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CONDENSED IMIDAZO-1,2,4-AZINES.

11.* THE REACTION OF 2,6-DIPHENYLIMIDAZO[1,2-b]-1,2,4-TRIAZINE WITH FORMALDEHYDE

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UDC 543.51: 547'837'785

The structure of four main products contained in the reaction mixture obtained in the oxymethylation of 2,6-diphenylimidazo[1,2-b]-1,2,4-triazine was established by the method of chromato-mass spectrometry, with the enlistment of PMR spectroscopy.

We have shown [2] that 2,3,6-trisubstituted imidazo[1,2-b]-1,2,4-triazine readily enters into an electrophilic substitution reaction with the formation of substitution products at the $C_{(7)}$ atom of the bicycle.

In this work we consider the oxymethylation of 2,6-diphenylimidazo[1,2-b]-1,2,4-triazine (I) [3], which has two free positions in the ring (at the $C_{(3)}$ and $C_{(7)}$ atoms), which suggests the possibility of electrophilic substitution not only at the imidazole ring but also at the triazine fragment of the molecule.

*For communication 10, see [1].

Kherson Industrial Institute, Kherson 325008; L. Ya. Karpov Physicochemical Scientific Research Institute, Moscow 107120. Translated from Khimiya Geterostiklicheskikh Soedinenii, No. 11, pp. 1565-1568, November, 1984. Original article submitted February 15, 1984.

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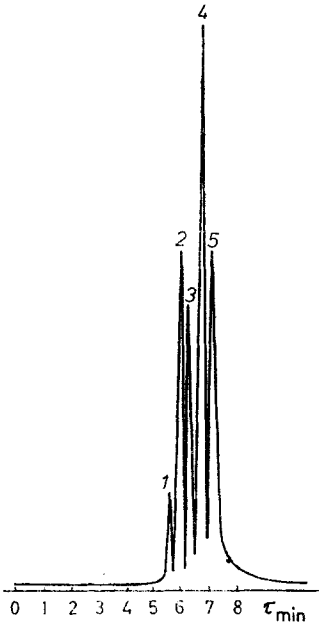


Fig. 1. Chromatogram of the oxymethylation product of 2,6-diphenylimidazo[1,2-b]-1,2,4-triazine [1-5) numbers of the chromatographic peaks].

TABLE 1. Mass Spectra of Compounds I-V

Chromatographic peak (compound)	Values of m/z (%)*
1 (I)	51 (19), 63 (18), 76 (20), 77 (31), 89 (23), 90 (24), 102 (13), 103 (18), 104 (15), 114 (30), 115 (64), 116 (34), 136 (26), 142 (67), 169 (83), 170 (12), 244 (25), 245 (83), 246 (15), 272 (100), 273 (22).
2 (II)	51 (12), 63 (12), 76 (12), 77 (21), 102 (13), 103 (22), 104 (30), 115 (34), 155 (12), 156 (36), 182 (16), 183 (24), 184 (12), 245 (25), 286 (100), 287 (17)
3 (III)	51 (11), 76 (10), 77 (33), 102 (13), 103 (43), 104 (20), 115 (16), 116 (10), 155 (15), 156 (11), 182 (10), 244 (14), 285 (100), 286 (12), 316 (48).
4 (IV)	43 (33), 51 (18), 63 (11), 76 (14), 77 (54), 102 (13), 103 (43), 104 (20), 115 (40), 116 (36), 128 (10), 129 (12), 142 (13), 155 (18), 170 (19), 172 (11), 181 (11), 257 (10), 271 (18), 272 (12), 284 (35), 285 (100), 286 (26), 300 (55), 301 (53), 302 (16), 344 (62), 345 (12)
5 (V)	39 (16), 50 (13), 51 (30), 52 (14), 63 (16), 75 (13), 76 (22), 77 (56), 89 (27), 102 (56), 103 (49), 104 (45), 115 (33), 116 (29), 129 (10), 130 (10), 142 (10), 169 (16), 170 (10), 171 (13), 271 (16), 272 (10), 285 (46), 286 (10), 301 (15), 302 (100), 303 (18), 315 (16), 332 (64), 333 (15)

*The peaks of the ions with an intensity ≥ 10% of the maximum are cited.

