INTRAMOLECULAR CYCLIZATION OF 2,2'-DIPROPIONYLAZOXYBENZENES. X-RAY STRUCTURAL INVESTIGATION OF 1-(2-PROPIONYLPHENYLAMINO)-2-METHYL-2-METHOXYINDOLIN-3-ONE

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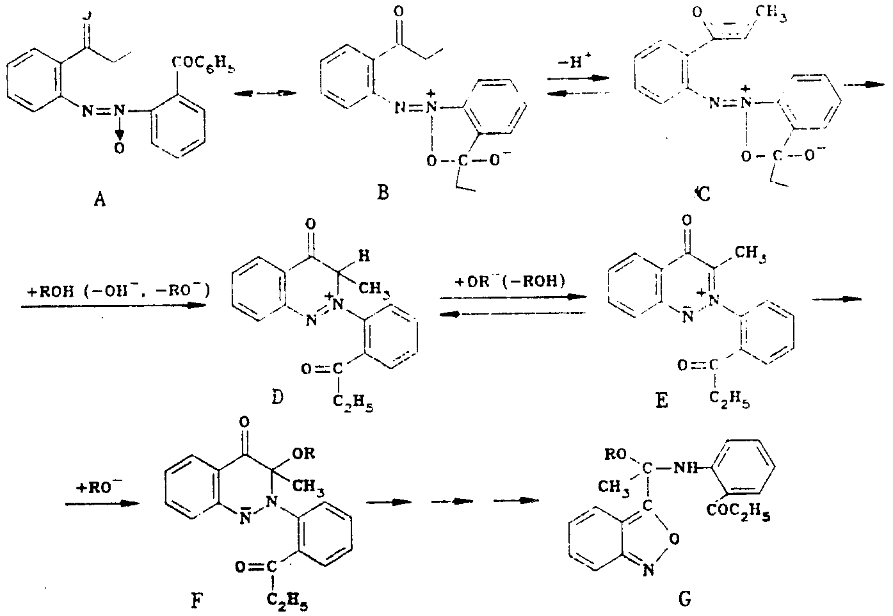
X-ray structural analysis has revealed that the product of base-promoted intramolecular rearrangement of 2,2'-dipropionylazoxybenzenes has a 1-(2-propionylphenylamino)-2-methyl-2-methoxyindolin-3-one structure, not that of 3-[1-alkoxy-1-(2-propionylphenylamino]ethylbenzo[c]isoxazole, as was previously thought.

In previous studies [1, 2] of the base-catalyzed reactions of 2,2'-dipropionylazoxybenzenes in alcohol media the product formed in quantitative yield was assigned the 3-(1-arylamino)ethylbenzo[c]isoxazole structure (G, Scheme 1), based on its UV, IR, NMR, and mass spectral data.

Scheme 1



Since this type of transformation of azoxybenzenes had not been described previously, we initiated a series of experiments in order to determine a feasible mechanism for this reaction. We have established that rearrangement of 2,2'-dipropionylazoxybenzenes takes place in the presence of catalytic amounts of base, is intramolecular in nature, and involves a solvent molecule as reagent. We have also found that the size or volume of the alkyl radical in the alcohol participating in the reaction can be a restraining factor, and that there must be two propionyl groups present in the molecule, in the 2 and 2'-positions of the azoxybenzene for the reaction to occur, with one of the propionyl groups involved in intramolecular deoxygenation of one of the reaction intermediates.

Taking into account these experimental facts, as well as the proposed structure of the reaction product, we hypothesized an appropriate scheme for the transformation of dipropionylazoxybenzenes (Scheme 1).

