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REARRANGEMENT OF 2,2'-DIPROPIONYLAZOXYBENZENES TO 3-[1-ALKOXY-1-(2-PROPIONYLARYLAMINO)ETHYL]BENZO[c]ISOXAZOLES

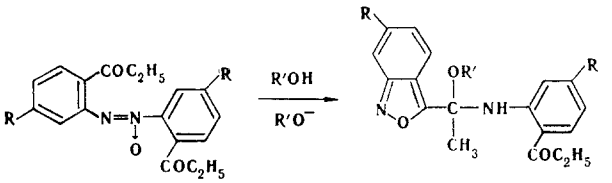
S. S. Mochalov, A. N. Fedotov, and Yu. S. Shabarov

UDC 547.786.3'556.2:542.952:543.422.51

2,2'-Dipropionylazoxybenzenes undergo rearrangement to the corresponding 3-[1-alkoxy-1-(2-propionylarylamino)ethyl]benzo[c]isoxazoles in the case of base catalysis; this transformation is realized only in the case of ortho,ortho' orientation of the propionyl groups in the substrate molecule and with the participation of the solvent as a reagent. A mechanism for the rearrangement that assumed the participation of one of the propionyl groups in intramolecular reduction of the azoxy group to an azo group is proposed.

We have previously shown that 2,2'-dipropionylazoxybenzenes undergo rearrangement to 3-[1-alkoxy-1-(2-propionylarylamino)ethyl]benzo[c]isoxazoles under the influence of catalytic amounts of bases in alcohol [1]. It was noted that the solvent, viz., the alcohol, participates in the previously unknown transformation; the size of the alkyl group in the molecule of the latter may have a decisive effect on the course of the rearrangement. For example, in alcohols with normal and iso structures the corresponding benzo[c]isoxazoles are formed, whereas no reaction occurs in tert-butyl alcohol. Since this type of transformation of 2,2'-dipropionylazoxybenzenes was previously unknown, we made an attempt to establish its mechanism.

A study of the behavior of azoxy compounds I-V* under the conditions for the rearrangement that we found showed that neither the direction of the reaction nor the degree of transformation depends substantially on the type of substituent in the para position relative to both the propionyl fragment undergoing modification and the propionyl fragment that remains unchanged — the corresponding benzo[c]isoxazoles are formed in high yields (see Tables 1 and 2).



I-V VI-XIV

I R=H; II R=t-C$_4$H$_9$; III R=Br; IV R=NO$_2$; V R=

As we have already noted, only alcohols were used as the solvents in the study of the transformations of azoxybenzenes of the I-V type. We found that in aprotic solvents, viz., benzene, dioxane, tetrahydrofuran (THF), ether, and carbon tetrachloride, starting substrates I-V undergo virtually no transformations under the influence of catalytic amounts of bases,

*We have previously described the synthesis of the indicated azoxy compounds [2].

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 743-748, June, 1983. Original article submitted July 19, 1982.

0009-3122/83/1906-0593$07.50

TABLE 1. Yields, Constants, and Results of Elementary Analysis of Substituted Benzo[c]isoxazoles (VI-XIV)

Compound	R	R'	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
VI	H	C_2H_5	151—153	71.1	6.5	8.4	$C_{20}H_{22}N_2O_3$	71.3	6.5	8.3	94
VII	H	CH_3	114—116	70.3	6.1	8.5	$C_{19}H_{20}N_2O_3$	70.4	6.1	8.6	95
VIII	t-C_4H_9	CH_3	142—143	74.3	8.3	6.5	$C_{27}H_{36}N_2O_3$	74.3	8.2	6.4	94
IX	Br	CH_3	159—160	47.5	3.8	5.9	$C_{19}H_{18}Br_2N_2O_3$	47.3	3.7	5.8	91
X	NO_2	CH_3	176—177	55.2	4.4	13.7	$C_{19}H_{18}N_4O_7$	55.1	4.3	13.5	82
XI	Cyclopropyl	CH_3	—*	74.1	6.8	7.1	$C_{25}H_{28}N_2O_3$	74.2	6.9	6.9	96
XII	H	$(CH_3)_2CH$	116—117	71.7	6.9	8.0	$C_{21}H_{24}N_2O_3$	71.6	6.8	7.9	91
XIII	H	p-C_4H_9	—*	72.4	7.0	7.8	$C_{22}H_{26}N_2O_3$	72.1	7.1	7.6	80
XIV	H	s-C_4H_9	85—87	72.2	7.0	7.7	$C_{22}H_{26}N_2O_3$	72.1	7.1	7.6	86

*Viscous oil.