Preliminary mass spectrometric analysis and the PMR spectrum of the product of oxymethylation of I showed that the substance isolated is not individual. In the analysis of this reaction mass by the method of gas-liquid chromatography, in addition to the unreacted triazine I (∿4%, time of emergency τ_{min} = 5'4'6"), four more major components (II-V) were identified in a ratio of ∿ 15:16:47:18%, respectively, τ_{min} = 6'00", 6'18", 6'48", and 7'06". The structures of the individual components II-V contained in the mixture (Fig. 1) were established by the method of chromato-mass spectrometry (CMS) in conjunction with high-resolution mass spectrometry (HRMS). Individual components of the mixture were identified on the basis of an analysis of the mass spectra obtained, recorded repeatedly at the maxima of the chromatographic peaks (Table 1). On the basis of the CMS data it was shown that the chromatographic peak 1 and the mass spectrum of the individual compound I, recorded by the direct input technique (the time of emergency τ_{min} coincide).

At the maximum of chromatographic peak 2 (Fig. 1), the molecular ion (M^+) of the product II was recorded, with m/z 286,* which is 14 amu greater than the molecular weight of the starting material. According to HRMS, the gross formula of this ion is $C_{18}H_{14}N_4$ (found 286.1207, calculated 286.1218). In contrast to the initial compound I, signals of protons of the methyl group (2.13 ppm, s) are observed in the PMR spectrum of the reaction product II. The absence of signals of the protons of the systems AB and ABX demonstrates that the methyl group is not contained in any of the phenyl rings but is bonded directly to one of the ring carbon atoms of the imidazotriazine I (in the $C_{(3)}$ or $C_{(7)}$ position). This assignment is also confirmed by the absence of the peaks of the ions $[C_6H_4CH_3]^+$ and $[CH_3C_6H_4CN]^+$ in the mass spectrum of substance II. Thus, on the basis of the data cited above, the component II discussed can be assigned one of two alternative structures possessing a methyl substituent in the $C_{(3)}$ or $C_{(7)}$ position.

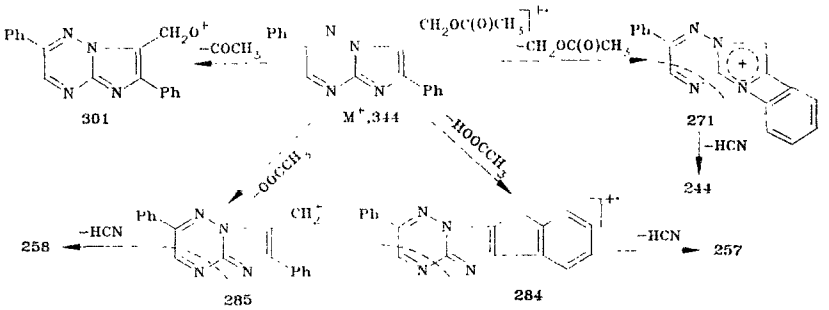
For a final establishment of the structure of component II, its mass spectrum must be analyzed and compared with the original mass spectrum of the imidazotriazine I. In the mass spectrum of compound I, M^+ 272 at the first stage of decomposition splits out a molecule of HCN (the peak 245, see Table 1). Such fragmentation is characteristic of most N-heterocyclic compounds and can occur when the $N_{(4)}$ atoms and CH group in the third position of the triazine fragment of the molecule are included in the particle to be eliminated. Thus, other α-carbon atoms of the initial bicycle I are replaced by phenyl groups, and decomposition with elimination of a C_6H_5CN molecule from M^+ becomes preferential. In contrast to compound I, the mass spectrum of component II does not contain the peak of the ion $[M-HCN]^+$, but elimination of the CH_3CN group from M^+ is observed, which unambiguously demonstrates the structure of component II as 2,6-diphenyl-3-methylimidazo[1,2-b]-1,2,4-triazine.

In the mass spectrum obtained at the maximum of the chromatographic peak 3 (component III), a peak M^+ 316 is recorded, which is 44 amu greater than in the initial compound I and 30 amu greater than for component II (Table 1).

