THE VICARIOUS INTRAMOLECULAR SUBSTITUTION REACTIONS. I. SYNTHESIS OF CONDENSED INDOLIZINES BASED ON 2-QUINOXALYLACETONITRILES

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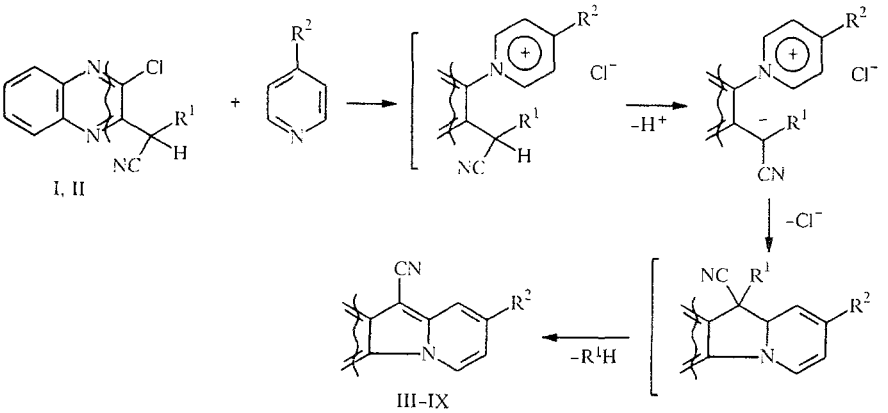
The interaction of α-substituted 2-(3-chloro)quinoxalylacetonitriles with azines to give condensed indolizino[2,3-b]quinoxalines has been studied. A mechanism for the reaction has been proposed which includes an intramolecular vicarious substitution of hydrogen in the azolium salt nucleus. The limits of utility of the reaction have been determined and some chemical properties of the compounds synthesized have been studied.

The vicarious nucleophilic substitution of hydrogen reaction [1, 2], which has been intensively developed by M. Makosha's group, is currently a powerful synthetic instrument for the directed modification of the structure of a variety of heterocyclic compounds. The principal limitation of this method is the need to use a nitro-substituted heterocycle, since an anion is formed at one stage in the reaction and the nitro group is capable of effectively delocalizing the negative charge. In this work the possibility has been studied of carrying out an intramolecular vicarious nucleophilic substitution of hydrogen in the nucleus of unsubstituted azines based on the previously described [3, 4] substituted 3-chloroquinoxalyl-2-acetonitriles (I, II).

When compounds I and II are boiled in pyridine the solution becomes red and 12-cyanoindolizino[2,3-*b*]quinoxaline (III) is isolated in excellent yield, no matter what R^1 is, after working up the reaction mixture. The first step in the reaction mechanism is evidently formation of a quaternary pyridinium salt in which the sp^3 hybridized carbon atom bonded to three electron-accepting groups is readily deprotonated in the presence of excess pyridine. Nucleophilic attack by the carbanion formed at an α-carbon of the pyridine nucleus with subsequent elimination of the corresponding sulfinic acid or diethyl phosphite leads to the conjugated system III.



I R^1 = *p*-$MeC_6H_4SO_2$, II R^1 = $(C_2H_5O)_2PO$; III R^2 = H; IV R^2 = Me; V R^2 = EtCOO; VII R^2 = *p*-Me_2N-C_6H_4; VIII R^2 = *p*-NO_2-C_6H_4-CH_2; IX R^2 = C_6H_5CO

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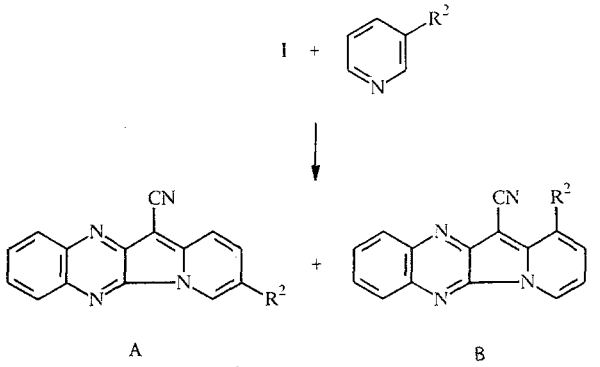
The proposed reaction mechanism is in fact a special case of intramolecular vicarious substitution of hydrogen in the heteroaromatic nucleus. The distinguishing characteristics of this reaction are, firstly, the preliminary formation of an activated azinium ion (which considerably increases the rate of the subsequent nucleophilic substitution) and, secondly, its intramolecular nature.

