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STUDIES OF 4H-3,1-BENZOXAZINES.

13.* BROMINATION OF 1,2-DIHYDRO-4H-3,1-BENZOXAZINES

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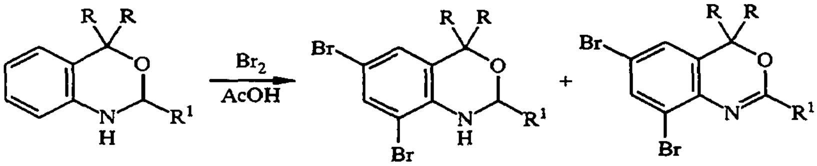
Bromination of 2,4-substituted 1,2-dihydro-4H-benzoxazines with bromine in acetic acid was conducted. It was shown that either the corresponding 6,8-dibromo-1,2-hydrobenzoxazines or the products of their dehydrogenation — 6,8-dibromobenzoxazines, are primarily formed as a function of the structure of the dihydrobenzoxazine and the concentration of bromine in the reaction mixture. The structure of 6,8-dibromo-2-(5-nitrofuryl-2)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine was investigated by XSA. A stacking interaction between the nitrofuran fragment of one molecule and the condensed benzene ring of the other was detected in the crystal.

In a previous communication [2], using a single example, it was shown that bromination of 1,2-dihydro-4H-3,1-benzoxazines takes place at the benzene ring annelated with the heterocycle with formation of a dibromo-substituted ring, and the bromine atoms enter into the *ortho* and *para* positions of the relative amine group, that is, similar to bromination of aniline. Traces of another product not mentioned in [2] were also found. Bromination of a series of compounds with different substituents in positions 2 and 4 of the oxazine fragment of the molecule was conducted in the present study to investigate the transformations that take place in more depth.

Starting compounds (Ia-h) were brominated with a solution of bromine in acetic acid at 0-5°C [3] with a six-fold excess of bromine and with different concentrations of bromine in the reaction mixture.



Ia-h IIa-c IIIa, b

Ia, f-h, IIa, IIIa R = C_2H_5; Ib, d-e, IIb, IIIb R = C_6H_5; Ic R = CH_3; Ia, b, IIa, b, IIIa, b R^1 = 5-nitrofuryl-2; Ic, IIc R^1 = CCl_3; Id R^1 = CH_3; Ie R^1= C_6H_5; If R^1 = furyl-2; Ig R^1 = 5-methylfuryl-; Ih R^1 = 5-bromofuryl-2

It was found that outside of the dependence on the concentration of bromine, only the derivatives containing acceptor substituents in position 2 of the hetero ring (trichloromethyl, nitrofuryl) react smoothly. Compounds having furyl, 5-methyl-, and 5-bromofuryl (If-h) residues in position 2 were totally resinified during the reaction, probably under the effect of the HBr liberated. In the case of compounds with electron-donor substituents (Id and Ie), the reaction did not continue to the end, and a large part of the starting compound went out of the reaction in the form of nonreactive hydrobromides.

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*See [1] for Communication 12.

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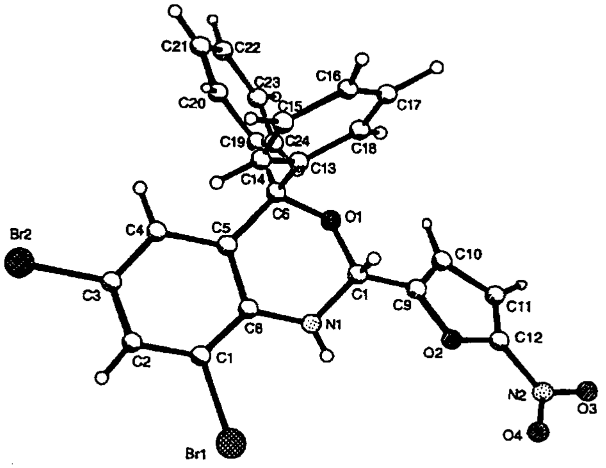

Fig. 1. Projection of the three-dimensional model of the molecule of 6,8-dibromo-2-(5-nitrofuryl-2)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (IIb).

With low concentrations (2-3%) of bromine, compounds Ia-c are basically converted into the corresponding 6,8-dibromo derivatives (IIa-c). With higher concentrations of bromine in the reaction mixture, products of a further transformation — dehydrogenation — appear in the reaction mixture, and when the concentrations of bromine are 10% and higher, these products (IIIa, b) become the basic products. In other words, in high concentrations, bromine oxidizes the products of bromination IIa, b with formation of conjugation-stabilized compounds IIIa, b. Special experiments showed that addition of 1,2-dihydro derivatives IIa, b in a concentrated solution of bromine in acetic acid results in their rapid oxidation into the corresponding benzoxazines IIIa, b. Trichloromethyl derivative IIc is stable in these conditions, perhaps because dehydrogenation does not lead to a sufficiently developed conjugation system.

