8-Oxo-2,7,9-trimethylimidazo[4.5-c]imidazo[1.2-a]pyridine-3-azo-4'-benzoic Acid (XI). A solution of 0.12 g Na_2CO_3 in 5 ml of water was treated with 0.28 g (2.04 mmoles) of p-aminobenzoic acid, 0.15 g (2.17 mmoles) $NaNO_2$, and 2 ml of water. The solution was then poured onto a mixture of 2.5 g ice and 0.5 ml 36% HCl and an alcoholic solution of 0.43 g (2.00 mmoles) of compound IVb was added. After 15 min the resulting bright red precipitate was filtered, washed with water and acetone, and dried. Yield 0.50 g (69%), mp 348-350°C (from DMF). Found: C 58.8; H 4.8; N 23.0%. $C_{18}H_{16}N_6O_3$. Calculated: C 59.3; H 4.4; N 23.1%.

LITERATURE CITED

1. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soedin., No. 1, 97 (1986).
2. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soedin., No. 1, 138 (1973).
3. I. A. Svertilova and Yu. M. Yutilov, USSR Inventor's Cert. No. 521,277; Byull. Izobr., No. 26, 80 (1976).
4. Yu. M. Yutilov, K. M. Khabarov, and I. A. Svertilova, VINITI, No. 4182-79, December 10, 1979.
5. W. W. Paudler and H. L. Blewitt, J. Org. Chem., 31, 1295 (1966).
6. W. W. Paudler and H. L. Blewitt, J. Org. Chem., 30, 4081 (1965).

EFFECTS OF ACIDS ON ORIENTATION IN THE REACTION OF 5-FORMYL-4-(1-PYRIDINO)AZOLE 2-OXIDES WITH AROMATIC AMINES

R. O. Kochkanyan, A. N. Zaritovskii, A. B. Kruglova, and N. A. Klyuev

UDC 547.821.3'775'556.9'551:543.422

Azole betaines containing vicinal formyl and pyridinium groups react with aromatic amines to give, when protonated by weak or strong acids, azolidine-2,4-dione-5-aldehyde azomethines (I) or 4-aryliminoazolidin-2-ones (II), respectively. Compound (I) is formed by the intramolecular migration of the oxygen in the 4-position of the azole, and (II) by decarbonylation of the original betaine. The orientation in the reaction of dicentric nucleophiles (hydrazines and o-phenylenediamine) is independent of the extent of protonation, giving betaine hydrazones and azolo[4,5-b]benzodiazepines, respectively. The PMR mass spectra of the products are discussed.

The orientation of nucleophilic substitution in betaines, including nucleotides, displays special features as a result of the presence of charged centers, and it has received little attention. Studies in this area could lead to an understanding of the processes occurring in point mutations resulting from replacement of a pair of heterocyclic bases in nucleotides.

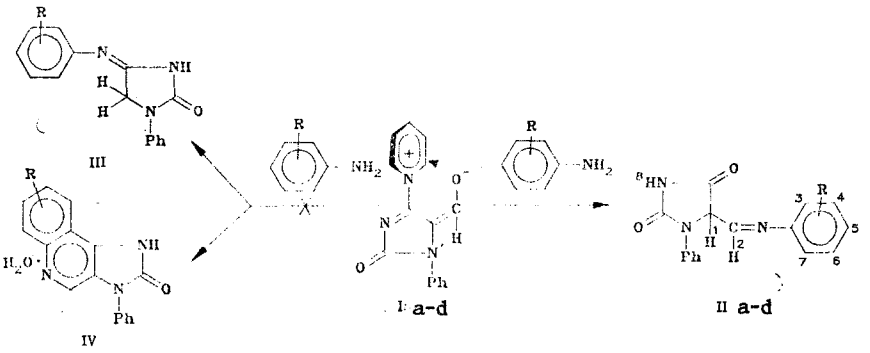
Azole betainealdehydes (I) may be regarded as systems with a masked electrophilic function resulting from the participation of the formyl group in delocalization of the negative charge. This feature of betaines can, depending on the reaction medium, have a marked effect on the orientation of nucleo philic substitution reactions, as a result of the selective solvation of the solvent at the cationoid or anionoid moieties. We have previously reported that mineral acid salts of betaines react with tertiary nitrogeneous bases [1] and triarylphosphines [2] with replacement of one cation by another to give new betaine salts, and when the betaines themselves react with ammonia or hydrogen sulfide tricyclic systems are obtained. We have not examined the reaction of betaines with nitrogeneous bases containing a primary