The spectroscopic characteristics and the melting point of the synthesized product III are in agreement with the previously described 12-cyanoindolizino[2,3-b]quinoxaline [5].

Various 4-substituted pyridines react analogously to pyridine to give the 2-substituted indolizino[2,3-b]quinoxalines (IV-IX) in high yields.

The nitrile groups of compounds III-IX appear as sharp intense absorptions in the 2195-2210 cm^{-1} region in their IR spectra. The most characteristic feature of the ^1H NMR spectra is a weak field one-hydrogen doublet at 8.9-9.1 ppm corresponding to the 4-H proton of molecules III-IX. As models of these molecules show, this proton lies in the region of the deshielding effect of the unshared pair of atom $N_{(6)}$, which explains the paramagnetic shift of this signal.

In pyridinium salts formed from symmetrically substituted pyridines positions 2 and 6 are equally susceptible to nucleophilic attack. A different situation arises when 3-substituted pyridines are used since the α- and α'-positions are not equivalent and two possibilities for nucleophilic attack occur.



A B

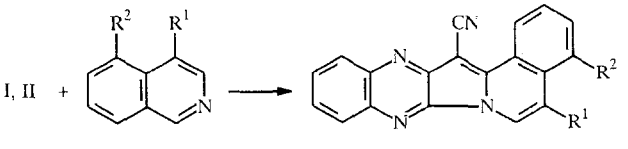
$R^2 = CH_3$, CH_3CH_2COO

In fact reaction of 3-methylpyridine with nitrile I gave a 40:60 mixture of isomers A and B which were unable to separate. The isomer ratio may be assessed from the integrated intensities of the corresponding signals in the ^1H NMR spectrum of the reaction mixture.The C_2H_5OCO group in ethyl nicotinate is considerably more bulky than the CH_3 group. This immediately affects the product ratio since the steric hindrance to attack at position 6 is considerably less than at position 2. Consequently, formation of isomer A predominates and it was isolated by crystallization (compound X). The weak field 4-H singlet at 10.25 ppm observed in the ^1H NMR spectrum unambiguously confirmed the proposed structure for X.

No matter what the electronic nature of the substituent, 2-substituted pyridines did not react with the halogenonitriles I and II. This lack of reactivity is explained by the steric hindrance to formation of the quaternary salt in the first step of the reaction.

The behavior observed in the reactions of the substituted 2-chloroquinoxalylacetonitriles I and II with pyridines was confirmed on switching to the benzo analogs of pyridine – quinoline and isoquinoline.

Isoquinoline and its 4- and 5-monosubstituted derivatives react readily with compounds I and II to form substituted 14-cyanobenz[5,6]indolizino[2,3-b]quinoxalines (XII-XIV) in high yield.



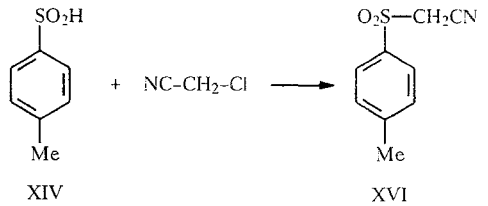
XI-XIII

XI $R^1 = H$, $R^2 = H$; XII $R^1 = H$, $R^2 = NO_2$; XIII $R^1 = Br$, $R^2 = H$

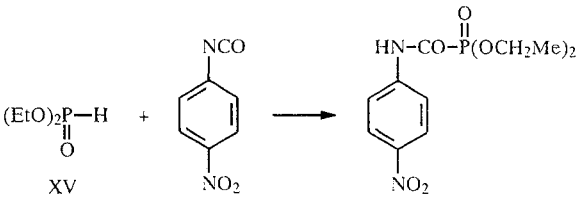
The mechanism for this reaction is evidently analogous to that proposed above for pyridines. It is characteristic that of the two possible directions of intramolecular nucleophilic attack by the carbanion — at $C_{(1)}$ or $C_{(3)}$ of the isoquinoline nucleus — only the former occurs in all cases to give the isomers shown as demonstrated by the ^1H NMR spectra of the

compounds synthesized. The singlet for the 1-H proton of the isoquinoline nucleus was absent while weak field signals for the corresponding 6-H proton appeared in the 9.4-9.7 ppm region (a singlet for XIII and doublets for XI and XII). The reason for the paramagnetic shift of these signals is analogous to that for the pyridine derivatives — the deshielding effect of the unshared pair of atom $N_{(8)}$ — which confirms the formation of the rigid cyclic structures XI-XIII.

