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ARYL-SUBSTITUTED 1,10*b*-DIHYDRO-5H-PYRAZOLO[1,5-*c*]-1,3-BENZOXAZINES

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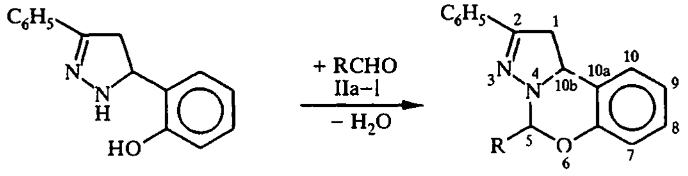
Substituted 1,10b-dihydro-5H-pyrazolo[1,5-c]1,3-benzoxazines have been obtained by condensation of 5-(2-hydroxyphenyl)-3-phenylpyrazole with aromatic aldehydes. The detailed structure of the compounds obtained has been elucidated from their ^{1}H NMR spectra by application of the nuclear Overhauser effect and the conclusions have been confirmed by an X-ray diffraction study.

The reaction of 2-hydroxysubstituted azoles with carbonyl compounds is a suitable method for the synthesis of products with a partially hydrogenated azolobenzoxazine system which deserve attraction particularly because of their physiological activity [1, 2]. In the present study some 2-substituted 1,10*b*-dihydro-5H-pyrazolo[1,5-*c*]-1,3-benzoxazines have been prepared by this route, factors which affect their formation have been studied, and peculiarities of their spacial structures are discussed. Synthesis of the desired compounds was carried out by boiling equimolar quantities of 5-(2-hydroxyphenyl)-3-phenylpyrazoline (I) with the corresponding aromatic aldehydes IIa-l in methanol, isopropanol, pyridine, or dimethylformamide.



I

IIa–l

II, III a R = C_6H_5, b R = 4-$CH_3C_6H_4$, c R = 4-FC_6H_4, d R = 2-$O_2NC_6H_4$, e R = 2-$CF_3C_6H_4$,
f R = 2-ClC_6H_4, g R = 2,4-$Cl_2C_6H_3$, h R = 4-HOC_6H_4, i R = 2-HOC_6H_4, j R = 2,4-$(CH_3O)_2C_6H_3$,
k R = 3,4-$(OCH_2O)C_6H_3$, l R = 3-CH_3O-4-HOC_6H_3

The reaction times and yields of products IIIa-l depend to an important extent both on the reaction conditions and on the nature of the substituents in the starting aldehyde. Aldehydes IIc-g, which contain electron withdrawing substituents, condensed with *o*-hydroxyphenylpyrazoline in methanol in 5-10 min to produce desired products in close to quantitative yields. With aldehydes IIa,b the yields were 70 and 63% after 30 and 60 minutes under the same conditions. On the other hand aldehydes IIh-l did not react with pyrazoline I in methanol. Compounds

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TABLE 1. Characteristics of Compounds IIIa-l

Compound	Empirical formula	Found, % / Calculated, % N	mp, °C	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Reaction time, min	Yield, % (method)
IIIa	$C_{22}H_{18}N_2O$	$\frac{8.6}{8.6}$	152 [2]	285 (21.1)	30 10 10	70 (A) 65 (B) 79 (C)
IIIb	$C_{23}H_{20}N_2O$	$\frac{8.3}{8.2}$	182	286 (18.4)	60	63 (A)
IIIc	$C_{22}H_{17}FN_2O$	$\frac{8.2}{8.1}$	142	285 (17.0)	5	98 (A)
IIId	$C_{22}H_{17}N_3O_3$	$\frac{11.4}{11.3}$	159	282 (17.0)	10	95 (A)
IIIe	$C_{23}H_{17}F_3N_2O$	$\frac{7.3}{7.1}$	105	282 (14.8)	5	97 (A)
IIIf	$C_{22}H_{17}ClN_2O$	$\frac{7.7}{7.8}$	121	283 (15.5)	5	95 (A)
IIIg	$C_{22}H_{16}Cl_2N_2O$	$\frac{7.1}{7.1}$	159	282 (16.1)	5	99 (A)
IIIh	$C_{22}H_{18}N_2O$	$\frac{8.4}{8.2}$	125-127	282 (15.7)	30 15	35 (B) 40 (C)
IIIi	$C_{22}H_{18}N_2O$	$\frac{8.1}{8.2}$	188-190	284 (16.0)	60 15	30 (B) 65 (C)
IIIj	$C_{24}H_{22}N_2O_3$	$\frac{7.5}{7.3}$	135	286 (19.2)	60 15	60 (B) 70 (C)
IIIk	$C_{23}H_{18}N_2O_3$	$\frac{7.7}{7.6}$	206-208	286 (23.3)	30 10	80 (B) 70 (C)
IIIl	$C_{23}H_{20}N_2O_3$	$\frac{7.6}{7.5}$	191-192	285 (19.7)	15	45 (C)

