NEW TRANSFORMATIONS OF o-SUBSTITUTED AZOXYBENZENES

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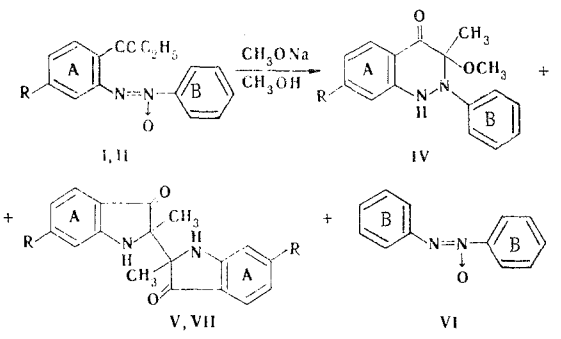
Under the influence of equimolar amounts of bases, o-propionylazoxybenzenes undergo previously unknown transformations to difficult-to-obtain cinnolinones, bisindoxyls, and indolinones. The ratios of the resulting transformation products depend on the substituent in the para position with respect to the propionyl group. Possible pathways for the transformations of monopropionylazoxybenzenes are discussed.

Little study has been devoted to the reactions of o-substituted azoxybenzenes. In addition, as demonstrated in papers devoted to the study of the transformations of the indicated azoxy compounds [1, 2], the latter may prove to be extremely promising starting compounds for the synthesis of the most diverse heterocyclic systems. In this connection, in the present research we studied the behavior of 2-propionyl-, 2-propionyl-5-tert-butyl-, and 2-propionyl-5-bromoazoxybenzenes (I-III) under the influence of sodium alkoxides in alcohol.

The previously undescribed azoxbenzenes I-III necessary for the study were obtained by oxidation of the corresponding azo compounds with hydrogen peroxide in acetic acid.

We found that I-III remain virtually unchanged under the influence of catalytic amounts of a base in alcohol — conditions under which it is known [1] that o,o'-dipropionylazoxybenzenes undergo quantitative conversion to substituted benzo[c]isoxazoles. Azoxy compounds I-III undergo transformations only in the presence of equimolar amounts of the sodium alkoxide in the corresponding alcohol; each of the azoxybenzenes I-III gives a mixture of substances with varying composition. Thus 2-phenyl-3-methyl-3-methoxycinnolinone (IV), 2,2'-dimethyl-2,2'-diindoxyl (V), and azoxybenzene (VI) are formed as the principal products in the action of sodium methoxide on 2-propionyl-N,N,O-azoxybenzene (I) in methanol. However, if 5-tert-butyl derivative II is subjected to similar treatment, only diindoxyl VII and the same azoxybenzene VI can be isolated from the reaction mixture.



I, II IV

V, VII VI

I, IV, V R = H; II, VII R = $(CH_3)_3C$—

Azoxybenzene III behaves completely differently under the adopted conditions: instead of the expected bisindoxyl of the VII type, 2-methoxy-2-methyl-6-bromo-3-indolinone (VIII) is formed when III is treated with sodium methoxide in methanol. However, if the reaction is carried out in ethanol under the influence of the corresponding alkoxide, 2-ethoxy-3-indolinone (IX) is obtained. In both cases azoxybenzene VI is also a second product.

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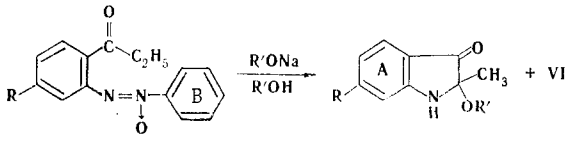


III VIII, IX

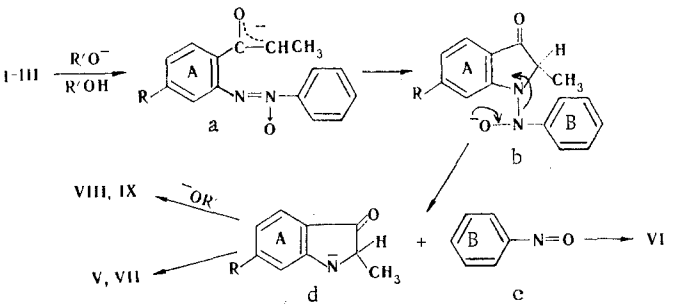
III, VIII, IX R=Br; VIII R′=CH_3; IX R′=C_2H_5

The structures of all of the compounds obtained for the first time were confirmed by data from the IR, UV, PMR, and mass spectra and the results of elementary analysis (see the experimental section).