Institute of Physical Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk, 340114.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 233-238, February, 1986. Original article submitted December 12, 1984; revision submitted March 19, 1985.

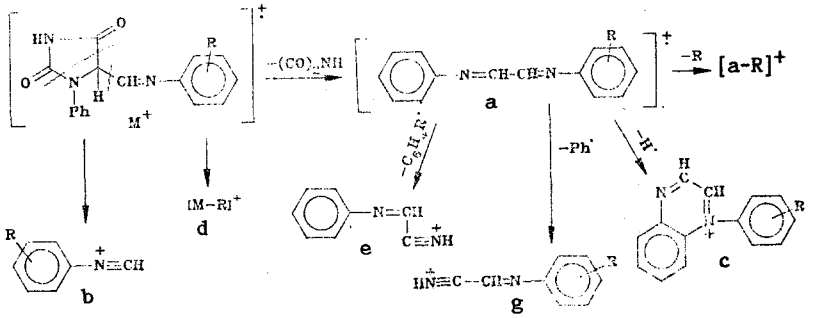
0009-3122/86/2202-0186$12.50

amino group, and the influence of the structure, the amine, and the reaction medium on the orientation of the substitution.



The betaines (I) react with anils in acetic acid when the molar ratio of reactants is 1:1 to give azolidine-2,4-dione-5-aldehyde azomethines (II). Bearing in mind the alternative possibility of the formation of the isomeric 4-aryliminoazolidin-2-ones (III) by direct substitution of the cation in the 4-position of the azole ring or of azolo[4,5-c]quinolines (IV), hydrated with one molecule of water, we examined the mass, PMR, and IR spectra of the products.

The molecular masses of the compounds (II) (R=H, p-NO_2, m-CH_3, and p-I) found by mass spectrometry were in agreement with the calculated values for each of the azolidine-2,4-dione-5-aldehyde azomethines. The mode of fragmentation of the molecular ion (M^+) under electron impact was fully in accordance with the proposed structures for the azomethines (II), and is well described by the following scheme:



The PMR spectra also fully confirmed the structures of (II) (Table 1).

Let us consider the PMR spectrum of (IIe) (R = p-NO_2) as an example. The broad singlet at low field with δ 11.55 ppm is characteristic of the amino group. The protons of the N-phenyl substituent are poorly resolved (multiplet at δ 7.45-7.65 ppm). The 3,7 and 4,6 protons of the p-nitrophenyl substituent give rise to two doublets at 7.35 and 8.17 ppm, J = 10 Hz. Protons 1-H and 2-H form another system of signals appearing as two doublets with δ 7.13 and 9.85 ppm, with J = 12 Hz. The integral plot gives the ratios of these signals as 1:5:2:2:1:1, confirming the correctness of the assignment of the signals and of the structure as the azomethine (II).

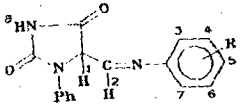
The spectra of (Ia-d) (Table 1) show superposition of the signal for the 1-H proton and the signals for the protons of the substituted ring on the resonance for the N-unsubstituted benzene ring protons to give complex multiplets.

The IR spectra of (II) show absorption for two carbonyl groups and the associated amino-group which, in conjunction with the results given above, unambiguously establishes their structure as azolidine-2,4-dione-5-aldehyde azomethines.

In the reaction of the betaines (I) with o-aminobenzenesulfonic (orthanilic) acid in acetic acid, elimination of the sulfo group occurs to give compounds which are identical with the products of the condensation of the betaines with aniline, as shown by the absence of depression in the mixed melting point.