IIIh-l were successfully obtained by boiling the reagents in isopropanol or pyridine. When the condensation reactions were carried out in boiling dimethylformamide a considerable decrease in yield of reaction products occurred accompanied noticeable resinification of the reaction mixture.

The UV spectra of compounds IIIa-l (Table 1) are completely analogous to the spectra of previously described dihydropyrazolobenzoxazines [2]. The IR spectra contain bands at 1250 and 1160 cm^{-1} (ν^{as}COC and ν^{s}COC) and overlapping bands of the C=C and C=N skeletal vibrations of the aromatic and pyrazoline rings in the 1600 cm^{-1} region.

The ^{1}H NMR spectra provided the most information about the structure of compounds IIIa-l (Table 2). Spectra of solutions in ordinary $CDCl_3$ taken immediately after their preparation contained two groups of proton signals for the pyrazoline and oxazine rings with different ratios of the integrated intensities. Taking into account the presence of two chiral centers in compounds III, this phenomenon may be explained by the formation in solution of an equilibrium between diastereomers A and B (their structures are shown below) *via* the intermediate opening of the oxazine ring under the influence of impurities of DCl in the $CDCl_3$ (anomerization). In fact the spectrum of compound IIIa in $CDCl_3$ (freed from DCl by passage through basic Al_2O_3) contained only one set of signals, characteristic of the single isomer A, which remained unchanged for 3-5 h. Addition of ~0.1% HCl to this solution gave a mixture of the isomers with a ratio A:B = 70:30 in less than 5 minutes and this mixture did not change with time.

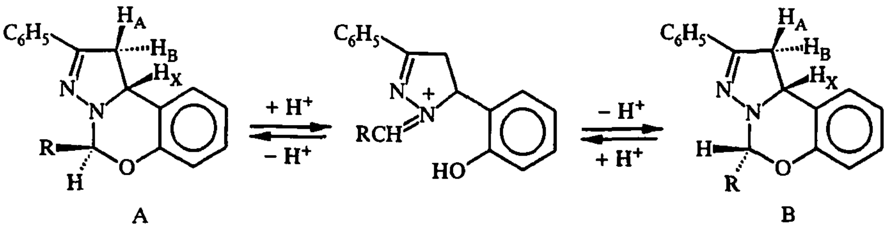

TABLE 2. ^{1}H NMR Spectra of Compounds IIIa-l (δ, ppm)

Compound	Isomer	2-H (1H, s)	6-H_AH_B		6a-HX (1H, dd)	Other protons[*2]	Isomer content, %
			H_A[*] (1H, br. d)	H_B (1H, dd)			
IIIa	A	6.89	3.23	3.53	4.76		70
	B	6.00	3.21	3.51	5.33		30
IIIb	A	6.84	3.27	3.55	4.81	2.30 (3H, s, CH_3)	75
	B	6.01	3.35	3.52	5.35	2.40 (3H, s, CH_3)	25
IIIc	A	6.92	3.27	3.57	4.78		80
	B	6.05	3.25	3.55	5.35		20
IIId	A	(7.38)[*3]	3.51	3.25	4.57		15
	B	6.75	3.47	3.23	5.34		85
IIIe	A	[*3]	[*4]	[*4]	4.62		~5
	B	6.36	3.51	3.25	5.37		~95
IIIf	A	(7.24)[*3]	3.26	3.55	4.67		20
	B	6.37	3.23	3.51	5.41		80
IIIg	A	6.99	3.24	3.53	4.61		20
	B	6.25	3.20	3.45	5.35		80
IIIh	A	6.83	3.26	3.56	4.80		70
	B	5.97	3.23	3.53	5.34		30
IIIi	A	6.85	3.35	3.55	4.67	8.86 (1H, s, OH)	70
	B	5.92	3.30	3.50	5.41	9.64 (1H, s, OH)	30
IIIj	A	5.94	3.28	3.58	4.82	3.77 (3H, s, CH_3) 3.90 (3H, s, CH_3)	30
	B	5.10	3.26	3.53	5.42	3.87 (3H, s, CH_3) 3.98 (3H, s, CH_3)	70
IIIk	A	6.01	3.20	3.52	4.80	5.87 (3H, br. s, CH_2)	70
	B	5.10	3.17	3.50	5.30	5.96 (3H, br. s, CH_2)	30
IIIl	A	5.98	3.28	3.58	4.84	3.82 (3H, s, CH_3)	70
	B	5.15	3.26	3.54	5.36	3.99 (3H, s, CH_3)	30