The results obtained in this research show that, in contrast to 2,2'-dipropionylazoxybenzenes, the conversion of which to benzo[c]isoxazoles is realized under the influence of catalytic amounts of a base, regardless of the nature of the substituents in the aromatic rings [1], the reactions of monopropionylazoxybenzenes I-III proceed only under the influence of equimolar amounts of the base, and a definite dependence of the direction of the process on the properties of the substituents in the acylated benzene ring of the starting azoxybenzene (ring A) is observed.

Considering the composition of the reaction products obtained from azoxybenzene I (see the scheme), it is natural to assume that in this case the processes are initiated by two independent means, viz., by attack by the enolate anion that is formed during the process at either of the nitrogen atoms of the azoxy group of the starting substrate, i.e., at the nitrogen atom bonded to the oxygen atom or at the other nitrogen atom. The substances formed as a result of each of the reaction pathways do not undergo interconversion; for example, cinnolinone IV, which might be a precursor of bisindoxyl V if the processes were reversible in character, is not converted to the indicated compound under the adopted reaction conditions.

In all of the investigated transformations of monopropionylazoxybenzenes I-III one of the reaction products was always symmetrical azoxybenzene VI, the composition of which contains only the B benzene rings of the starting substrates; symmetrical azoxybenzenes that contain A benzene rings were not observed in a single case. These facts make it possible to assume that cleavage of the —N=N— bond in monopropionylazoxybenzenes I-III during their transformations under the influence of bases occurs in the reaction complex after the formation of the indoxyl ring.

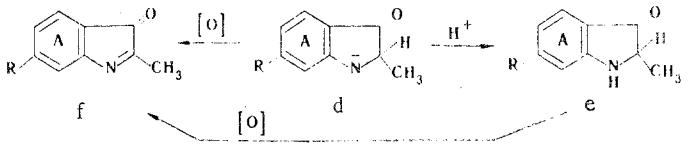


It might be assumed that in one of the steps of the transformation of starting azoxybenzene intermediate b, which is formed as a result of intramolecular attack by the enolate anion at the nonoxidized nitrogen atom of the azoxy group, undergoes cleavage to indoxyl fragment d and nitrosobenzene c. The former is then converted to bisindoxyls V and VII or indolinones VIII and IX, while the latter is converted to a symmetrical azoxy compound.

The fact that bisindoxyls V and VII, indolinones VIII and IX, and azoxybenzene VI are formed in close-to-equimolar amounts constitutes indirect evidence in favor of the indicated scheme of the transformation of o-propionylazoxybenzenes I-III; the possibility that the formation of the bisindoxyls (of the V and VII type) and indolinones VIII and IX from the second part of cleaved intermediate complex b occurs with the participation of the nitrosobenzene c that is formed under the reaction conditions is not excluded.

In fact, anions of the d type may be stabilized both by capture of a proton from the solvent (dihydroindolinone e is formed) and as a result of oxidation; both anions of the d

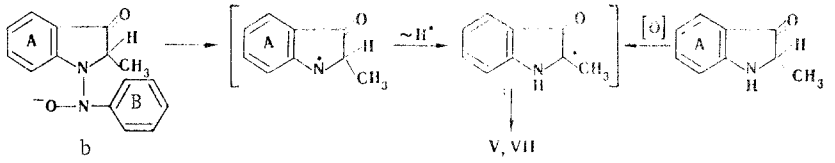
type and indolinones of the e type should be readily oxidized, since it is known that dihydroindolinones are oxidized under mild conditions [3, 4].