When the reaction of the betaines (I) with orthanilic acid was carried out in alcohol or aqueous alcohol, a product was obtained which did not contain a sulfo group, and had empirical

TABLE 1. PMR Spectral Data (in DMSO-D_6) for Imidazolidine-2,4-dione-5-aldehyde Azomethines (IIa-e)



Compound	R	Chemical shifts, δ, ppm (J, Hz)									
		8-H	2-H	H_R	C_6H_5	1-H	3-H	7-H	4-H	6-H	5-H
Ia	H	11,36, s (J=12)	9,32,d	—			6,88—7,64, m				—
Ib	4-I	11,05, s (J=12)	9,06,d	—			6,6—7,68, m				—
Ic	4-CH_3	11,09, s (J=12)	9,25,d	2,06, s			6,8—7,62, m				—
Id	2-COOH	11,55, s	9,06,d (J=12)	10,88, s			6,6—8,13, m				—
Ie	4-NO_2	11,55, s	9,85 (J=12)		7,45—7,65, m	7,13, d (J=12)	7,35, d (J=10)			8,17, d (J=10)	

formula $C_{15}H_{13}N_3O$. Its PMR spectrum showed a multiplet at 6.14-7.10 ppm, and two singlets at 4.71 and 10.31 ppm, which from their integral intensities (10:2:1) could be due to the resonance of the protons of two phenyl groups, a methylene, and an amino group. This was confirmed by their IR spectra, which showed absorption for one carbonyl group at 1680 cm^{-1}, and for N–H and C=N at 3280 and 1630 cm^{-1}, respectively.

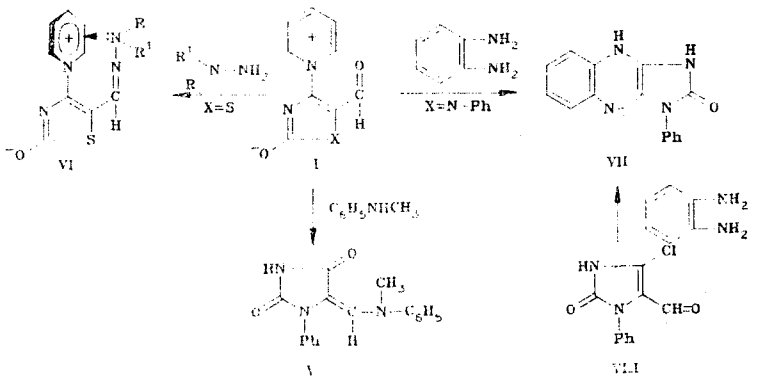
We therefore conclude that in alcoholic or aqueous alcoholic solution there is a change in the orientation of the reaction of the betaines (I) with amines, the reaction involving fission of a C–C bond* and cleavage of the formyl group with simultaneous nucleophilic replacement of the pyridine by the arylimino group to give 1-phenyl-4-phenyliminoimidazolidin-2-one (III), which was synthesized directly by the route shown below.

Elimination of the sulfo group under these relatively mild conditions is, in accordance with literature reports [6], due in our opinion to the assistance of the betaine in the transfer of a proton from the amino group of orthanilic acid to the carbon atom directly bonded to the sulfonyl group. When an excess of the aromatic amine is used, the orientation of the reaction changes the orientation of the nucleophilic substitution. For example, when the betaines (I) react with a threefold excess of aniline in acetic acid, instead of the azomethines (II), (III) are obtained.

