PSEUDO-CROSS-CONJUGATED MESOMERIC BETAINES. 1. SYNTHESIS OF PSEUDO-CROSS-CONJUGATED MESOMERIC BETAINES FROM QUINOXALINE DERIVATIVES

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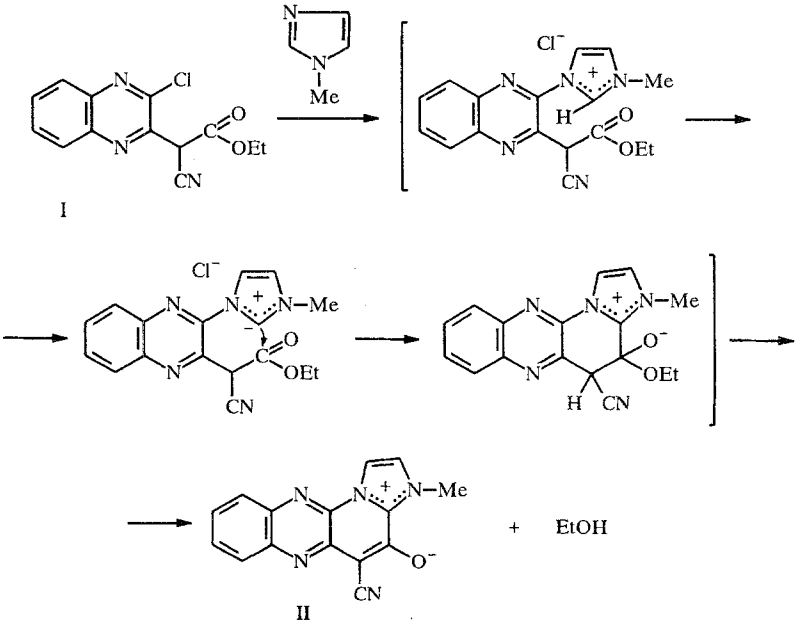
A new method for the synthesis of pseudo-cross-conjugated mesomeric betainic heterocyclic compounds with an angular nitrogen atom has been developed consisting in the reaction of 1,4-dielectrophile — α-carbethoxy-2-(3-chloro)quinoxalylacetonitrile with azoles. Experimental regularities have been studied and a reaction mechanism has been proposed including the stage of formation of an ylide from a quaternary azolium salt. A pseudo-cross-conjugated mesomeric betainic heterocyclic compound containing a thiazole ring compound has been synthesized for the first time.

The development of experimental approaches to new classes of organic compounds is one of the major problems in synthetic organic chemistry. One of these new classes is comprised of pseudo-cross-conjugated mesomeric betainic heterocyclic compounds [1]. The most interesting and promising synthetic approach to these very unusual compounds is based on the ability of quaternary azolium salts to form ylide structures in the presence of bases [2, 3]. This determines the activity of two neighboring atoms of the azolinium ring — $N_{(1)}$ and $C_{(2)}$ under electrophilic attack conditions. In particular, the authors of [4] studied the reaction of various 1-alkylazoles with 1,3-dielectrophiles — carbon suboxide, substituted malonyl chlorides, etc., which led to the annelation of 5-membered rings to the azolium ring. It was of interest to study the possibility of the synthesis of pseudo-cross-conjugated mesomeric betaines (PCCMB) containing more complex, including heterocyclic systems also. The possibility in principle of using α-carbethoxy-2-(3-chloro-2-quinoxalyl)acetonitrile (I) for this purpose as a 1,4-dielectrophile was shown by us in [5]. In the present work, the experimental results are described of the investigation of the reaction of compound I with 1-substituted (benz)imidazoles, 1-ethyl-1,2,4-triazole and also with thiazole and benzothiazole.