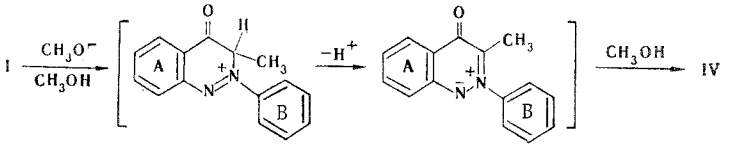
Nitrosobenzene c evidently oxidizes either e or anion d to indolinone f, thereby reducing it to symmetrical azoxy compound VI. The indolinones of the f type that are formed as a result of oxidation are extremely reactive compounds [4, 5] and, in all likelihood, may actually be responsible for the formation of both bisindoxyls V and VII and indolinones VIII and IX. In the first case the —C=N— double bond of f is attacked by the enolate anion obtained from 2-methyldihydroindolinone e under the reaction conditions, which leads to an intermediate, protonation of which gives bisindoxyls V and VII.* In the second case f reacts with the alkoxide anion, which leads to indolinones VIII and IX.

The difference in the behavior of azoxy compounds I and II and their bromo-substituted analog III under identical conditions, when either bisindoxyls V and VII or alkoxyindolinones VIII and IX are formed, should evidently be associated with the rate of formation of an indolinone of the f type; the oxidation of the intermediate of the d type probably takes place somewhat faster than its protonation by the solvent if there is a bromine atom in the 6 position of intermediate d. The latter leads to preponderant formation of the bromoindolinone. In the absence of a competitively reacting nucleophile (the corresponding enolate anion) the bromoindolinone of the f type reacts with the alkoxide anion and, after protonation, gives VIII and IX.

It should be noted that in this case one also evidently cannot exclude a radical pathway for the formation of bisindoxyls V and VII from consideration; the latter could also have been formed from both the radicals that should be obtained in the case of homolytic cleavage of intermediate b and from the dihydroindolinone radicals that develop in the oxidation of structures of the e type.



The formation of indolinone IV from monopropionylazoxybenzene I is evidently associated with a second pathway of intramolecular attack by the enolate anion that is formed from the propionyl substituent — at the oxidized nitrogen atom of the azoxy group — and, upon the whole, evidently takes place via the scheme



Under the assumption that one can regulate the degree of attack by the enolate anion on one or the other nitrogen atom of the azoxy group of the substrate by introduction of the corresponding substituents in the benzene B ring of azoxybenzenes I-III, we studied its behavior under the adopted conditions. We expected that the electron-acceptor effect of the acetyl fragment would create favorable conditions for attack by the enolate anion at the oxygen-containing nitrogen atom of the azoxy group and thereby would lead to the primary formation of the corresponding cinnolinone XI. However, in this case also we were able to isolate only bisindoxyl V and 4,4'-diacetylazoxybenzene (XII) from the reaction mixture.

*A similar pathway for the formation of bisindoxyls from indolinones obtained by different pathways is discussed in [4, 5].

TABLE 1. 2-Propionyl-5-R-4'-R''-azobenzenes and 2-Propionyl-5-R-4'-R''-N,N,O-azoxybenzenes I-III and X