TABLE 2. PMR Spectra of Substituted Benzo[c]isoxazoles (VI-XIV)

Compound	Chemical shift, δ, ppm				
	R	CH_3	C_2H_5	NH	Ar
VI	t 1.28; q 3.3	s 1.33	q 3.01; t 1.14	s 10.30	m 6.62—7.85
VII	s 3.12	s 1.34	q 2.99; t 1.17	s 10.15	m 6.50—7.83
VIII*	s 3.12	s 1.50	q 3.11; t 1.31	s 10.33	m 6.65—7.86
IX	s 3.18	s 1.38	q 3.02; t 1.18	s 10.32	m 6.90—7.80
X	s 3.30	s 1.51	q 3.21; t 1.21	s 10.34	m 7.48—8.21
XI†	s 3.31	s 1.50	q 3.09; t 1.23	s 10.29	m 6.25—7.90
XII	m 0.75—1.51 (6H); m 3.80 (1H)	s 1.30	q 3.01; t 1.15	s 10.26	m 6.70—7.89
XIII	m 0.65—1.71 (7H); m 3.21—3.69 (2H)	s 1.35	q 3.08; t 1.19	s 10.30	m 6.73—8.02
XIV	m 0.64—1.51 (8H)	s 1.32	q 3.08; t 1.19	s 10.31	m 6.68—7.93

*Signal of the tert-butyl group of VIII: s, 1.28 (9H).
†Signals of the protons of the cyclopropyl group of XI: m, 0.61-1.12 (4H), m, 1.91 (1H).

in the period of time during which in alcohol they undergo rearrangement completely.

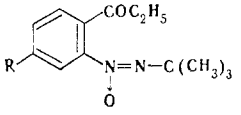
When an equimolar mixture of azoxy compounds I and III is treated with catalytic amounts of sodium methoxide in methanol, it gives two benzo[c]isoxazoles VI and IX, each of which corresponds to the starting azoxybenzene. This fact indicated that the conversion of azoxy compounds I-V to the final reaction products proceeds without prior cleavage of the —N=N— bond in the starting substrates, and that, consequently, the formation of the benzo[c]-isoxazole and phenylamino fragments of VI-XIV is realized due to an intramolecular transformation.

It follows from the structure of VI-XIV that in the transformation of 2,2'-dipropionylazoxybenzenes only one acyl grouping is modified. It would appear that it is important to ascertain whether the presence of a second propionyl group in the starting substrates is necessary for the successful occurrence of the rearrangement and whether it is necessary to know the role that it plays in the overall process. To attempt to decide these issues we made a special attempt to synthesize monopropionylazoxybenzenes XV-XVIII and studied their behavior under the standard reaction conditions.

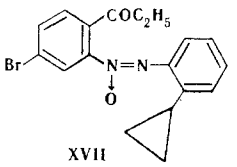
The previously undescribed unsymmetrical monopropionyl-substituted azoxybenzenes XV-XVIII that are necessary for the investigation were obtained by means of known reactions, and their structures were confirmed by physicochemical methods.

In this case, in addition to the elucidation of the role of the second acyl grouping, it seemed possible to establish how the relative orientation of the oxygen atom in the —N,N,O— triad in XV-XVIII affects the course of the transformation. However, we found that neither in methanol or ethanol appreciable changes in the starting substrates occur under the action of catalytic amounts of the sodium alkoxide on either azoxybenzene XVIII or on XV-XVII. These results constituted evidence that in the conversion of 2,2'-dipropionylazoxy-

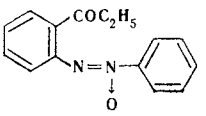
benzenes I-V to complex anthranils VI-XIV the presence of a second propionyl grouping is the determining factor.