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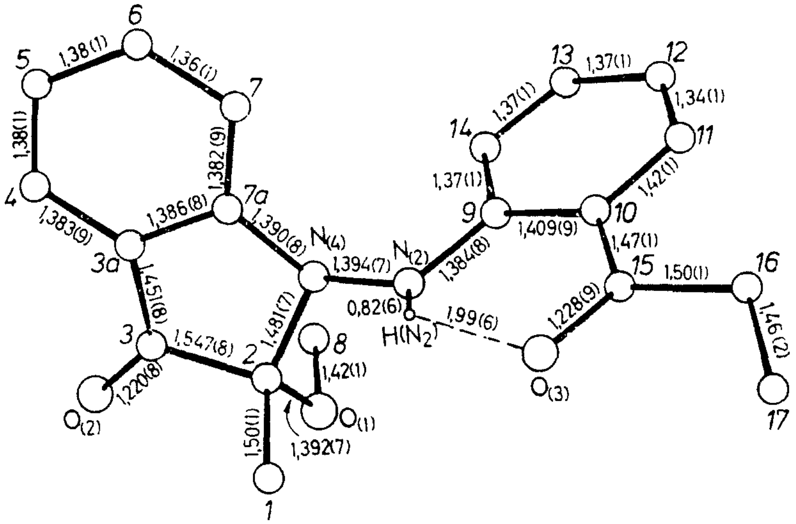
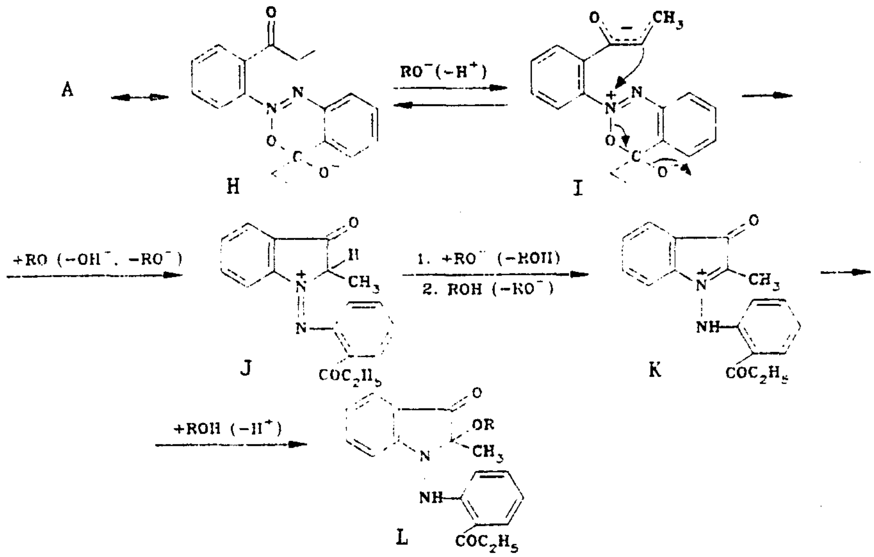


Fig. 1. Molecular structure of I and its bond lengths, Å.

This hypothetical heterocyclization scheme presumes regioselective attack of the carbanion C formed upon treatment with base at the distance nitrogen atom in the azoxy group, resulting in the formation of an intermediate with a cinnoline structure D; this appears to us to be the key step involved in the conversion of azoxy compounds into the reaction product G.

However, in another earlier study [3] it was shown that azoxybenzenes containing only one propionyl group gave, in addition to reaction products derived from intermediate cinnoline-type precursors (type E), compounds containing an indolinone ring. These results suggested to us that reactions of ortho-disubstituted azoxybenzenes could in principle proceed via an alternative pathway leading to a different final result.

Scheme 2



As can be seen from Scheme 2, in this case attack of the intermediate carbanion I also occurs at the nitrogen atom carrying the oxygen group; however, the anion is formed initially from the propionyl group closer to this nitrogen atom.

Since the principal criterion underlying in each case the proposed rearrangement scheme of dipropionylazoxybenzenes is the structure of the final reaction product (other criteria, as will be shown, are common to both reaction variations), we decided to return to the question of its structure. Toward this end, the reaction of 2,2'-dipropionylazoxybenzene (A) was carried out in the presence of a catalytic amount of sodium hydroxide in methanol solution, and the structure of the resulting product was examined by x-ray analysis (XRA).

The IR, UV, and PMR spectral data were found to be identical to those reported in the literature [1] for the reaction product of azoxybenzene A under the same reaction conditions. However, based on x-ray structural analysis, we conclude that