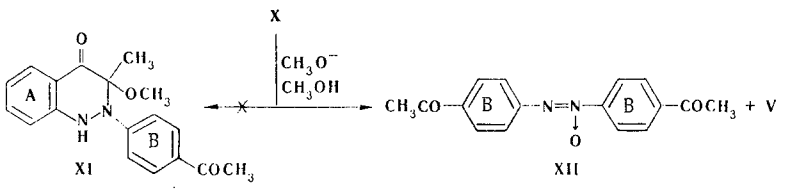
Compound	R	R''	mp, °C	IR spectrum, cm^{-1}; UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
Azobenzene	H	H	—*	1460 (N=N), 1690 (C=O), 228 (3,05), 322 (4,30); 445 (2,73)	75,5	5,9	11,9	$C_{15}H_{14}N_2O$	75,6	5,9	11,8	52
„	$(CH_3)_3C$	H	—*	1465 (N=N), 1675 (C=O); 234 (3,11), 328 (3,20), 453 (2,71)	77,6	7,4	9,6	$C_{19}H_{22}N_2O$	77,5	7,5	9,5	82
„	Br	H	—*	1460 (N=N), 1680 (C=O)	56,8	4,2	7,1	$C_{15}H_{13}BrN_2O$	56,8	4,1	7,2	74
„	H	CH_3CO	82—84†	1460 (N=N), 1685 (C=O)	72,7	5,8	10,1	$C_{17}H_{16}N_2O_2$	72,9	5,7	10,0	33,5
I	H	H	74—76†	1450 (NO), 1480 (N=N), 1690 (C=O); 323 (3,34), 249 (4,19)	70,1	5,4	11,1	$C_{15}H_{14}N_2O_2$	70,1	5,5	11,0	61
II	$(CH_3)_3C$	H	—*	1450 (NO), 1500 (N=N), 1720 (C=O); 328 (3,96), 256 (2,86)	73,7	7,1	9,2	$C_{19}H_{22}N_2O_2$	73,5	7,1	9,0	72
III	Br	H	53—54†	1440 (NO), 1480 (N=N), 1690 (C=O); 316 (3,32), 254 (4,33)	54,2	3,9	8,6	$C_{15}H_{13}BrN_2O_2$	54,0	3,9	8,4	68
X	H	CH_3CO	65†	1450 (NO), 1480 (N=N), 1690 (C=O)	69,1	5,5	9,6	$C_{17}H_{16}N_2O_3$	68,9	5,4	9,5	23

*Viscous oil.
†From ethanol.

TABLE 2. Products of the Reaction of Azoxybenzenes I-III and X

Compound	mp, °C	IR spectrum, cm^{-1}; PMR spectrum, ppm; mass spectrum, m/z (%)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IV	165—166*	1720 (C=O), 3300 (NH); 1,51 (s, 3H), 3,25 (s, 3H), 5,85 (br s, 1H), 6,85—7,72 (m, 9H); M^+ 268 (5,1), 236 (19,9), 221 (18,2), 207 (48,7), 164 (19,8), 162 (100), 146 (44,8), 145 (29,4), 134 (14,9), 132 (20,9), 119 (45,1), 117 (49,1), 104 (50,2), 91 (47,7), 77 (88,7)	71,6	5,9	10,4	$C_{16}H_{16}N_2O_2$	71,8	6,1	10,3	18
VII	215—216*	1680 (C=O), 3360 (NH); 1,15 (s, 6H), 1,33 (s, 18H), 6,12 (br s, 2H), 6,64—7,65 (m, 6H); 203 (100), 189 (37,9), 187 (50,1), 176 (24,8), 175 (22,6), 174 (99,8), 161 (82,1), 159 (73,8), 117 (68,8), 91 (23,9), 77 (24,7)	77,5	8,1	7,0	$C_{26}H_{32}N_2O_2$	77,2	8,1	7,9	32
VIII	—†	1685 (C=O), 3380 (NH); 1,52 (s, 3H), 3,12 (s, 3H), 5,83 (br s, 1H), 6,81—7,48 (m, 3H); 227 (35,1), 226 (29,6), 225 (100), 224 (31,9), 223 (44,7), 210 (24,2), 154 (28,8), 149 (22,7), 145 (23,4)	46,9	4,1	5,6	$C_{10}H_{10}BrNO_2$	46,9	3,9	5,5	27
IX	—†	1690 (C=O), 3370 (NH); 1,16 (t, 3H), 1,48 (s, 3H), 3,11—3,75 (dq, 2H), 5,92 (br. s., 1H), 6,91—7,62 (m, 3H)	48,8	4,5	5,3	$C_{11}H_{12}BrNO_2$	48,9	4,4	5,2	24
XII	75—76*	1440 (NO), 1480 (N=N), 1690 (C=O)	68,2	5,1	10,1	$C_{16}H_{14}N_2O_3$	68,1	4,9	9,9	25

*From methanol.
†Viscous oil.



XI XII

In analyzing the compositions of the products of the reaction of I-III and X it is easy to see that the yields of bisindoxyls V and VII and indolinones VIII and IX always correspond to the yields of symmetrical azoxybenzenes VI and XII. Taking into account the sta-

bilities of both these and other compounds under the reaction conditions and upon prolonged storage it may be assumed that the relative percent of transformation of starting substrates I-III and X via the pathway that assumes attack by an enolate anion of the *a* type on the nonoxidized nitrogen atom of the azoxy group corresponds to the amounts of V-IX and XII isolated in each case.