I

II

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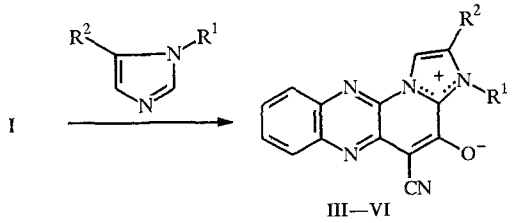
On fusing chloroquinoxalylacetonitrile I with an excess of 1-methylimidazole, a cyclic product II which did not contain chlorine was obtained in a high yield.

The 1-methylimidazolium quaternary salt, which obviously forms at the first stage of the reaction, is deprotonated in the presence of an excess of 1-methylimidazole with the formation of an ylide. The subsequent nucleophilic attack by a carbanion may proceed at alternative reaction centers — at the nitrile group carbon atom (as we have shown previously in [6, 7]) and at the ester group carbon atom. It was found that in this case the direction of the reaction is governed by the principle of "rigid molecules of acids and bases" [8]. A "rigid" Lewis base — a carbanion attacks primarily the more rigid Lewis acid — the carbon atom of the ethoxycarbonyl group. The elimination of an ethanol molecule at the concluding stage of the reaction eventually leads to 3-methyl-5-cyanoimidazolium [1′,2′:1,6]pyrido[2,3-b]quinoalin-4-olate (II).

The spectra characteristics of the compounds obtained confirm the proposed structural formula II. In the mass spectrum there is an intense molecular peak with m/z 275, while in the IR spectrum the absorption band of the nitrile group is located at 2205 cm^{-1}, which is characteristic for similar cyclic structures [9]. In the PMR spectrum recorded in CF_3COOD, a doublet of the 1-H proton (J = 1.6 Hz) is observed at 8.91 ppm, while the doublet of the 2-H proton spin-coupled with it — at 8.03 ppm. The considerable paramagnetic shift of the 1-H proton signal is explained by the descreening effect of the unshared electron pair of the 11-N nitrogen atom present in the direct vicinity of this proton. The presence of a weak field doublet corresponding to the 1-H proton in the PMR spectra thus serves as a confirmation of the formation of a cyclic immobilized in the space structure of II. The N-methyl group singlet in the PMR spectrum of compound II is observed at 4.65 ppm, while in the usual 1-methylimidazolium salts, the position of this singlet is in the 4.0 ppm region [10]. The more than 0.6 ppm shift to the weak field is explained by the entry of the methyl group into the region of the descreening action of the unshared pair of electrons of the neighboring $C-O^-$ group. The use of the Overhauser homonuclear effect in the experiment $\{N-CH_3\}$ results in a 10% increase in the intensity of the 2-H proton signal. Approximately the same effect is observed for the N-methyl group signals at {2-H}, which should have been expected considering the convergence of these protons in the space in structure II. In the ^{13}C NMR spectrum of compound II (solvent — CF_3COOD), the carbon atom signal of the $N-CH_3$ is present at 39.35 ppm, of the nitrile group at 139.97 ppm, and the $C_{(4)}$ carbon atom signal resonates in the weakest field at 166.67 ppm.

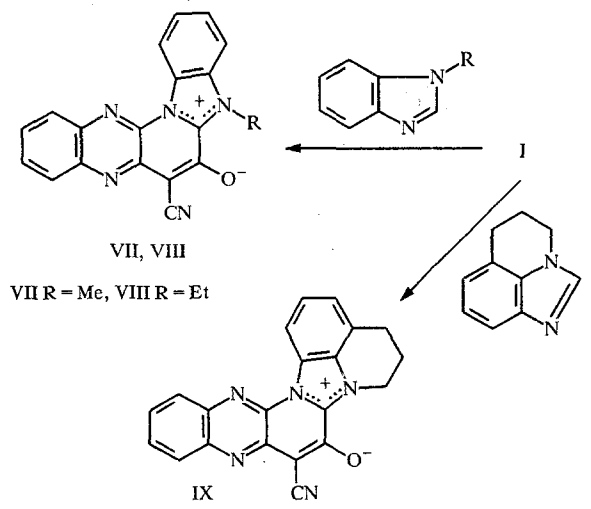
The reaction of compound I with 1-substituted imidazoles proceeds in a similar way. In all cases, the corresponding mesomeric betaines III-VI were isolated from the reaction mixture:



III—VI

III R^1 = Et, R^2 = H; IV R^1 =Me , R^2 = Cl ; V R^1=Ph, R^2 = H; VI R^1 = 4-$O_2NC_6H_4$, R^2 = H

1-Alkylbenzimidazoles and 5,6-dihydroimidazo(ij)quinoline on reaction with the chloro derivative I form the corresponding mesomeric betaines VII-IX:



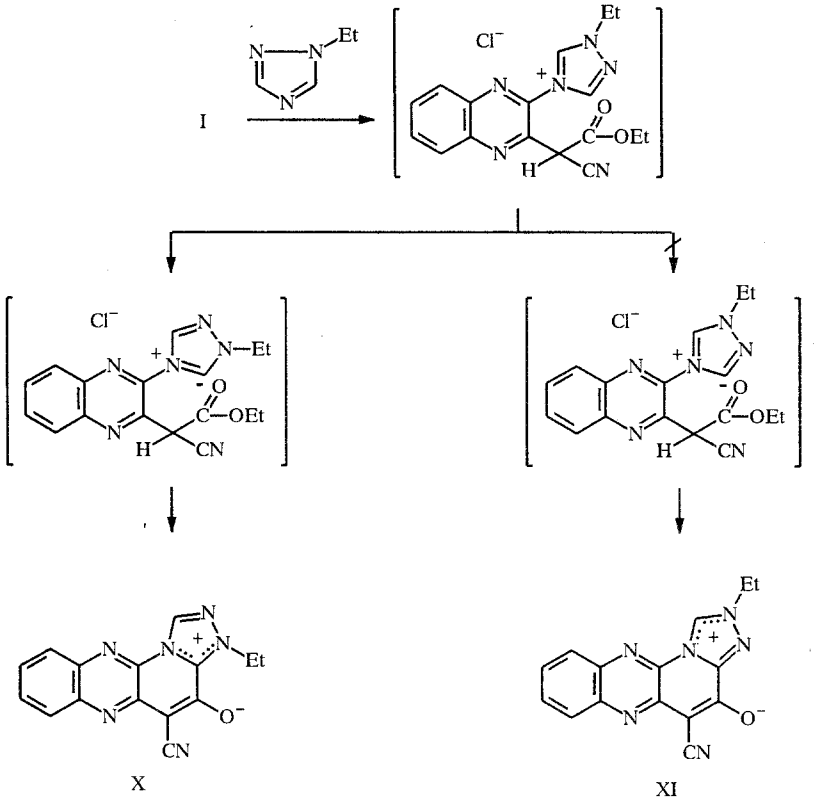
VII, VIII

VII R = Me, VIII R = Et

IX

The structure of the compounds formed (taking into account their spectral characteristics and the cited proofs of the betaine structure II, Table 1) does not raise any doubts.

While the reaction with (benz) imidazoles excludes the possibility of formation of isomeric cyclic products, from 1-ethyl-1,2,4-triazolium quaternary salt two different ylides can be formed, and correspondingly two isomeric cyclic products X and XI:

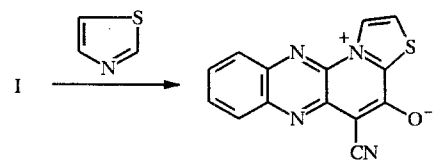


X XI

According to the TLC data only one end product is formed. We made the selection of the alternative structures on the basis of the PMR spectrum. Thus, the quartet of the $N-CH_2$ is located at 5.07 ppm (solvent — DMSO-D_6). In the PMR spectrum of 1-ethyl-1,2,4-triazole recorded in the deuterotrifluoroacetic acid (i.e., actually in the spectrum of the triazolium salt), this quartet is located at 4.61 ppm. Such a considerable paramagnetic shift of this signal can be explained by the entry of the methylene protons into the descreening cone of the unshared electron pair of the $C-O^-$ group, which is realizable only in structure X. For the molecule of XI this shift is impossible. On carrying out the experiment on the homonuclear Overhauser effect {1-H}, the intensity of the methylene group quartet does not increases, which also confirms the proposed structural formula of X.