The stability to hydrolysis of the internuclear bond between the pyridine and imidazole rings, which is unaffected by heating the betaines in water or aqueous acetic or mineral acids, together with the high rate of formation of the azomethines (II), lead to the conclusion that replacement of pyridine by the oxygen atom when the reaction is carried out in acetic acid, as is the case with triphenylphosphine [2], is a intramolecular process. This is quite feasible when it is recalled that the oxygen atom of the formyl group in the betaines is oriented with respect to the pyridinium cation as a result of electrostatic interaction to give an intramolecular charge-transfer complex (CTC), such as we have reported previously [7]. On this basis, attack of the amine on the carbonyl group enhances this interaction and the nucleophilic replacement of pyridine by the oxygen atom. This is also supported by the fact that the color which develops in the reaction is not due to the intermediate formation of 4-pyridino-5-formylazole-2-oxide azomethines, since a similar effect is seen in the reaction of the betaines with N-methylaniline, leading to the formation of 5-(N-methyl-N-phenylaminomethylidene)azolidine-2,4-dione (V).

The above conclusions are supported by the observation that the reaction of betaines with dicentric nucleophiles such as hydrazine and o-phenylenediamine, the two nucleophilic centers of which compete with the oxygen atom in the formation of CTC with the pyridinium cation in the transition state, lead to different products. For example, in the reaction of the betaines (I) with α,α-methylphenylhydrazine, either in acetic acid or in alcoholic solution, the 5-formyl-4-(1-pyridino)azole-2-oxide hydrazones (VI) are formed exclusively, i.e., when there is no interaction between the betaine and the aromatic amine, no nucleophilic substitution by oxygen is observed.

A similar situation occurs in the reactions of betaines with o-phenylenediamine in acetic acid to give 1H,10H-2-oxazolo[4,5-b]-1,5-benzdiazepines (VII). The structures of (V-VII) were confirmed by their elemental analyses, IR, PMR, and mass spectra, and by direct synthesis.

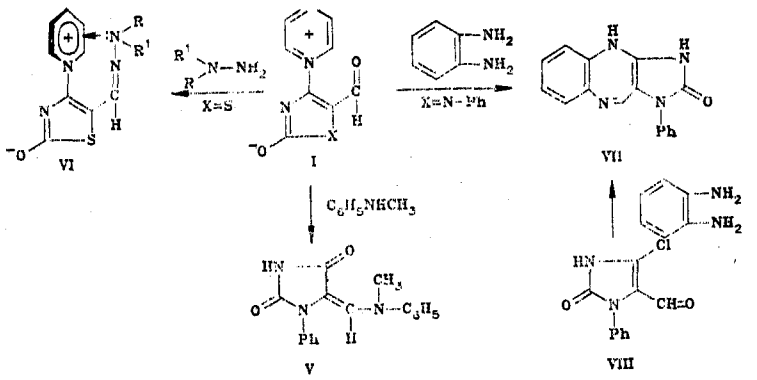


*Fission of a C–C bond is typical of betaines or ylid systems in alcoholic and aprotic media, but has not been observed in acetic acid [3-5].

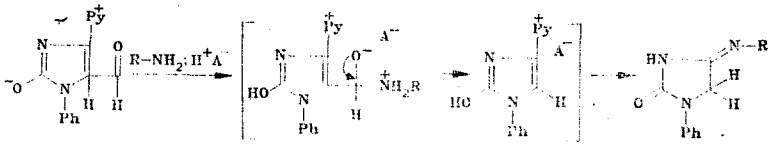
It may be assumed on the basis of these considerations that when an excess of aromatic amine is used, and the reaction is carried out in acetic acid, by using competitive solvation of the base by the pyridinium cation it is possible to achieve the result obtained in the reaction of betaines with dicentric nucleophiles. This should result in reorientation of the course of the reaction to give, instead of the azomethines (II), the 4-aryliminoazo-2-azolidones (III), and this is found experimentally.

Returning to the examination of the reaction of betaines with anilines in acetic acid, the following explanation of the reaction mechanism is proposed. The betaines (I) in acetic acid are weakly protonated, the reaction merely amounting to solvation of the acid at the anionic moiety of the betaine as a result of the formation of hydrogen bonds, since they crystallize from acetic acid as the bases.