At the same time, the low yield of cinnolinone IV in the reaction of I or the complete absence of cinnolinones in the products of separation of the reaction mixtures obtained under standard conditions from II, III, and X cannot serve as an indication that the process initiated by intramolecular attack by enolate anion *a* on the nitrogen atom of the azoxy group that is bonded to the oxygen atom is realized either to a very small extent (the yield of cinnolinone IV is only 18%) or is not realized at all. Both the low yield of IV and the absence of it or similar substances in the products of the reactions of II, III, and X can be explained by the relative instabilities of the cinnolinone structures. This is confirmed, on the one hand, by the fact that a multicomponent mixture of substances is formed in the case of treatment of cinnolinone IV under the adopted conditions and, on the other, by the relatively low stability of IV during storage under normal conditions.

Thus, in contrast to dipropionylazoxy compounds, monopropionylazoxybenzenes under the influence of a base undergo transformations that are initiated by attack by the resulting enolate anion both at the oxidized and nonoxidized nitrogen atoms of the azoxy group. Five- and six-membered heterocyclic systems that differ from those that are obtained from symmetrical dipropionylazoxy compounds are formed as a result of these transformations.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were obtained with Varian T-60 and XL-100 spectrometers with tetramethylsilane as the standard. The IR spectra of liquid films or mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Cary-15 spectrophotometer. The mass spectra were obtained with a Varian MAT-11 spectrometer at an ionizing voltage of 70 eV. Chromatographic isolation of the substances was carried out on activity II Al_2O_3 by elution with ether–petroleum ether (40-70°C) (1:3).

Substituted 2-Propionylazobenzenes (Standard Method). A mixture of 0.047 mole of 2-nitroso-5-R-propiophenone and 0.04 mole of 4-R''-aniline in 100 ml of acetic acid was stirred at 20°C for 6 h, after which it was poured into 800 ml of water, and the aqueous mixture was extracted with chloroform (400 ml). The organic solution was washed with water and dried with $MgSO_4$. The solvent was evaporated, and the residue was chromatographed with a column filled with Al_2O_3 to give the corresponding azobenzenes. The yields of the reaction products, the results of elementary analysis, and the physicochemical characteristics are presented in Table 1.

Substituted 2-Propionyl-N,N,O-azoxybenzenes I-III and X (Standard Method). A total of 70 ml of 30% hydrogen peroxide was added in 10 ml portions every 30 min to a solution of 0.05 mole of 2-propionyl-5-R-4'-R''-azobenzene in 100 ml of acetic acid heated to 70-80°C, after which the reaction mixture was cooled to 20°C and poured into water (300 ml). The organic products were extracted with chloroform (150 ml), and the chloroform solution was washed with water until the wash water was neutral, after which it was dried with $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on Al_2O_3. This procedure was used to obtain the corresponding 2-propionyl-N,N,O-azoxybenzenes I-III and X (Table 1).

Reaction of Azoxy Compounds I-III and X with Sodium Alkoxide in the Corresponding Alcohol (Standard Method). A solution of 0.02 mole of sodium in 40 ml of methanol (or ethanol) was added gradually to a solution of 0.02 mole of azoxybenzene I-III or X in 100 ml of methanol (or ethanol), and the mixture was stirred for 4 h. A stream of carbon dioxide gas was then passed through it (up to pH 8), and the resulting precipitate was removed by filtration and washed with the corresponding alcohol. The combined filtrate was evaporated, and the residue was chromatographed on Al_2O_3.

2-Propionyl-N,N,O-azoxybenzene (I) gave 0.96 g (18%) of 2-phenyl-3-methyl-3-methoxycinnolinone (IV),* 0.64 g (22%) of 2,2'-dimethyl-2,2'-diindoxyl (V) (mp 173-174°C [4]), and 0.52 g (26%) of azoxybenzene (VI) (mp 35-36°C [6]).