We demonstrated experimentally the elimination of p-toluenesulfinic acid (XIV) or diethyl phosphite (XV) in the last stage of the reaction. Since it is difficult to isolate these compounds from the reaction mixture and to identify them because of their instability at high temperatures [6], we treated the reaction mixture with chloroacetonitrile and p-nitrophenyl-isocyanate.



XIV XVI

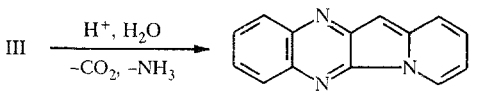


XV XVII

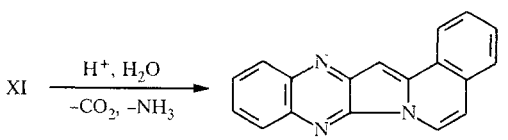
Subsequent isolation of tosylacetonitrile (XVI) and diethyl p-nitrophenylcarbamoylphosphonate (XVII) from the reaction mixtures confirmed the formation of the compounds mentioned above unambiguously.

Quinoline (pK_a = 4.9) and the various methylquinolines, despite their similar basicities to isoquinoline (pR_a = 5.14 [7]), did not react with the chloro compounds I and II. The reason is evidently the same as for the 2-substituted pyridines: the 8-CH group of the quinoline nucleus screens the nitrogen atom and hinders the formation of the quinolinium ion.

It seemed interesting to study some chemical properties of the compounds synthesized. When compounds III and XI were heated in sulfuric acid hydrolysis of the CH groups occurred with subsequent decarboxylation to give compounds XVIII and XIX, respectively.



XVIII



XIX

There are no nitrile absorption bands in the IR spectra of compounds XVIII and XIX, but singlets for the 12-H (XVIII) and 14-H protons (XIX) appear in the ^1H NMR spectra.

The presence of an enamine unit in the structures of molecules XVIII and XIX explains the activity of the "liberated" carbon atom in electrophilic substitution reactions. For example, the corresponding monobromo derivatives XX and XXI were obtained by bromination of the condensed indolizines in pyridine (see scheme on the following page).

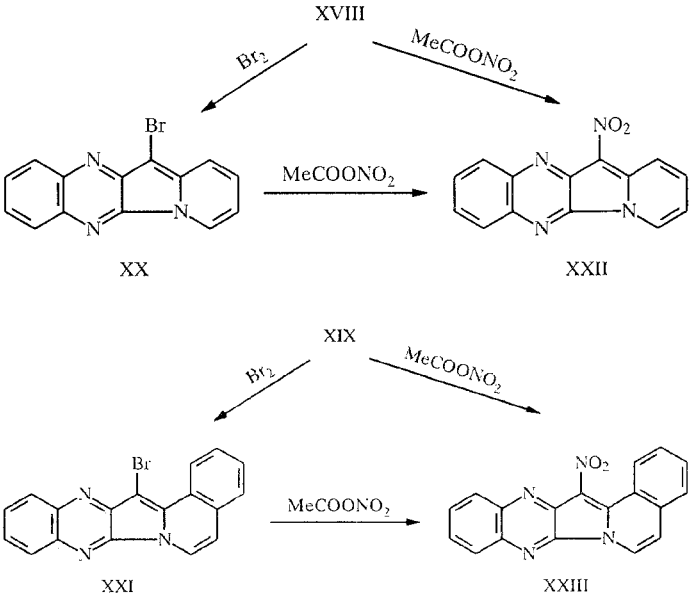
The reaction of XX and XXI with acetyl nitrate gave the products of *ipso*-substitution of the bromine atom with a nitro group: the nitroindolizines XXII and XXIII were isolated from the reaction mixtures in preparative yields. Note that we successfully obtained compounds XXII and XXIII by direct nitration of the initial indolizines XVIII and XIX.