Consequently, the first step is attack of the amine on the aldehyde group of the betaine. The reaction then proceeds by a concerted mechanism, with the acetic acid facilitating the transfer of a proton from the ammonium group in the transition state on carbon $C_{(5)}$ of the azole ring, thus facilitating the intramolecular replacement of pyridine by the oxygen of the formyl group, as observed in the formation of four-membered rings in enamines



This mechanism is supported by the fact that addition of a mineral acid (HCl or H_2SO_4) or monochloroacetic acid (which are capable of protonating the betaine) to the reaction mixture results in the formation of (III) rather than the azomethines (II), i.e., in the presence of mineral acids, the relatively stable N-protonated form is produced, in which transformation of carbon $C_{(5)}$ of the azole ring from the sp^2- to the sp^3-hybridized state is rendered difficult. This makes the intramolecular replacement of pyridine by the oxygen atom less energetically favorable, and assists the elimination of formanilide:



EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument, in vaseline oil, and mass spectra on a Varian MAT-311 spectrometer, ionizing electron energy 70 eV. The samples were introduced directly into the ion source of the mass spectrometer at a temperature of 100-150°C. PMR spectra were obtained on a Varian XL-100, operating frequency 100 MHz, at a temperature of 30°C, solvent deuterodimethyl sulfoxide, internal standard HMDS. UV spectra were obtained on an SF-4 instrument, in methanol.

Azolidine-2,4-dione-5-aldehyde Azomethines (II). A mixture of 10 mmoles of the betaine (Ia-d) and 10 mmoles of the aromatic amine was boiled in acetic acid for 20-30 min. The mixture was then cooled, and the yellow crystalline powder which separated was filtered off. (IIa) (R = H), yield 76%, mp 257°C (from DMF). Found: C 68.8; H 4.8; N 15.3%. $C_{16}H_{13}N_3O_2$. Calculated: C 68.8; H 4.6; N 15.1%. (IIb) (R = p-I), yield 63%, mp 265°C (from dioxane). Found: C 47.6; H 2.8; I 31.1; N 10.4%. $C_{16}H_{12}IN_3O_2$. Calculated: C 47.4; H 2.9; I 31.3; N 10.4%. (IIc), yield 74%, mp 242°C (from toluene). Found: C 69.9; H 5.6; N 14.5%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.1; N 14.3%. (IId), yield 71%, mp 304-305°C (from nitrobenzene). Found: C 63.5; H 4.2; N 13.2%: $C_{17}H_{13}N_3O_4$. Calculated: C 63.2; H 4.0; N 13.0%.

(IIe), yield 75%, mp 281°C (from dioxane). Found: C 59.3; H 3.8; N 17.4%. $C_{16}H_{12}N_4O_4$. Calculated: C 59.2; H 3.7; N 17.3%.

Reaction of Betaine (Ia) with Orthanilic Acid. The betaine (Ia) (2.65 g, 10 mmoles) was dissolved in 10 ml of acetic acid, and 1.73 g (10 mmoles) of orthanilic acid was added. The mixture was boiled for 40-50 min, and the bright yellow solid which separated on cooling was isolated to give 1.61 g (58%) of product, mp 257°C (from DMF). Melting point of a sample mixed with azomethine (IIa), 257°C.

1-Phenyl-4-phenyliminoimidazolidin-2-one (IIIa). A. The azomethine (Ia) (1.32 g, 5 mmoles) was dissolved in a 1:1 mixture of methanol and water, and 0.86 g (5 mmoles) of orthanilic acid added. The mixture was boiled for 50 min, and the solid which separated was filtered off and washed with methanol to give 0.69 g (55%) of product, mp 295-296°C (sub., DMF). Found: C 71.8; H 5.3; N 16.9%. $C_{15}H_{13}N_3O$. Calculated: C 71.7; H 5.2; N 16.7%.

B. 1-Phenyl-5-formyl-4-(1-pyridino)imidazole 2-oxide (Ia) (2.65 g, 10 mmoles) was dissolved in acetic acid, and boiled with a threefold excess of aniline for 5-10 min. The finely crystalline white solid which separated was filtered off and washed with methanol to give 2.2 g (90%) of product, mp 295-296°C (sub., DMF). Melting point of sample mixed with (IIIa), 295-296°C (sub.).