In the structure of all the PCCMB synthesized until now, only the nitrogen containing heterocyclic compounds acted as the cationic fragment. Attempts to synthesize pseudo-cross-conjugated mesomeric betaines from thiazole or benzothiazole were unsuccessful [4]. The introduction of sulfur-containing heterocycles into this reaction was of special interest considering the exclusive role of the thiazolium ylides in thiamine metabolism [11].

We found that on boiling the starting compound I in an excess of thiazole, 5-cyanoquinoxalino[2′,3′:5,6]pyrido[2,1-b]thiazolium-4-olate (XII) is formed in a good yield. The reaction mechanism is clearly analogous to that shown above for the reaction with 1-methylimidazole:



XII

The structure of the synthesized mesomeric betaine XII was confirmed by spectral analysis (see Table 1), and the composition by elemental analysis.

TABLE 1. Spectral Properties of Compounds II-XIII*

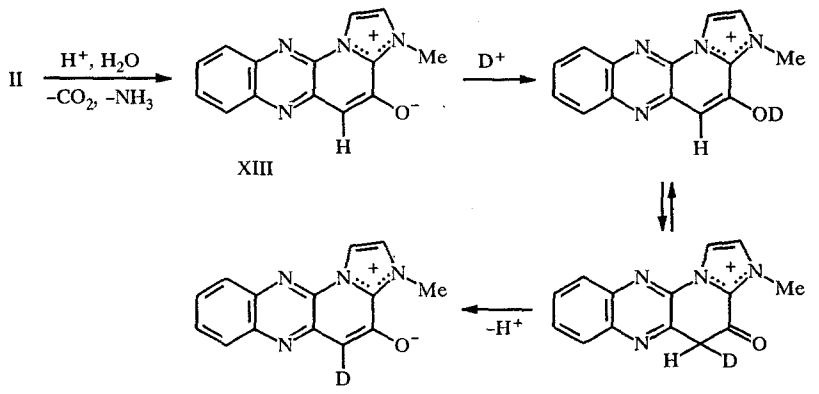
Compound	Empirical formula	IR spectrum ν, cm⁻¹	PMR spectrum, δ, ppm (J, Hz)	Yield, %
II	$C_{15}H_9N_5O$	2205	4,65 (3H, s, CH_3); 8,03 (1H,d , 1,6, 2-H); 8,05...8,53 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,91 (1H,d, 1,6, 1-H)	90
III	$C_{16}H_{11}N_5O$	2207	1,79 (3H, t, CH_3); 5,14 (2H, q, CH_2); 8,12 (1H, d 1, 7, 2-H); 8,15...8,57 (4H, m, 7-H, 8-H, 9-H, 10-H)	95
IV	$C_{15}H_8ClN_5O$	2202	4,61 (3H, s, CH_3); 8,03...8,52 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,93 (1H, s, 1-H)	78
V	$C_{20}H_{11}N_5O$	2214	7,65...7,85 (5H, m, C_6H_5); 8,11 (1H, d; 2,0, 2-H); 8,13....8,61 (4H, m 7-H, 8-H, 9-H, 10-H); 9,09 (1H, d, 2,0, 1-H)	81
VI	$C_{20}H_{10}N_6O_3$	2203	7,98 (2H,d, 8,0, Hα and Hβ); 8,25 (1H,d, 2,0, 2-H); 8,27...8,54 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,61 (2H, d, 8,0, Hα and Hβ); 9,17 (1H,d, 2,0, 1-H)	88
VII	$C_{19}H_{11}N_5O$	2209	4,89 (3H, s, CH_3); 8,15...8,67 (4H, m, 7-H, 8-H, 9-H, 10-H)	81
VIII	$C_{20}H_{13}N_5O$	2212	1,85 (3H, t, CH_3); 5,44 (2H, q , CH_2); 8,16...8,57 (7H, m , 2-H, 3-H, 4-H, 9-H, 10-H, 11-H, 12-H)	71
IX	$C_{21}H_{13}N_5O$	2206	2,64 (2H, m, α-CH_2); 3,35 (2H, q , β-CH_2); 5,35 (2H, m , γ-CH_2); 7,83...8,65 (4H, m, 9-H, 10-H, 11-H, 12-H)	65
X	$C_{14}H_8N_6O$	2205	1,56 (3H, q , CH_3); 5,07 (2H, q , CH_2); 7,82...8,11 (4H, m, 7-H, 8-H, 9-H, 10-H); 10,46 (1H, s, 1-H)	79
XII	$C_{14}H_6N_4OS$	2210	8,18...8,62 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,77 (1H, d, 3,7, 2-H); 9,82 (1H, d, 3,7, 1-H)	52
XIII	$C_{14}H_{10}N_4O$	—	4,67 (3H, s , CH_3); 8,13 (1H, d , 1,8, 2-H); 8,29 (1H, s, 5-H); 8,32...8,73 (4H, m , 7-H, 8-H, 9-H, 10-H)	87