The structure of the synthesized compounds is unambiguously confirmed by the elementary composition and spectral data (Tables 1 and 2). The SSCC of the protons in the condensed benzene ring (protons H_b and H_c, Table 2) confirm their mutual *meta* position, and the chemical shift of these protons confirms their position relative to the nitrogen-containing substituent. Conversion of 1,2-dihydro derivatives IIa, b to the corresponding benzoxazines III is accompanied by the appearance of an intense absorption band of a C=N group (1620-1630 cm^{-1}) and the disappearance of the bands of stretching vibrations of the NH group in the IR spectrum. In the UV spectra, there is a bathochromic shift of the band of a π,π-transition (Table 1), which indicates an increase in the conjugation system. In the mass spectra, in addition to a decrease in the molecular ion by two mass units, there is also a change in the character of its fragmentation.

We focused on the fact that compounds IIa, b, colorless in solution, crystallize into yellow crystals, and the color of the crystals does not change on repeated recrystallizations. This suggested some specific intermolecular interaction in the crystal which leads to the formation of a charge-transfer complex and consequently the appearance of color. To elucidate the character of this interaction and more finely study the structure of compounds II, an x-ray structural study of a single crystal of compound IIb grown from alcohol solution was conducted.

The projection of the molecular model of compound IIb is shown in Fig. 1, and the coordinates of the atoms, bond lengths in the molecule, and some valence and dihedral angles are reported in Tables 3-5.

There are four symmetrically independent molecules in the unit cell of the crystal, but since their geometry is indistinguishable, an overall view of one of them is shown in Fig. 1. As Table 4 indicates, there are no strongly distorted bonds in molecule IIb which differ in length from the standard bonds. The condensed benzene ring is planar (plane 1, the average deviation does not exceed 0.0046 Å). The 1,2-dihydrooxazine fragment annelated with it has a distorted twist-boat conformation. The deformation parameters calculated according to [4] are: $S = 0.84$, $\theta = 58°$, $\varphi = 107°$. The $N_{(1)}$ and $O_{(1)}$ atoms go out on one side of plane 1 by 0.1058 and 0.5368 Å, and atoms $C_{(6)}$ and $C_{(7)}$ go out on the other side by 0.0313 and 0.1174 Å. The $H_{(1N)}$ hydrogen atom and nitrofuran and benzene $C_{(13)}$-$C_{(18)}$ rings are located on pseudoequatorial, while the $H_{(7)}$ atom and $C_{(19)}$-$C_{(24)}$ phenyl group are located on pseudoaxial bonds.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	R_f	UV spectrum (ethanol), λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	M$^+$	Yield, %
		C	H	N	Hal						
IIa	$C_{16}H_{16}Br_2N_2O_4$	41,32 41,77	3,52 3,50	6,15 6,09	34,42 34,73	150...152	0,57	251 (4,04), 305 (4,10)	3300 (NH); 1510, 1340 (NO_2)		68
IIb	$C_{24}H_{16}Br_2N_2O_4$	51,42 51,83	2,53 2,90	5,33 5,04	28,35 28,73	173...176	0,65	252 (4,12), 310 (4,20)	3390 (NH); 1520, 1350 (NO_2)	554*	75
IIc	$C_{11}H_{10}Cl_3Br_2NO$	30,41 30,10	2,39 2,28	3,40 3,19	60,85 60,77	105...106	0,85	242 (3,99), 285 (3,49)	3380 (NH)		85
IIIa	$C_{16}H_{14}Br_2N_2O_4$	41,58 41,95	3,24 3,08	6,35 6,12	35,06 34,88	202...204	0,54	271 (4,07), 366 (4,18)	1620 (C=N); 1510, 1330 (NO_2)		65
IIIb	$C_{24}H_{14}Br_2N_2O_4$	51,62 52,01	2,75 2,55	5,28 5,05	29,05 28,84	231...232	0,60	268 (4,15), 368 (4,28)	1630 (C=N); 1520, 1340 (NO_2)	552*	72

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*The values of m/z of the molecular ions are reported for light isotopes of bromine.