TABLE 1. Bond Angles in Molecule I

Angle	ω°	Angle	ω°	Angle	ω°
$C_{(2)}O_{(1)}C_{(8)}$	114,2(5)	$C_{(2)}C_{(3)}C_{(3a)}$	108,1(5)	$C_{(10)}C_{(9)}C_{(14)}$	120,2(6)
$N_{(2)}N_{(1)}C_{(2)}$	116,9(4)	$C_{(3)}C_{(3a)}C_{(4)}$	131,7(6)	$C_{(9)}C_{(10)}C_{(11)}$	115,9(7)
$N_{(2)}N_{(1)}C_{(7a)}$	118,9(5)	$C_{(3)}C_{(3a)}C_{(7a)}$	106,8(5)	$C_{(9)}C_{(10)}C_{(15)}$	123.8(6)
$C_{(2)}N_{(1)}C_{(7a)}$	109,4(4)	$C_{(4)}C_{(3a)}C_{(7a)}$	121,5(6)	$C_{(11)}C_{(10)}C_{(15)}$	120.3(7)
$N_{(1)}N_{(2)}C_{(9)}$	119,2(5)	$C_{(3a)}C_{(4)}C_{(5)}$	117,0(6)	$C_{(10)}C_{(11)}C_{(12)}$	123,1(9)
$O_{(1)}C_{(2)}N_{(1)}$	113,0(5)	$C_{(4)}C_{(5)}C_{(6)}$	120,8(7)	$C_{(11)}C_{(12)}C_{(13)}$	119,6(9)
$O_{(1)}C_{(2)}C_{(1)}$	106,2(5)	$C_{(5)}C_{(6)}C_{(7)}$	122,6(7)	$C_{(12)}C_{(13)}C_{(14)}$	120,0(8)
$O_{(1)}C_{(2)}C_{(3)}$	114,4(5)	$C_{(6)}C_{(7)}C_{(7a)}$	117,3(7)	$C_{(9)}C_{(14)}C_{(13)}$	121,2(7)
$N_{(1)}C_{(2)}C_{(1)}$	113,4(5)	$N_{(1)}C_{(7a)}C_{(3a)}$	111,9(5)	$O_{(3)}C_{(15)}C_{(10)}$	120,6(7)
$N_{(1)}C_{(2)}C_{(3)}$	100,5(4)	$N_{(1)}C_{(7a)}C_{(7)}$	127,4(6)	$O_{(3)}C_{(15)}C_{(16)}$	118,8(7)
$C_{(1)}C_{(2)}C_{(3)}$	109,5(5)	$C_{(3a)}C_{(7a)}C_{(7)}$	120,7(6)	$C_{(10)}C_{(15)}C_{(16)}$	120,6(7)
$O_{(2)}C_{(3)}C_{(2)}$	123,2(5)	$N_{(2)}C_{(9)}C_{(10)}$	119,2(6)	$C_{(15)}C_{(16)}C_{(17)}$	115,1(8)
$O_{(2)}C_{(3)}C_{(3a)}$	128,7(6)	$N_{(2)}C_{(9)}C_{(14)}$	120,5(6)		

TABLE 2. Atomic Coordinates (×10^4) and Equivalent Isotropic Temperature Factors B (Å^2) in the Molecular Structure of I

Atom	x	y	z	B
$O_{(1)}$	3950(4)	2540(5)	3164(2)	4,5(1)
$O_{(2)}$	3323(4)	5233(4)	3912(2)	5,7(2)
$O_{(3)}$	5733(5)	4052(6)	964(2)	6,4(2)
$N_{(1)}$	3162(5)	4206(6)	2288(2)	3,6(2)
$N_{(2)}$	3825(5)	3770(6)	1756(2)	4,8(2)
$C_{(1)}$	5451(8)	4480(9)	2944(3)	5,0(3)
$C_{(2)}$	3956(7)	4033(7)	2931(3)	3,6(2)
$C_{(3)}$	3197(6)	5202(7)	3324(3)	4,0(2)
$C_{(3a)}$	2366(6)	6185(7)	2874(3)	3,5(2)
$C_{(4)}$	1639(6)	7514(8)	2965(3)	4,5(2)
$C_{(5)}$	985(7)	8213(8)	2420(5)	5,7(3)
$C_{(6)}$	1072(8)	7604(10)	1818(4)	5,6(3)
$C_{(7)}$	1785(7)	6301(9)	1724(3)	4,6(2)
$C_{(7a)}$	2437(6)	5581(7)	2264(3)	3,4(2)
$C_{(8)}$	2610(10)	1967(9)	3246(4)	5,8(3)
$C_{(9)}$	3110(8)	2896(7)	1277(3)	3,9(2)
$C_{(10)}$	3729(8)	2581(8)	711(3)	4,5(2)
$C_{(11)}$	2956(12)	1627(10)	253(4)	6,6(3)
$C_{(12)}$	1703(12)	1069(11)	337(4)	7,9(4)
$C_{(13)}$	1115(8)	1422(9)	889(4)	6,5(3)
$C_{(14)}$	1821(9)	2325(8)	1353(3)	5,1(2)
$C_{(15)}$	5090(9)	3164(8)	585(3)	4,9(2)
$C_{(16)}$	5722(12)	2691(10)	−8(3)	7,2(3)
$C_{(17)}$	7152(16)	3181(12)	−33(5)	9,1(4)

TABLE 3. Hydrogen Atom Coordinates (×10^3) in the Molecular Structure of I

Atom	x	y	z
$H_{(N2)}$	446(5)	430(7)	164(3)
$H_{(1,1)}$	552(6)	540(6)	277(3)
$H_{(1,2)}$	588(5)	442(6)	339(2)
$H_{(1,3)}$	590(5)	381(6)	267(2)
$H_{(4)}$	166(5)	793(6)	341(2)
$H_{(5)}$	59(6)	905(6)	250(3)
$H_{(6)}$	66(6)	806(6)	148(3)
$H_{(7)}$	188(5)	584(6)	130(2)
$H_{(8,1)}$	273(6)	116(7)	346(3)
$H_{(8,2)}$	203(5)	206(6)	287(2)
$H_{(8,3)}$	211(5)	250(6)	359(2)
$H_{(11)}$	340(6)	148(7)	−8(3)
$H_{(12)}$	115(6)	54(6)	2(2)
$H_{(13)}$	28(6)	104(7)	96(3)
$H_{(14)}$	146(5)	247(6)	174(2)
$H_{(16,1)}$	508(5)	311(6)	−39(3)
$H_{(16,2)}$	569(5)	158(6)	−3(2)
$H_{(17,1)}$	743(5)	270(6)	−41(3)
$H_{(17,2)}$	735(7)	415(6)	5(3)
$H_{(17,3)}$	786(5)	302(6)	38(3)

these spectral parameters correspond to the structure of 1-(2-propionylphenylamino)-2-methyl-2-methoxyindolin-3-one (I), and not to compound G, as reported previously.