XV R=H; XVI R=NO$_2$



XVII



XVIII

One might have assumed that the role of the second propionyl group consists in inducing an additional positive charge on the nitrogen atom of the azoxy group closest to it and, consequently, to facilitation of intramolecular nucleophilic attack on its carbanion, which arises as a result of the action of the base on the first propionyl group (presumably the first step in the rearrangement). However, one could not exclude also the possibility of intramolecular participation of the second acyl fragment in rearrangement of the resulting intermediates, which leads to the final reaction product with regeneration of the carbonyl-containing radical.

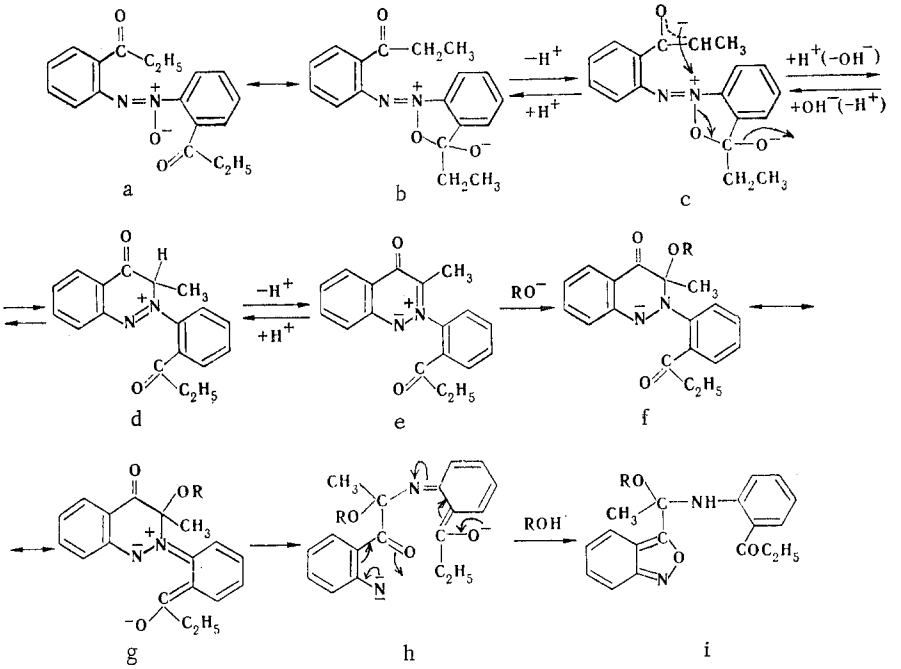
To verify the first assumption we synthesized azoxybenzene XIX, in which one of the acyl groups was in the para position of the phenyl rings of the azoxybenzene, while the other was in the ortho position. We found that under conditions for which 2,2'-dipropionylazoxybenzenes are converted to benzo[c]isoxazoles, 2,4'-diacyl derivative XIX remains absolutely unchanged.

This result provides a basis for the assumption that one of the propionyl substituents in 2,2'-dipropionylazoxybenzenes I-V in a definite stage is involved in an intramolecular basically catalyzed transformation, and is regenerated as a result. For example, one cannot exclude the possibility that one of the propionyl groups of 2,2'-dipropionylazoxybenzenes I-V participates in a redox process (base-catalyzed) due to intramolecular reaction of the oxygen atom of the azoxy group with the carbonyl fragment of the o-propionyl substituent, a consequence of which may be both the high rate of rearrangement and, in general, the possibility of its realization.

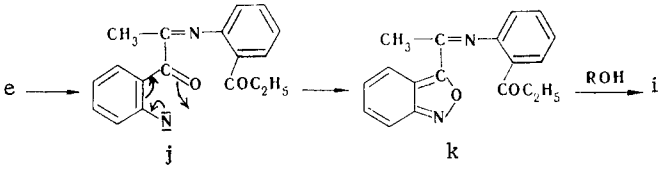
Taking into account the facts that provide evidence that the conversion of 2,2'-dipropionylazoxybenzenes to benzo[c]isoxazoles is realized intramolecularly under the influence of catalytic amounts of a base with the participation of the solvent as a reagent, that the volume of the alkyl radical in the alcohol molecule may be a restrictive factor in the process, and that one of the propionyl groupings is evidently necessary for the intramolecular deoxidation of the corresponding intermediates that develop under the reaction conditions, one may propose the following mechanistic scheme for the formation of benzo[c]isoxazoles of the VI-XIV type.