C. Equimolar amounts of 4-thiohydantoin and aniline hydrochloride were boiled in methanol for 15-20 min. The solid which separated on cooling was filtered off and washed with methanol to give 79% of product, mp 295-296°C (sub., DMF). Melting point of a sample mixed with (IIIa) 295-296°C (sub.).

1-Phenyl-5-(N-methyl- or N-phenylaminomethylidene)imidazolidine-2,4-dione (V). The betaine (2.65 g, 10 mmoles) was dissolved in acetic acid, and 1.1 ml (10 mmoles) of N-methylaniline added. The mixture was boiled for 20-25 min, and cooled to give a bright yellow solid, yield 1.77 g (61%), mp 283°C (DMF). IR spectrum: 1680 (C=O), 1720 (C=O), 3280 cm^{-1} (N-H). Found: C 69.4; H 5.2; N 14.3%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.1; N 14.3%.

2-Formyl-4-(1-pyridino)thiazole 2-Oxide α,α-Methylphenylhydrazone (VI). A mixture of 2.06 g (10 mmoles) of 5-formyl-4-(1-pyridino)thiazole 2-oxide and 1.22 g (10 mmoles) of α,α-methylphenylhydrazine in 10 ml of acetic acid was heated for 5-10 min at 60°C. The dark red needles which separated were filtered off to give 2.08 g (67%) of product, mp 230°C (DMF). PMR spectrum (DMSO-D_6): 3.35 (3H, s, CH_3), 7.27 (5H, m, C_6H_5), 7.45 (1H, s, CH=N), 9.40 (2H, d, $C_5H_5\overset{+}{N}$), 8.75 (1H, t, $C_5H_5\overset{+}{N}$), 8.30 ppm (2H, t, $C_5H_5\overset{+}{N}$). Mass spectrum, m/z (peaks ≥ 3% of maximum): 50 (22), 51 (41), 52 (32), 56 (8), 60 (26), 63 (11), 64 (10), 65 (21), 67 (9), 70 (12), 77 (10), 78 (55), 79 (100), 80 (50), 91 (9), 92 (16), 93 (14), 104 (18), 105 (44), 106 (99), 107 (69), 108 (8), 133 (16), 134 (5), 144 (41), 158 (18), 159 (17), 177 (12), 204 (48), 205 (12), 250 (34), 251 (7), 310 (M^+, 4). UV spectrum (in methanol), λ_{max} (log ε): 260 (4.1), 350 (4.5), 500 nm (3.5). Found: C 62.0; H 3.7; N 18.1; S 10.2%. $C_{16}H_{14}N_4OS$. Calculated: C 61.9; H 3.9; N 18.1; S 10.3%.

1H,10H-2-Oxoimidazo[4,5-b]-1,5-benzodiazepine (VII). A. A mixture of 2.65 g (10 mmoles) of the betaine (I) and 1.08 g (10 mmoles) of o-phenylenediamine in methanol with the addition of a catalytic amount of hydrochloric acid was boiled for 20-30 min. The deep blue crystalline solid which separated was filtered off and washed with methanol to give 2.2 g (80%) of product, mp 340°C (DMF). IR spectrum: 1630 (C=N), 1720 (C=O), 3260 cm^{-1} (N-H). Found: C 69.7; H 4.4; N 20.2%. $C_{16}H_{12}N_4O$. Calculated: C 69.5; H 4.3; N 20.2%.

B. A mixture of 8.9 g (40 mmoles) of 1-phenyl-4-chloro-5-formylimidazolin-2-one (VIII) and 0.48 g (60 mmoles) of o-phenylenediamine was boiled in 30 ml of ethanol for 20 min. The solid which separated was filtered off and washed with ethanol to give 6.7 g (61%) of product, mp 340°C (DMF). Melting point of a sample mixed with material obtained as in method A, 340°C.