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[*] Coupling constants: J_{AB} = -15.3 to -16.1, J_{AX} = 0.8 to 1.5, J_{BX} = 9.4 to 9.8 Hz.

[*2] Aromatic protons of compounds IIIa-l resonate in the 6.7-8.3 range.

[*3] Signal overlapped by the aromatic proton multiplet.

[*4] Signals overlapped by the analogous signals of diastereomer B.

The stereochemistry of the isomers of compounds IIIa-l can be decided from an analysis of the ^{1}H NMR spectroscopic data for the CH–CH_2 unit (in all cases the proton signals form an ABX system with J_{AB} = -14.5 to -16.2, J_{AX} = 1.2-1.5, J_{BX} = 9.0-9.8 Hz) and the oxazine ring. The values of J_{BX} are typical for constants of the type $J_{aa'}$, which shows that proton H_X has an axial orientation in both diastereomers. However for each of the pairs (IIIA and IIIB) the chemical shifts of protons 5-H and also 10b-H (H_X) are notably different. For example the signal for the 5-H proton of isomer A is shifted by 0.7-0.8 ppm to weaker field in comparison with the analogous signal of isomer B. This indicates the equatorial orientation of this proton in IIIA molecules, because in this way it lies close to the plane of the annelated benzene nucleus and is subject to its descreening influence. In this case the observed shift to stronger field of proton 10b-H (H_X) in isomer A (by 0.5-0.7 ppm in comparison with isomer B) is well explained by the screening effect of the axially oriented 5-aryl substituent in molecules IIIA. This difference in the position of the substituent at $C_{(5)}$ in the two isomers is confirmed by the nuclear Overhauser effect with compound IIIa as an example. Double resonance at the frequency of the 5-H proton in isomer B led to an increase in the intensity of the 10*b*-H signal which shows that these protons are in a cisoid *aa*-orientation; this effect is absent for isomer A.

Thus an equilibrium is observed between diastereomers A and B in solutions of compounds III in $CDCl_3$ in the presence of traces of acid. The diastereomers have the aryl substituent at position 5 of the oxazine ring in axial and equatorial orientations respectively. Analysis of the data on the isomeric composition of the compounds obtained (Table 2) shows that there is a noticeable dependence on the nature of the substituent R. In solutions of compounds IIIa-c,h,i,k,l isomer A predominates which can be explained by the smaller eclipsing of the axial aryl

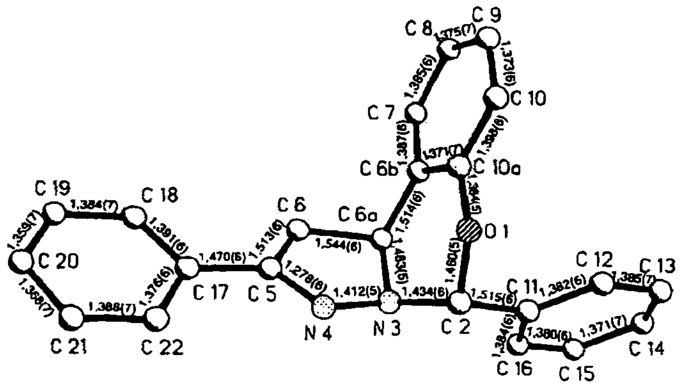

Fig. 1. Structure and bond lengths for molecule of compound IIIa (hydrogens omitted).*