It is apparent from the scheme that the spatial closeness of the nucleophilic center of the azoxy group (the oxygen atom) and the electrophilic center (the carbon atom of the carbonyl group of the propionyl residue of the dipropionylazoxybenzene) actually may facilitate deoxidation of the azoxy group in an alcoholic medium and the formation of an intermediate of the d type — the key structure in the rearrangement.

The results that we obtained in a study of the behavior of monopropionylazoxybenzenes under similar conditions [3] constitute evidence in favor of the fact that the conversion of 2,2'-dipropionylazoxybenzenes may be realized precisely through intermediates of similar structure (d-f). We found out that monopropionylazoxybenzenes — structural analogs of the compounds investigated in this research, in addition to other reaction products — give alkoxycinnolinones — compounds, the formation of which can be explained only by assuming the formation of intermediates of the d-f type and protonation of the latter from them by the solvent. It is evident that the initial stages of the transformation of dipropionylazoxybenzenes I-V are similar. However, the formation of alkoxycinnolinones from intermediates of the f type does not occur in this case, evidently because of the fact that the negative charge on the nitrogen atom in intermediate f is partially extinguished due to intramolecular coordination with the close-in-space carbonyl group. The latter evidently leads to the result that a process accompanied by cleavage of the —N—N— bond with the subsequent formation of benzo[c]isoxazole i rather than protonation and the formation of the corresponding cinnolinone becomes the favorable process.



An additional confirmation that the process takes place precisely through intermediates of the d-f type was obtained by an attempt to elucidate the possibility of conversion of the starting substrate to a benzo[c]isoxazole through intermediates that could have been formed by cleavage of the —N—N— bond in an earlier step, as, for example, in the step involving the formation of intermediate e. It is known that such structures can undergo cleavage of the —N—N— bond with conversion to the corresponding reaction products [4]. The formation of the benzo[c]isoxazole of the i type could then also be realized by the following mechanism:



However, we found that compound k, which we prepared especially, does not add fragments of alcohol under the adopted reaction conditions, and this can be regarded as evidence in favor of the fact that intermediates of the k type are not formed in the transformation of dipropionylazoxybenzenes I-V.

Also in favor of the proposed scheme of the rearrangement of 2,2'-dipropionylazoxybenzenes is the fact that it (i.e., the mechanistic scheme) satisfactorily explains the catalytic role of the base introduced into the reaction. It is apparent from the scheme that for the successful occurrence of the reaction a base is necessary only in the initial stage of the transformation, since the entire subsequent course of the rearrangement is initiated by the particles of a basic nature that are liberated during the reaction.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were recorded with Varian T-60 and XL-100 spectrometers with tetramethylsilane as the internal standard. The IR spectra of liquid films or suspensions in mineral oil were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compound in ethanol were recorded with a Cary-15 spectrophotometer. The mass spectra were obtained with an MKh-1303 spectrometer at an ionizing voltage of 80 eV. Thin-layer chromatography (TLC) and column chromatography were carried out on activity II aluminum oxide with ether–pentane (1:3) as the eluent.

2,2'-Dipropionylazoxybenzenes (I-V). These compounds were obtained by reduction of the corresponding o-nitropropiophenones with phenylhydrazine in toluene [2].

3-[1-Methoxy-1-(2-propionylphenylamino)ethyl]benzo[c]isoxazole (VI). A solution of 0.005 mole of sodium hydroxide in 25 ml of methanol was added to a solution of 0.1 mole of

2,2'-dipropionylazoxybenzene (I) in 100 ml of methanol, and the reaction mixture was stirred at 20°C. After 2 h, the solvent was evaporated, and the precipitated crystals were recrystallized from methanol.

