IId) (see Table 1).

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