TABLE 1. Characteristics of Compounds III-XXIII

Compound	Molecular formula	mp, °C	^{1}H NMR spectrum, ppm (splitting, J, Hz)**	Yield, %
III	$C_{15}H_8N_4$	282	9,24 (1H, d, 4-H, 7)	98
IV	$C_{16}H_{10}N_4$	290	9,38 (1H, d, 4-H, 7); 8,58 (1H, s, 1-H); 7,60 (1H, d, 3-H, 7,1)	59
V	$C_{18}H_{12}N_4O_2$	277	9,07 (1H, d, 4-H, 8); 8,56 (1H, s, 1-H); 7,49 (1H, d, 3-H, 8); 4,51 (2H, q, CH_2—); 1,49 (3H, t CH_3—)	69
VI	$C_{21}H_{12}N_4O$	>300	9,35 (1H, d, 4-H, 7); 8,50 (1H, d, 3-H, 7)	70
VII	$C_{23}H_{17}N_5$	>300	9,62 (1H, d, 4-H, 7,1); 8,62 (1H, d, 3-H, 7,1); 8,45 (1H, s, 1-H), 3,59 (6H, s, $(CH_3)_2N$)	67
VIII	$C_{22}H_{13}N_5O_2$	280	9,44 (1H, d, 4-H, 7,1); 4,58 (2H, d, CH_2—)	85
IX	$C_{22}H_{12}N_4O$	215	9,43 (1H, d, 4-H, 6,9)	62
X	$C_{18}H_{12}N_4O_2$	>300	10,25 (1H, s, 4-H); 8,96 (1H, d, 2-H, 6,9); 8,71 (1H, d, 1-H, 6,9); 4,71 (2H, q, CH_2—); 1,62 (3H, t, CH_3—)	35
XI	$C_{19}H_{10}N_4$	>300	9,28 (1H, d, 6-H, 8,8); 9,20 (1H, d, 1-H, 9,5); 7,87 (1H, d, 2-H, 9,5)	97
XII	$C_{19}H_9N_5O_2$	>300	9,66 (1H, d, 1-H, 9,5); 9,36 (1H, d, 6-H, 8,7); 8,60 (1H, d, 5-H, 8,7)	75
XIII	$C_{19}H_9N_4Br$	>300	9,44 (1H, s, 6-H); 9,33 (1H, d, 1-H, 9,2)	86
XVIII	$C_{14}H_9N_3$	160	9,32 (1H, d, 4-H, 7); 8,52 (1H, d, 1-H, 8); 8,07 (1H, s, 10-H); 7,40 (1H, t, 3-H)	70
XIX	$C_{18}H_{11}N_3$	258	9,45 (1H, d, 1-H, 9); 9,38 (1H, d, 6-H, 8,1); 8,76 (1H, s, 14-H)	73
XX	$C_{14}H_8BrN_3$	244	9,00 (1H, d, 4-H, 7,1); 6,86 (1H, t, 3-H)	82
XXI	$C_{18}H_{12}BrN_3$	293	9,33 (1H, d, 1-H, 9); 8,66 (1H, d, 6-H, 8,5); 7,08 (1H, d, 5-H, 8,5)	88
XXII	$C_{14}H_8N_4O_2$	>300	9,12 (1H, d, 4-H, 7,2)	42
XXIII	$C_{18}H_{12}N_4O_2$	>300	9,73 (1H, d, 1-H, 9)	74

*Crystallization solvents were as follows: XIX methanol–water (2:1), XXII nitromethane, X and XX propanol, VIII, XI-XIII, XXI and XXIII DMF, the rest toluene.

**The spectra of compounds III, XXI-XXIII were taken in DMSO-D_6, V in $CDCl_3$, the rest in CF_3COOD.



EXPERIMENTAL

The course of the reactions and the purity of the compounds prepared were monitored by TLC on Silufol UV-254 strips with 9:1 chloroform–methanol as eluent. IR spectra of KBr disks were recorded with a Pye Unicam SP3-300 spectrometer. ^{1}H NMR spectra were recorded with a Bruker WP-100 FT machine with TMS as internal standard. Characteristics of the compounds synthesized are given in Table 1.

C, H, and N elemental analysis results corresponded to calculated values.

12-Cyanoindolizino[2,3-*b*]quinoxaline (III). Compound I or II (1 g) was dissolved in dry pyridine (10 ml) and boiled for 2-3 h (TLC monitoring). Excess pyridine was then removed in vacuum, water (20 ml) was added to the residue and product III was filtered off.