LITERATURE CITED

1. R. O. Kochkanyan, N. V. Spitsyn, and S. N. Baranov, Khim. Geterotsikl. Soedin., No. 2, 272 (1983).
2. R. O. Kochkanyan, S. S. Lukanyuk, T. A. Dmitruk, and N. G. Korzenevskaya, Zh. Obshch. Khim., 55, 155 (1985).
3. V. S. Garkusha-Bozhko, R. O. Kochkanyan, O. P. Shvaika, and S. N. Baranov, Khim. Geterotsikl. Soedin., No. 3, 372 (1976).

4. H. Wittman, P. Beutel, and E. Ziegler, Monatsh. Chem., 100, 1624 (1969).
5. H. Wittman, P. Beutel, and E. Ziegler, Monatsh. Chem., 100, 1619 (1969).
6. É. E. Gilbert, The Sulfonation of Organic Compounds [Russian translation], Khimiya, Moscow (1969), p. 372.
7. R. O. Kochkanyan, A. N. Zaritovskii, N. A. Klyuev, B. M. Zolotarev, and S. N. Baranov, Khim. Geterotsikl. Soedin., No. 2, 255 (1978).

REACTION OF PYRIDO[1,2-a]BENZIMIDAZOLE AND TETRAHYDROPYRIDO[1,2-a]BENZIMIDAZOLE WITH ACETYLENEDICARBOXYLIC ESTER

N. S. Prostakov, A. V. Varlamov, I. V. Shendrik, A. P. Krapivko, and N. I. Golovtsov

UDC 547.836.3;542.953:543.422'25

Previously unknown polynuclear condensed systems with bridgehead nitrogen atoms have been obtained by treating acetylenedicarboxylic ester with pyrido[1,2-a]-benzimidazole and tetrahydropyrido[1,2-a]benzimidazole.

We have developed a convenient method for the synthesis of pyrido[1,2-a]benzimidazole (I) [1] allowing us to expand studies of its properties. With the aim of obtaining new polynuclear condensed heterocyclic compounds with bridging nitrogen atoms we have turned to reactions of pyridobenzimidazole (I) (and the derived tetrahydropyrido[1,2-a]benzimidazole) with acetylenedicarboxylic ester (ADCE).

Both of these compounds can be regarded as 1,2-disubstituted benzimidazoles. Thus their reaction with ADCE can be the same as benzimidazole [2] but with the formation of more complex heterocycles.

The reaction of pyrido[1,2-a]benzimidazole (I) with ADCE in benzene takes place quantitatively at 20°C. In addition, adducts are formed with two and three molecules of ADCE and are separated using column chromatography. The first of these is red, crystalline material

TABLE 1. PMR Spectral Parameters for II, IV-VI

Compound*	Chemical shifts,† δ, ppm										CH_3O	J, Hz
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	10-H	11-H		
II	6,65	7,50	7,08	7,41	9,12	8,02	8,56	7,80	—	—	3,26; 3,37; 3,488; 3,492	(1—2) 7,5; (1—3) 1,2; (1—4) 0,4; (2—3) 7,5; (2—4) 1,2; (3—4) 7,5; (5—6) 6,0; (5—7) 1,4; (5—8) 0,7; (6—7) 7,8; (6—8) 1,5; (7—8) 8,0
V	6,69	7,03	7,03	6,69	3,67	2,01	1,53	1,53	—	—	3,71; 3,73; 3,78; 4,02	—
VI	6,90	7,10	7,10	6,90	3,85	1,98	2,45	—	5,47	5,91	3,49; 3,65; 3,69; 3,82	$^3J_{10,11}=5$
IV	7,69	7,23	7,21	7,28	4,07	2,11	2,02	3,09	—	—		

*For IV-VI, the chemical shifts for the methylene protons are assigned as the center of the corresponding multiplets.
†Benzene ring protons 1H-4H, nitrogen ring protons 5H-8H, 10H, 11H.

P. Lumumba People's Friendship University, Moscow, 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 239-241, February, 1986. Original article submitted October 29, 1984; revision submitted March 26, 1985.

 0009-3122/86/2202-0192$12.50