The gross formula $C_{19}H_{16}N_4O$ was determined for the ion 316 according to HRMS (found 316.1318, calculated 316.1324). The latter finding suggests the presence of an OCH_3 or CH_2OH group (in addition to the supplementary CH_3 group) in component III in comparison with the starting material I. In the PMR spectrum of the reaction mixture a singlet is observed at δ = 5.11 ppm, which, by analogy with 7-hydroxymethyl-2,3,6-triphenylimidazo[1,2-b]-1,2,4-triazine [2], can be assigned to the signals of the protons of the methylene group of the hydroxymethyl substituent. The presence of a hydroxymethyl group in the molecule of substance III is confirmed by an analysis of its mass spectrum, in which a peak of the ion $[M-CH_2OH]^+$ is present (the CH_2OH radical is eliminated as a result of steric factors [4]). To determine the position of the hydroxymethyl substituent in the molecule of component III we compared its mass spectrum with the spectrum of the model 7-hydroxymethyl-2,3,6-triphenylimidazo[1,2-b]-1,2,4-triazine [2]. It was found that the spectra of both compounds are characterized by the presence of a peak of the ion $[M-OH]^+$ (299; β-decomposition relative to the hetaryl ring) and also show elimination of a CH_2OH group. Thus, the complete identity of the primary acts of fragmentation of the model hydroxymethyl compound and of substance III permits us to conclude that the latter is 7-hydroxymethyl-2,6-diphenyl-3-methylimidazo[1,2-b]-1,2,4-triazine.

In the mass spectrum of the main product of the reaction (content in the mixture 47%), obtained at the maximum of chromatographic peak 4 (compound IV), the peak M^+ 344 is observed. Its composition corresponds to the gross formula $C_{20}H_{16}N_4O_2$ (according to the data of HRMS, found 344.1268, calculated 344.1273). The initial acts of decomposition of M^+ involve splitting out of ketene (302) and an acetyl residue (301). Such a picture of fragmentation of M^+ indicates the presence of an acetyl group in the molecule of substance IV [5]; its presence is also confirmed by the appearance of the fragment ion $[COCH_3]^+$ in the mass spectrum. Direct elimination of CH_3COO and CH_3COOH particles from M^+ (metastable transitions 236.1 and 234.5 are recorded) is evidence in support of a lengthening of the chain before the ester group (β-decomposition relative to the hetaryl ring). This premise is also confirmed by the formation of the ion $[M-CH_2OCOCH_3]^+$ (271, Table 1). Subsequently the indicated initial acts of decomposition can occur only if there is no methyl substituent at the $C_{(3)}$ atom. In view of this, the aggregate of data obtained permit us to ascribe the structure of 7-acetoxymethyl-2,6-diphenylimidazo[1,2-b]-1,2,4-triazine to component IV, with initial decomposition under electron impact occurring according to the scheme:

*Here and henceforth the numbers characterizing an ion define the value of m/z.

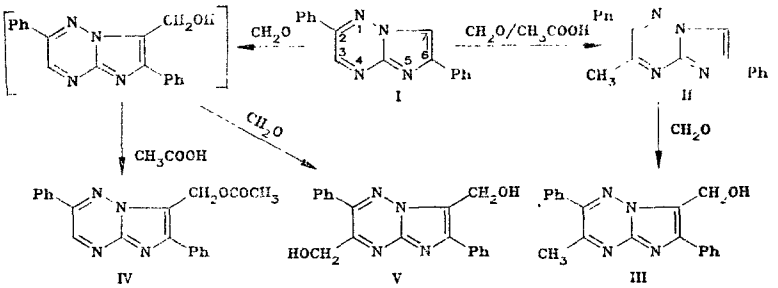


The data of the PMR spectra obtained for the reaction product do not contradict the proposed structure for compound IV. The following signals can be seen in the PMR spectrum: 1.48 (s, CH_3CO), 5.62 (s, CH_2), and 9.28 ppm (s, C_3H).

According to the data of gas-liquid chromatography, component V of the mixture (chromatographic peak 5, Fig. 1) is present in an amount of 18%. The peak M^+ 332 is registered in the mass spectrum of this product. According to HRMS, a gross formula $C_{19}H_{16}N_4O_2$ was determined for the ion 332 (found 332.1269, calculated 332.1273). Elimination of OH (ion 315), CH_2O, and CH_2OH particles (ions 302 and 301, respectively) from M^+, just as in the case of component III, is associated with the presence of a hydroxymethyl group in the molecule of compound V. Repeated elimination of OH, CH_2O, and CH_2OH particles (the ions 285, 272, and 271, respectively) from the ion $[M - CH_2O]^+$ is evidence of the presence of a second hydroxymethyl group in the molecule. Considering that there are no signals of the protons characterizing substitution of the phenyl rings in the PMR spectrum, we can assert that the hydroxymethyl groups are at the $C_{(3)}$ $C_{(7)}$ atoms, and component V represents, 3,7-dihydroxymethyl-2,6-diphenylimidazo[1,2-b]-1,2,4-triazine.