2-Methyl-12-cyanoindolizino[2,3-*b*]quinoxaline IV. Compound I (1 g) was dissolved in dry 4-picoline (10 ml) and the solution boiled for 3 h. The product IV, obtained after work up as described for quinoxaline III, was dissolved in the minimum amount of chloroform, added to a silica gel column, and eluted with chloroform. The residue after evaporation of the chloroform was recrystallized.

2-R^2-12-cyanoindolizino[2,3-*b*]quinoxalines V-IX. Compound I (0.003 mole) was fused with a 5-7 fold excess of the corresponding 4-substituted pyridine at 130-150° C for 2-3 h. The cooled reaction mixture was treated with water (30 ml), the solid product filtered off and purified by column chromatography as described above for compound IV.

3-Carbethoxy-12-cyanoindolizino[2,3-*b*]quinoxaline X. A solution of compound I (0.71 g, 0.002 mole) in ethyl nicotinate (3 ml) was kept at 140°C for 3 h. Compound X was isolated and purified as described above for V-IX.

14-Cyanobenz[5,6]indolizino[2,3-*b*]quinoxaline XI. Compound I or II (0.002 mole) was fused with isoquinoline (2 g) at 140° C for 1 h. The cooled mixture was treated with water (10 ml) and product XI was filtered off.

Compounds XII and XIII were synthesized analogously.

Demonstration of the Formation of Acid XIV during the Reaction of I with Pyridine. Tosylacetonitrile XVI. Nitrile I (5.1 g, 0.03 mole) was boiled in pyridine (100 ml) for 2 h in an argon atmosphere. Pyridine was evaporated off in vacuum, the residue was treated with 20% sodium carbonate solution (20 ml), the residue was filtered off and washed with water (20 ml). The combined aqueous filtrate was evaporated to dryness in vacuum and the residue was dissolved in dimethylformamide (7 ml, free from dimethylamine), chloracetonitrile (0.03 mole) was added and the mixture was boiled for 1 h. The solvent was evaporated in vacuum and water (20 ml) was added to the residue. The solid product XVI was filtered off and recrystallized from isopropanol to give pure XVI (1.1 g, 21%), the physical constants of which coincided with literature values [8].

Demonstration of the Formation of Diethyl Phosphite in the Reaction of II with Isoquinoline. Diethyl *p*-Nitrophenylcarbamoylphosphonate XVII. Compound II (0.03 mol) was fused with isoquinoline (7 ml) at 120°C for 1.5 h in an argon atmosphere. The cooled reaction mixture was treated with hexane (3 x 50 ml) and the residue was filtered off. A solution of p-nitrophenylisocyanate (0.03 mole) in hexane (150 ml) containing 5 drops of dry triethylamine was added to the combined filtrates. The mixture was boiled for 3 h, cooled, filtered, the filtrate evaporated, and the residue chromatographed on a silica gel column (eluent 4:1 toluene–isopropanol) to give compound XVII (0.67 g, 8%), the physical constants of which coincided with literature data [9].

Indolizino[2,3-*b*]quinoxaline XVIII. A solution of compound III (1 g) in 75% sulfuric acid (10 ml) was boiled for 2 h (TLC monitoring). The reaction mixture was poured onto ice (200 g), the solution obtained was neutralized with aqueous ammonia, and the precipitated product XVIII was filtered off. Benzo[5,6]indolizino[2,3-*b*]quinoxaline XIX was synthesized analogously.

12-Bromoindolizino[2,3-*b*]quinoxaline XX. A solution of bromine (0.0035 mole) in pyridine (10 ml) was added dropwise with stirring over 1 h to a solution of XIX (0.66 g, 0.003 mole) in dry pyridine (15 ml). Stirring was continued for 3 h after which pyridine was removed in vacuum. Water (20 ml) was added to the residue and product XX was filtered off.

14-Bromobenz[5,6]indolizino[2,3-*b*]quinoxaline XXI was synthesized analogously.

12-Nitroindolizino[2,3-*b*]quinoxaline XXII. A solution of fuming nitric acid (0.085 ml) in acetic anhydride (10 ml) was added dropwise and with stirring at a temperature of 0-3° C to a solution of compound XXI (0.6 g, 0.002 mol) in acetic anhydride (20 ml). The solution was then stirred for a further 12 h while the temperature rose slowly to room temperature. Compound XXII was obtained after work up as described for compound XX.

14-Nitrobenz[5,6]indolizino[2,3-*b*]quinoxaline XXIII was prepared analogously.

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