*The results of elementary analysis and the physicochemical data are presented in Table 2.

2-Propionyl-5-tert-butyl-N,N,O-azoxybenzene (II) gave 1.29 g (32%) of 2,2'-dimethyl-6,6'-di-tert-butyl-2,2'-diindoxyl (VII)* and 0.57 g (29%) of azoxybenzene (VI).

The reaction of 2-propionyl-5-bromo-N,N,O-azoxybenzene (III) in methanol gave 1.38 g (27%) of 2-methyl-2-methoxy-6-bromoindolinone (VIII)* and 0.47 g (24%) of azoxybenzene (VI).

The reaction of III in ethanol gave 1.30 g (24%) of 2-methyl-2-ethoxy-6-bromoindolinone (IX)* and 0.43 g (22%) of azoxybenzene (VI).

The reaction of 2-propionyl-4'-acetyl-N,N,O-azoxybenzene (X) gave 0.64 g (22%) of 2,2'-dimethyl-2,2'-diindoxyl (V) and 0.68 g (24%) of 4,4'-diacetylazoxybenzene (XII).*

LITERATURE CITED

1. S. S. Mochalov, A. N. Fedotov, and Yu. S. Shabarov, Zh. Org. Khim., 16, 462 (1980).
2. H. Rembges and F. Krohnke, Chem. Ber., 103, 3437 (1970).
3. L. Klab and J. Bayer, Chem. Ber., 45, 2150 (1912).
4. A. Hassner and M. J. Haddadin, J. Org. Chem., 28, 224 (1963).
5. A. Hassner and M. J. Haddadin, Tetrahedron Lett., No. 21, 975 (1962).
6. A. McKillop, R. A. Raphael, and E. C. Taylor, J. Org. Chem., 35, 1670 (1970).

*See previous footnote.

REACTIONS OF HETEROCYCLIC CATIONS WITH N-CONTAINING NUCLEOPHILES. 13.* INVESTIGATION OF THE REACTION OF 2,4,6-TRIARYLPYRYLIUM SALTS WITH HYDRAZINES, SEMICARBAZIDE, AND THIOSEMICARBAZIDE

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The recyclization reactions of 2,4,6-triphenylpyrylium perchlorate with hydrazine and methyl-, phenyl-, benzoyl-, and benzalhydrazines in dimethylformamide (DMF), which proceed differently than in ethanol, were examined. 7-Oxo and 7-thioxo derivatives of 2,3a,5-triphenyl-3H-pyrazolo[1,5-c]pyrimidine were obtained by transformation of 2,4,6-triarylpyrylium salts with semicarbazide and thiosemicarbazide in DMF. The tautomeric forms of the products were established by mass spectrometry and chemical transformations.

It is known that 2,4,6-triarylpyrylium perchlorates (I) react with hydrazine in ethanol to give 4H-1,2-diazepines (II) [2-4]. Under the same conditions 2,4,6-triphenylpyrylium perchlorate (a) reacts with methylhydrazine to give primarily 1-methyl-3,5-diphenylpyrazole [5] and with phenylhydrazine to give 3,5-diphenyl-5-phenacyl-2-pyrazoline [2].

We have shown that the direction of these reactions can be changed if they are carried out in dimethylformamide (DMF). Thus the principal reaction product is 3,5-diphenylpyrazole (IIIa) when salt Ia is refluxed with hydrazine in DMF. Similarly, under the same conditions the reaction of salt Ia with phenylhydrazine leads to 1,3,5-triphenylpyrazole (IIIb). The previously described pyrazolo[2,3-a]quinoline (IV) [6] is formed simultaneously by intramolecular cyclization of the intermediate 1,3,5-triphenyl-5-phenacylpyrazoline. The recyclization of perchlorate Ia with methylhydrazine in DMF proceeds differently with the formation of 1-methylamino-substituted pyridinium salt V. 2,4,6-Triphenylpyridine (VIa) is isolated simultaneously, probably as a consequence of partial thermal destruction of salt V or methylhydrazine with the formation of ammonia.

*See [1] for Communication 12.
†Deceased.

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