TABLE 2. PMR Spectra of the Synthesized Compounds

Compound	Solvent	δ, ppm						SSCC, Hz
		H_R	H_{R^1}	Ha	Hb	Hc	NH	
IIa	$CDCl_3$	0,62 (t, 3H, CH_2CH_3)and1,85 (q,, 2H, CH_2CH_3); 0,90 (t, 3H, CH_2CH_3) and 1,96 (q, 2H, CH_2CH_3)	6,72 (d, 1H, β'-H), 7,30 (d, 1H, β-H)	5,68 s	7,44 d	7,00 d	4,77 (br. s)	$J_{CH_2CH_3}$ = 6,5, $J_{\beta\beta'}$ = 4,0, J_{bc} = 3,0
IIb	$CDCl_3$	7,20...7,35 (m, 10H, 2 × C_6H_5)	6,78 (d, 1H, β'-H), 7,42 (d, 1H, β-H)	5,72 d,	7,58 d	6,78 d	4,98 d	J_{NHHa} = 3,0, $J_{\beta\beta'}$ = 4,0, J_{bc} = 3,0
IIc	$CDCl_3$	1,51 (t, 3H, CH3), 1,60 (t, 3H, CH_3)	—	5,01 s	7,41 d	7,14 d	5,33	J_{bc} = 3,0
IIIa	$(CD_3)_2CO$	0,60 (t, 6H, 2 × CH_2CH_3), 1,80 (q, 4H, 2 × CH_2CH_3)	7,74 (d, 1H, β'-H), 7,77 (d, 1H, β-H)	—	7,87 d	7,60 d	—	$J_{CH_2CH_3}$ = 7,2, $J_{\beta\beta'}$ = 4,0, J_{bc} = 3,0
IIIb	$CDCl_3$	7,15...7,36 (m, 10H, 2 × C_6H_5)	* 6,72 (d, 1H, β'-H)	—	7,80 d	7,36 d	—	$J_{\beta\beta'}$ = 4,0, J_{bc} = 3,0

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*The signal of the β-H proton is masked by a multiplet of aromatic protons.

TABLE 3. Coordinates of Atoms (Å × 10^4) and Temperature Factors (Å × 10^3) of Compound IIb*

Atom	*x*	*y*	*z*	*U*
$Br_{(1)}$	5374(1)	4000(1)	6374(1)	62(1)
Br2	8426(1)	1783(1)	6262(1)	53(1)
$O_{(1)}$	5482(2)	2615(2)	1911(3)	34(1)
$O_{(2)}$	3458(2)	3831(2)	2394(3)	40(12)
$O_{(3)}$	2016(3)	5331(3)	1066(4)	98(2)
$O_{(4)}$	1967(3)	4702(3)	2863(5)	84(2)
$N_{(1)}$	5079(3)	3265(3)	3749(3)	41(1)
$N_{(2)}$	2313(4)	4837(3)	1859(5)	60(2)
$C_{(1)}$	6093(4)	3171(3)	5514(4)	37(2)
$C_{(2)}$	6871(3)	2859(3)	6087(4)	39(2)
$C_{(3)}$	7366(3)	2233(3)	5475(4)	37(2)
$C_{(4)}$	7099(3)	1919(3)	4305(4)	31(2)
$C_{(5)}$	6317(3)	2234(3)	3725(4)	31(1)
$C_{(6)}$	5993(3)	1889(3)	2442(4)	31(2)
$C_{(7)}$	4703(3)	2824(3)	2624(4)	37(2)
$C_{(8)}$	5812(3)	2885(3)	4337(4)	34(2)
$C_{(9)}$	4228(3)	3502(3)	1858(4)	35(2)
$C_{(10)}$	4373(4)	3833(4)	719(5)	49(2)
$C_{(11)}$	3645(4)	4412(4)	499(5)	51(2)
$C_{(12)}$	3131(3)	4384(3)	1516(5)	42(2)
$C_{(13)}$	5315(3)	935(3)	2445(4)	30(2)
$C_{(14)}$	5302(3)	258(3)	3350(4)	35(2)
$C_{(15)}$	4732(4)	-619(3)	3232(4)	42(2)
$C_{(16)}$	4157(4)	-816(4)	2224(5)	48(2)
$C_{(17)}$	4147(4)	-145(4)	1319(5)	51(2)
$C_{(18)}$	4730(3)	728(4)	1426(4)	45(2)
$C_{(19)}$	6820(3)	1815(3)	1561(4)	32(2)
$C_{(20)}$	7268(3)	998(3)	1546(4)	36(2)
$C_{(21)}$	7982(4)	887(4)	713(5)	47(2)
$C_{(22)}$	8262(3)	1592(4)	-130(5)	53(2)
$C_{(23)}$	7841(4)	2412(4)	-111(4)	51(2)
$C_{(24)}$	7124(3)	2523(4)	740(4)	42(2)

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*The coordinates of hydrogen atoms are not reported and can be obtained from the authors.