Generalizing the data obtained from the chromato-mass spectrometric investigation, we can conclude that the reaction of oxymethylation of 2,6-disubstituted imidazo[1,2-b]-1,2,4-triazine derivatives, catalyzed by acid, proceeds ambiguously, and not only the imidazole portion of the molecule but also the triazine ring are subjected to electrophilic attack, although the electron density of the triazine ring, according to quantum chemical calculations [2], is significantly lower.

Thus, the reaction of 2,6-diphenylimidazo[1,2-b]-1,2,4-triazine (I) with formaldehyde can be described by the scheme:



EXPERIMENTAL

The CMS investigation was conducted on an LKB-2091 instrument under standard conditions (ionizing voltage 70 eV, emission current of the cathode 300 μA, and accelerating voltage 3 kV). To separate the reaction product we used a packed column (l 2 m, d 2 mm) with the phase OV-101 (1.5%) on Chromosorb-W (100-120 mesh). The temperature of the injector of the chromatograph was 300°C; programmed system of heating of the column from 200 to 300°C at a rate of 10°/min. The PMR spectrum was recorded on a WH-90 MHz instrument (Bruker), internal standard TMS, solvent DMSO-D_6. The high-resolution mass spectra were obtained on a Varian MAT-311A instrument in the same system at a resolution M/ΔM - 15,000, PPC standard.

Procedure of the Oxymethylation of Compound I. To a solution of 0.54 g (2 mmoles) of the imidazotriazine I in 15 ml of acetic acid we added 8 ml of formalin and boiled the mixture for 4 h. The solution was evaporated under vacuum; a saturated solution of $NaHCO_3$ was added to the dry residue, and the precipitate of substances I-V was filtered off, washed with water, and dried. Weight 0.56 g. Mp 190-193°C.

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INVESTIGATION OF THE PROTOLYTIC EQUILIBRIA OF NITRAMINOTETRAZOLES IN AQUEOUS MEDIA

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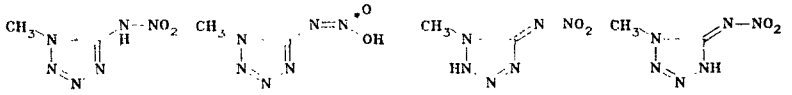
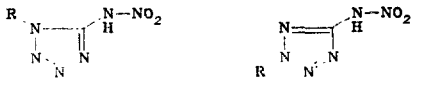
UDC 547.795.1: 541.124.7: 543.422.6'424

The UV and Raman spectra of a number of nitraminotetrazoles were recorded in aqueous media. The dependence of the spectral characteristics on the pH and H_0 was studied, and the dissociation constants of neutral and protonated molecules were determined. It was established that 5-nitramino- and 1-methyl-5-nitraminotetrazole exist in the nitrimine form in aqueous solutions.

Up to the present time, the dissociation and protonation of nitraminotetrazoles had not been systematically studied; there were only data on the dissociation constants of individual compounds of this series [1]. The question of the tautomeric form of nitraminotetrazoles, for which nitramine, isonitramine, and nitrimine structures have been proposed [1], also remained in dispute; thus, for 1-methyl-5-nitroaminotetrazole, respectively:



The purpose of this work was to determine the dissociation constants of the neutral molecules (pK_a), their protonated forms (pK_{BH^+}), and to interpret the data from the standpoint of the possibility of existence of tautomeric forms of nitraminotetrazoles I-V.



I-III IV,V

I R=H; II, IV R=CH_3; III, V R=C_2H_5

The values of pK_a and pK_{BH^+} of compounds I-V (Tables 1 and 2) were determined by methods of spectroscopy (UV, Raman) and potentiometric titration. Monotypic dependences of the UV and Raman spectra on the acidity of the medium are observed for I, II and IV, V, while differences of the UV spectra are observed for III.

The results obtained permit a sufficiently reliable interpretation of the structure only of compounds I and II. The low acidity of II ($pK_a \sim 6$) excludes the possibility of existence of this compound in nitramine or isonitramine tautomeric forms, which should be strong acids.

Evidence against an isonitramine tautomeric form was obtained in a study of the Raman spectra of compound II. It was found that the Raman spectra are unchanged when the nitrogen

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