A similar procedure was used to obtain benzo[c]isoxazoles VII-XIV. The yields of benzo[c]isoxazoles VI-XIV and their physicochemical characteristics and the results of elementary analysis of them are presented in Tables 1 and 2.

2-(tert-Butyl-N,N,O-azoxy)propiophenone (XV). This compound was obtained by condensation of 2-propionylnitrosobenzene with N,N-dichloro-tert-butylamine in the presence of cuprous chloride in acetonitrile by the method in [5]. The product, which was obtained in 54% yield, was a light-yellow oil. IR spectrum: 1430 (NO), 1460 (N=N), and 1715 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 318 (3.0), 243 (4.0), 207 nm (3.4). PMR spectrum: 1.21 (t, CH_3), 1.52 (s, t-C_4H_9), and 2.69 (q, CH_2), and 7.31-8.02 ppm (m, Ar). Found: C 66.8; H 7.7; N 12.1%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.7; H 7.7; N 12.0%.

4-Nitro-2-(tert-butyl-N,N,O-azoxy)propiophenone (XVI). This compound was synthesized by a similar method by condensation of 2-propionyl-5-nitrosobenzene with N,N-dichloro-tert-butylamine. The product was obtained in 34% yield and had mp 134°C. IR spectrum: 1435 (NO), 1475 (N=N), and 1715 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 313 (2.8), 239 (2.8), and 201 nm (3.1). PMR spectrum: 1.23 (t, CH_3), 1.48 (s, t-C_4H_9), 2.75 (q, CH_2), and 7.21-8.29 ppm (m, Ar). Found: C 56.0; H 6.0; N 15.2%. $C_{13}H_{17}N_3O_4$. Calculated: C 55.9; H 6.1; N 15.0%.

2-Propionyl-5-bromo-2'-cyclopropyl-O,N,N-azoxybenzene (XVII). This compound was obtained in 22% yield by a method similar to that in [2] by the stepwise addition of 2-propionyl-5-bromonitrosobenzene and 2-nitrosophenylcyclopropane to a solution of phenylhydrazine in toluene. The spectral characteristics of the product corresponded to those reported in the literature.

2-Propionyl-N,N,O-azoxybenzene (XVIII). This compound was obtained by oxidation of 2-propionylazobenzene with 30% hydrogen peroxide in acetic acid at 70-80°C by the method in [6]. The product was obtained in 75% yield in the form of a light-yellow oil. IR spectrum: 1440 (NO) and 1480 cm^{-1} (N=N). UV spectrum, λ_{max} (log ε): 253 (4.1) and 335 nm (5.02). Found: C 70.3; H 5.7; N 11.3%. $C_{15}H_{14}N_2O_2$. Calculated: C 70.1; H 5.5; N 11.0%.

2-Propionyl-4'-acetylazobenzene. This compound was synthesized by condensation of 2-nitrosopropiophenone with 4-aminoacetophenone in benzene. The red crystalline product (33.5%) had mp 82-84°C (from alcohol). IR spectrum: 1460 (N=N) and 1685 cm^{-1} (C=O). Found: C 72.7; H 5.8; N 10.1%. $C_{17}H_{16}N_2O_2$. Calculated: C 72.9; H 5.7; N 10.0%.

2-Propionyl-4'-acetyl-N,N,O-azoxybenzene (XIX). This compound was obtained by oxidation of 2-propionyl-4-acetylbenzene as described above. The light-yellow crystals were obtained in 23% yield and had mp 65°C (from alcohol). IR spectrum: 1450 (NO), 1480 (N=N), and 1690 cm^{-1} (C=O). PMR spectrum: 1.21 (t, CH_3), 2.52 (s, $COCH_3$), 2.81 (q, CH_2), and 7.41-8.52 ppm (m, ArO). Found: C 69.1; H 5.5; N 9.6%. $C_{17}H_{16}N_2O_3$. Calculated: C 68.9; H 5.4; N 9.5%.