The planar furan ring (the nitro group lies in the plane of the furan ring) almost ideally shields the $C_{(7)}-O_{(1)}$ bond (the $O_{(1)}-C_{(7)}-C_{(9)}-C_{(10)}$ torsion angle is equal to 5.2°). As a result, $O_{(1)}$-$H_{(10)}$ intramolecular contact (2.676 Å), which fixes this reciprocal position, is possible.

The position of the phenyl substituents at the $C_{(6)}$ atom can in our opinion be conveniently described by the angles of their rotation relative to an arbitrary plane drawn through the $C_{(5)}$, $C_{(6)}$, and $O_{(1)}$ atoms (plane 2). The $C_{(13)}$-$C_{(18)}$ benzene ring is rotated relative to plane 2 by 49.5° to one side and the $C_{(19)}$-$C_{(24)}$ benzene ring is rotated by 62.5° to the other side. As a result, both phenyl substituents are almost mutually perpendicular (the angle between their planes is equal to 86.5°), and the $H_{(20)}$ atom is at a distance of 2.43 Å from the plane of the $C_{(13)}$-$C_{(18)}$ benzene ring, which probably also causes strong distortion of the $C_{(19)}-C_{(6)}-C_{(13)}$ valence angle (up to 124°).

In the crystal, the nitrofuran ring of one molecule is positioned almost parallel to the condensed benzene ring of another molecule (Fig. 2, angle between planes of 0.8°). The distance between the centers of the rings of 3.55 Å implies the possibility of overlapping of their π systems (stacking interaction). Since the electron-acceptor nitro group decreases the energy level of

TABLE 4. Bond Lengths (Å) in the Molecule of Compound IIb*

Bond	d, Å	Bond	d, Å
$Br_{(1)}$—$C_{(1)}$	1,900(5)	$N_{(2)}$—$C_{(12)}$	1,439(7)
$Br_{(2)}$—$C_{(3)}$	1,902(5)	$C_{(1)}$—$C_{(2)}$	1,382(7)
$O_{(1)}$—$C_{(6)}$	1,453(5)	$C_{(1)}$—$C_{(8)}$	1,390(6)
$O_{(1)}$—$C_{(7)}$	1,406(5)	$C_{(2)}$—$C_{(3)}$	1,374(7)
$O_{(2)}$—$C_{(9)}$	1,365(6)	$C_{(3)}$—$C_{(4)}$	1,389(6)
$O_{(2)}$—$C_{(12)}$	1,359(6)	$C_{(4)}$—$C_{(5)}$	1,392(6)
$O_{(3)}$—$N_{(2)}$	1,223(7)	$C_{(5)}$—$C_{(6)}$	1,535(6)
$O_{(4)}$—$N_{(2)}$	1,205(7)	$C_{(5)}$—$C_{(8)}$	1,408(6)
$N_{(1)}$—$C_{(7)}$	1,445(6)	$C_{(6)}$—$C_{(13)}$	1,542(6)
$N_{(1)}$—$C_{(8)}$	1,384(6)	$C_{(7)}$—$C_{(9)}$	1,498(7)
$C_{(11)}$—$C_{(12)}$	1,324(7)	$C_{(9)}$—$C_{(10)}$	1,337(7)
$C_{(6)}$—$C_{(19)}$	1,522(6)	$C_{(10)}$—$C_{(11)}$	1,417(8)

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*The bond lengths of benzene rings can be obtained from the authors.

TABLE 5. Some Valence (φ) and Torsion (θ) Angles in the Molecule of Compound IIb

Angle	φ, deg	Angle	φ, deg
$O_{(1)}$—$C_{(6)}$—$C_{(5)}$	107,0(3)	$O_{(1)}$—$C_{(6)}$—$C_{(5)}$—$C_{(8)}$	24,2
$C_{(6)}$—$C_{(5)}$—$C_{(8)}$	119,3(4)	$C_{(6)}$—$C_{(5)}$—$C_{(8)}$—$N_{(1)}$	-4,9
$C_{(5)}$—$C_{(8)}$—$N_{(1)}$	120,2(4)	$C_{(5)}$—$C_{(8)}$—$N_{(1)}$—$C_{(7)}$	13,8
$C_{(8)}$—$N_{(1)}$—$C_{(7)}$	118,3(4)	$C_{(8)}$—$N_{(1)}$—$C_{(7)}$—$O_{(1)}$	-42,7
$N_{(1)}$—$C_{(7)}$—$O_{(1)}$	108,4(3)	$N_{(1)}$—$C_{(7)}$—$O_{(1)}$—$C_{(6)}$	66,5
$C_{(7)}$—$O_{(1)}$—$C_{(6)}$	113,7(3)	$C_{(7)}$—$O_{(1)}$—$C_{(6)}$—$C_{(5)}$	-56,1
$C_{(13)}$—$C_{(6)}$—$C_{(14)}$	124,0(4)	$O_{(1)}$—$C_{(7)}$—$C_{(9)}$—$C_{(10)}$	5,2