The general molecular structure of indolin-3-one I was established (Fig. 1), and its bond lengths and bond angles were determined (Table 1). The heterocycle in the molecule adopts an envelope conformation; the $C_{(2)}$ atom deviates by 0.247(6) Å from the plane of the other four atoms, which are coplanar within an accuracy of 0.025(6) Å, and the methyl group is located in a pseudoaxial position, the methoxy group in a pseudoequatorial position. Atom $N_{(1)}$ is pyramidal, while atom $N_{(2)}$ has a planar bond configuration; the unshared electron pairs on these two atoms, however, apparently do not interact with one another: The $C_{(7a)}N_{(1)}N_{(2)}C_{(9)}$ torsional angle τ is equal to −90.3(8)°. The propionyl group is oriented in the plane of the phenyl ring; this molecular conformation is stabilized by intramolecular hydrogen-bond formation $N_{(2)}$–$H(N_2)$...$O_{(3)}$ [N...O 2.624(8), N–H 0.82(6), O...H 1.99(6) Å, ∠N–H...O = 171(1)°]. The other geometric parameters for the indolin-3-one I molecule are within normal limits, and there are no short intermolecular contacts in the structure.

It is interesting that under electron-impact conditions compound I decays to give fragments which correspond more closely to the structure of benzo[c]isoxazole (G) than indolin-3-one I. We cannot exclude the possibility that type I indolinones under electron-impact conditions readily undergo rearrangement to the isomeric benzo[c]isoxazoles; this may have been a contributing factor in the erroneous conclusions drawn in previous studies concerning the structure of the 2,2'-dipropionylazoxybenzene reaction product.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on Varian T-60 and XL-100 spectrometers (with TMS standard, CCl_4 solvent). Infra-red spectra were obtained on an IR 220 spectrophotometer (using Vaseline mulls), UV spectra were measured on a Cary-15 spectrophotometer (in methanol solvent), and mass spectra were recorded on an MKh-1403 spectrometer (at an ionizing electron energy of 80 eV).

Crystals of compound I are monoclinic, at 20°C: $a = 9.702(1)$, $b = 8.739(1)$, $c = 20.865(2)$ Å, $\beta = 96.22(7)°$, $Z = 4$, space group $P2_1/c$. The elementary cell parameters and the intensities of 980 reflections with $I \leq 2\sigma$ (I) were measured using a Hilger Watts four-circle diffractometer ($\lambda_{MoK\alpha}$, graphite monochromator, θ/θ-scanning, $\theta \leq 30°$). The structure of I was solved by direct methods and refined by full matrix least squares using anisotropic approximations for all of the nonhydrogen atoms. All of the hydrogen atoms were visualized in a difference Fourier synthesis and refined isotropically with $B_{iso} = 5$ Å^2. The final dispersion factors were $R = 0.053$ and $R_w = 0.049$. All of the calculations were performed on an Eclipse S/200 computer using the INEXTL system of programs [4]. The atomic coordinates for the molecular structure of I are given in Tables 2 and 3.

1-(2-Propionylphenylamino)-2-methyl-2-methoxyindolin-3-one (I). To a solution of 3.1 g (10 mmoles) compound A in 100 ml methanol was added a solution of 5 mmoles NaOH in 25 ml methanol and the mixture was stirred at 20°C for 2 h. The solvent was evaporated and the resulting crystals were recrystallized from methanol. Yield 3.03 g (94%) of compound I, mp 115°C [2]. UV spectrum, λ_{max} (log ε): 234 (4.01), 263 (1.21), 367 nm (7.56). PMR spectrum: 1.16 (t, CH_2CH_3); 1.33 (s, CH_3); 3.01 (q, CH_2CH_3); 3.11 (s, OCH_3); 6.51-7.83 (m, Ar), 10.16 ppm (s, NH). IR spectrum: 1720 (C=O), 3280 cm^{-1} (NH). Mass spectrum, m/z (%): M^+ 324 (48), 293 (71), 292 (60), 277 (21), 263 (44), 249 (43), 235 (48), 176 (96), 144 (100), 120 (95), 119 (37), 105 (21), 92 (45).

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