*Compounds I, II were recrystallized from pyridine, the remaining compounds — from DMFA.

**The melting points of all the synthesized compounds are above 300°C.

We did not succeed in obtaining the corresponding PCCMB from benzothiazole. We believe that the reason for the passivity of benzothiazole in the reaction studied was the reduced electron density on the nitrogen atom in the benzothiazole molecule in comparison with thiazole, and the more so, with diazoles, and also probably the steric hindrances produces by the 7-H hydrogen atom at the stage of formation of the quaternary benzothiazolium salt.

On boiling compound II in 70% sulfuric acid, hydrolysis of the nitrile group takes place, and the subsequent decarboxylation leads to product XIII:



In the PMR spectrum of the betaine XIII obtained recorded in CF_3COOD, there is a singlet of the 5-H proton at 8.29 ppm. The remarkable fact is the deutero exchange of this proton — in the spectrum of this sample recorded after 120 h, this singlet disappears. The possible mechanism of deuteroexchange is given above.

EXPERIMENTAL

The mass spectra of the synthesized compounds were recorded on an MX 1331 spectrometer. The IR spectra were recorded on a Pye Unicam SP3-300 spectrophotometer in KBr tablets. The PMR and ^{13}C NMR spectra were obtained on a Bruker WP-100 Fourier type spectrometer using TMS as an internal standard. The course of the reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates, using a chloroform–methanol mixture (9:1) as eluent.

The elemental analysis data for C, H, N, and S corresponded to the values calculated according to the empirical formulas.

3-Methyl-5-cyanoimidazolium[1′,2′:1,6]pyrido[2,3-b]quinoxalin-4-olate (II). A 0.9-g portion (0.003 mole) of compound I was fused with 0.03 mole of 1-methylimidazole at 140-150°C for 3 h. The reaction mixture was cooled, 10 ml of cold 2-propanol was added, and the precipitate obtained was filtered and crystallized.

Compounds III-X were obtained in a similar way.

5-Cyanoquinoxalino[2′,3′:5,6]pyrido[2,1-b]thiazolium-4-olate (XII). A 0.9-g portion (0.003 mole) of compound I was boiled in 3 ml of thiazole for 6 h. The excess of thiazole was evaporated off in vacuo, 30 ml of water was added to the residue, the precipitate was filtered, dried and recrystallized from DMFA.

3-Methylimidazolium[1′,2′:1,6]pyrido[2,3-b]quinoxalin-4-olate (XIII). A 1-g portion of compound II was boiled in 10 ml of a 70% sulfuric acid for 4 h. The reaction mixture was poured onto 50 g of ice, neutralized with an ammonium hydroxide solution, and the precipitate that separated out was filtered off and recrystallized.

The physical and spectral characteristics of the synthesized compounds are given in Table 1.

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