3-[1-(2-Propionylphenylamino)ethyl]benzo[c]isoxazole (XXI). A mixture of 1.6 g (0.005 mole) of 3-[1-methoxy-1-(2-propionylphenylamino)ethyl]benzo[c]isoxazole (VII) in 100 ml of ethanol and 100 ml of 2 N HCl was heated to 50°C with stirring, after which it was stirred at the same temperature for 3 h. The alcohol was removed by filtration and recrystallized from ethanol to give 1 g (72%) of XXI with mp 110-111°C. IR spectrum: 1680 (C=N) and 1710 cm^{-1} (C=O). PMR spectrum: 1.25 (t, CH_2CH_3), 1.75 (s, CH_3), 3.02 (q, CH_2CH_3), and 6.79-7.91 ppm (m, Ar). Mass spectrum, m/z (%): M^+ 292 (12), 250 (25), 249 (100), 235 (23), 222 (24), 206 (24), 191 (7), 177 (22), 165 (14), 151 (10), 139 (8), 130 (11), 115 (12), 103 (8). Found: C 72.4; H 5.1; N 10.0%. $C_{18}H_{16}N_2O_2$. Calculated: C 74.0; H 5.5; N 9.6%.

Similar treatment of VI with 2 N hydrochloric acid led to benzo[c]isoxazole XXI in 68% yield. No melting-point depression was observed for a mixture of a sample of this product with the compound obtained in the preceding experiment.

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A SYDNONEIMINE BASE

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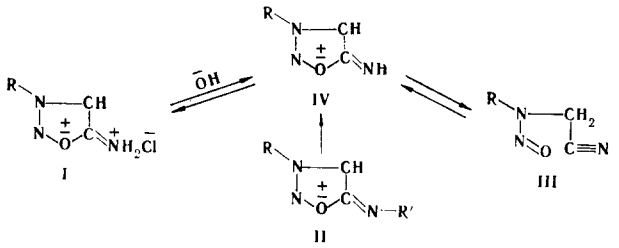
UDC 547.793.1.07:541.621.2:543.422.6'257.1

It was shown by means of the UV spectra that a sydnoneimine base is formed from 3-cyclohexylsydnoneimine hydrochloride by the action of an equivalent amount of sodium hydroxide in solutions of absolute alcohols. The sydnoneimine base is also formed in the case of solvolysis of N_6-trimethylsilyl-3-cyclohexylsydnoneimine in methanol. The sydnoneimine base in solutions exists in equilibrium with the chain isomer, viz., the nitrile. The fraction of the cyclic isomer increases as the electron-donor properties of the substituent in the 3 position become more pronounced.

Sydnoneimines — nitrogen analogs of sydnones — are known only in the form of salts I or N-exocyclic derivatives II [1]. Assumptions involving the hypothetical intermediate of these products, viz., sydnoneimine base IV, have been expressed in studies of alkaline ring closing [2] and the polarographic reduction of salts I [3], as well as in the formation of derivatives II from N-nitrosoaminoacetonitriles III in the presence of bases [4]; however, no confirmation whatsoever of its existence has yet been obtained.



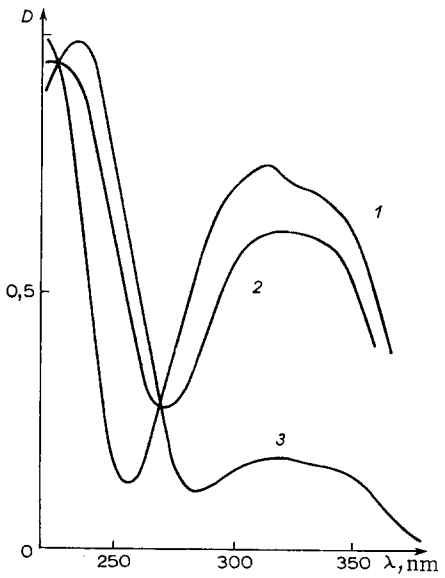


Fig. 1. UV spectra of N_6-trimethylsilyl-3-cyclohexylsydnoneimine in absolute methanol (Δt = 10 min).

Institute of Biophysics, Ministry of Public Health of the USSR, Moscow 123182. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 749-753, June, 1983. Original article submitted November 11, 1981; revision submitted July 26, 1982.

 0009-3122/83/1906-0598$07.50