the LUMO of the furan ring π system and the donor alkylamino group increases the energy level of the benzene ring HOMO, we can hypothesize that this stacking interaction causes the electronic transition manifested by the yellow color of the crystals of compound IIb.

EXPERIMENTAL

The IR spectra were recorded in suspension in liquid petrolatum on a Specord IR-71. The PMR spectra were made on Tesla BS-467 A (60 MHz, HMDS internal standard) and Varian HA-100D (100 MHz) spectrometers. The electronic absorption spectra were made on a Specord M-40 spectrophotometer in alcohol. The mass spectra were made on an LKB-2091 spectrometer with direct introduction of the substance in the ion source and ionizing electron energy of 70 eV at a temperature of 50°C. TLC was conducted on Silufol UV-254 plates, benzene was the eluent, and the developer was iodine vapors.

X-ray Structural Study. Light yellow monoclinic crystals of compound IIb, grown from alcohol solution, had the following unit cell parameters: $a = 14.024(3)$, $b = 14.177(2)$, $c = 10.973(2)$ Å, $\gamma = 97.91(1)°$; $V = 2153.81(1, 2)$ Å^3, $\rho = 1.66$ g/cm^3, $P2_{1/a}$ space group, $Z = 4$. The unit cell parameters and intensities of 1753 independent reflections with $I > 3\sigma(I)$ were obtained on a Nicolet P1 automatic diffractometer (MoKα radiation, θ/2θ scanning, $\sin\theta/WL_{(\max)} = 0.5385$). The structure was decoded by a direct method using the SHELXTL software package [5] and was refined in the anisotropic (isotropic for hydrogen atoms) approximation to divergence factors of $R = 0.024$ and $R_w = 0.025$.

Compounds Ia-h were synthesized by the method in [6].

6,8-Dibromo-2-(5-nitrofuryl-2)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (IIb). While cooling (ice-water bath), 2.46 g (15.4 mmole) of bromine was added by drops to a solution of 0.95 g (2.4 mmole) of 2-(5-nitrofuryl-2)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (Ib) in 45 ml of glacial acetic acid and then mixed for 1 h at room temperature. The precipitated crystals of product were separated by filtration, additional amounts of product were precipitated from the reaction mixture with

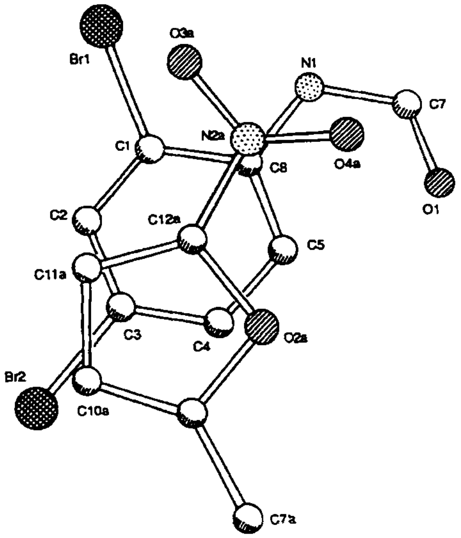

Fig. 2. Reciprocal position of fragments of molecule IIb at the site of intermolecular contact.

water, washed with a weak solution of sodium bisulfite, and dried in air. They were purified by chromatography in a column (silica gel band L 4/100 sorbent, benzene eluent).

Compounds IIa, c were prepared similarly.

6,8-Dibromo-2-(5-nitrofuryl-2)-4,4-diphenyl-4H-3,1-benzoxazine (IIIb). Here, 2.46 g (15.4 mmole) of bromine was added by drops to a solution of 0.95 g (2.4 mmole) of 2-(5-nitrofuryl-2)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (Ib) in 10 ml of glacial acetic acid while cooling (ice-water bath) and then stirred for 1 h at room temperature. The product was precipitated from the reaction mixture with water, washed with a weak solution of sodium bisulfite and dried in air, and purified by chromatography as indicated above.

Compound IIIa was obtained similarly.

The yields and characteristics of compounds IIa-c and IIIa, b are reported in Tables 1 and 2.

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