TABLE 3. Some Valence (ω) and Torsion (τ) Angles in Molecule of Compound IIIa

Angle	ω, deg	Angle	τ, deg
$C_{(10a)}–O_{(1)}–C_{(2)}$	112.9(3)	$C_{(6b)}–C_{(10a)}–O_{(1)}–C_{(2)}$	24.6(5)
$N_{(4)}–N_{(3)}–C_{(6a)}$	109.5(3)	$C_{(10a)}–O_{(1)}–C_{(2)}–N_{(3)}$	-54.8
$N_{(3)}–N_{(4)}–C_{(5)}$	108.7(3)	$O_{(1)}–C_{(2)}–N_{(3)}–C_{(6a)}$	58.3(4)
$C_{(2)}–N_{(3)}–N_{(4)}$	111.8(3)	$C_{(2)}–N_{(3)}–C_{(6a)}–C_{(6b)}$	-30.2(5)
$C_{(2)}–N_{(3)}–C_{(6a)}$	114.4(3)	$N_{(3)}–C_{(6a)}–C_{(6b)}–C_{(10a)}$	-0.1(6)
$N_{(4)}–C_{(5)}–C_{(6)}$	113.8(4)	$C_{(6a)}–C_{(6b)}–C_{(10a)}–O_{(1)}$	2.5(6)
$C_{(5)}–C_{(6)}–C_{(6a)}$	100.9(4)	$N_{(3)}–N_{(4)}–C_{(5)}–C_{(6)}$	-3.1(5)
$N_{(3)}–C_{(6a)}–C_{(6b)}$	101.5(3)	$N_{(4)}–C_{(5)}–C_{(6)}–C_{(6a)}$	-11.6(5)
$N_{(3)}–C_{(6a)}–C_{(6b)}$	111.3(3)	$C_{(5)}–C_{(6)}–C_{(6a)}–N_{(3)}$	20.1(4)
$C_{(6)}–C_{(6a)}–C_{(6b)}$	112.5(3)	$C_{(6)}–C_{(6a)}–N_{(3)}–N_{(4)}$	-23.8
$C_{(6a)}–C_{(6b)}–C_{(10a)}$	122.2(4)	$C_{(6a)}–N_{(3)}–N_{(4)}–C_{(5)}$	17.8(4)
$O_{(1)}–C_{(10a)}–C_{(6b)}$	121.1(4)	$N_{(4)}–N_{(3)}–C_{(6a)}–C_{(6b)}$	96.1(4)
$O_{(1)}–C_{(2)}–N_{(3)}$	111.3(3)	$C_{(6)}–C_{(6a)}–N_{(3)}–C_{(2)}$	-150.1(3)
		$C_{(10a)}–O_{(1)}–C_{(2)}–C_{(11)}$	70.3(4)
		$C_{(6a)}–N_{(3)}–C_{(2)}–C_{(11)}$	-64.9(4)

substituent by the bonded pyrazoline ring. The considerable increase in the content of diastereomers B is observed for compounds IIId-g,j with *o*-substituted aryls, and this increase parallels the volume of the *o*-substituents. This phenomenon is probably connected with the specific stereochemical properties of the *o*-substituted phenyl nuclei, which, when in the axial orientation, in its turn increase the steric strain in the system.

The structure of isomer A of compound IIIa in the solid state was established by X-ray diffraction, the results of which (Fig. 1, Tables 3 and 4), confirm in particular the conclusion about its relative configuration reached from the ^{1}H NMR spectra. According to the X-ray diffraction analysis the pyrazoline and oxazine have a *cis*-junction (torsion angle $N_{(4)}–N_{(3)}–C_{(6a)}–C_{(6b)}$ 96.1(5)°) with a pseudoaxial orientation of the proton on the common carbon atom. The pyrazoline ring has the "envelope" conformation with atom $C_{(6a)}$ 0.37(1) Å out of the $N_{(3)}N_{(4)}C_{(5)}C_{(6)}$ plane. The oxazine ring has the sofa conformation with atom $C_{(6a)}$ 0.63 Å out of the plane of the remaining atoms. The phenyl substituent at $C_{(2)}$ has a pseudoaxial orientation (torsion angles $C_{(6a)}–N_{(3)}–C_{(2)}–C_{(11)}$ and $C_{(6a)}–N_{(3)}–C_{(2)}–H_{(11)}$ 64.9(4)° and 176.4(2)° respectively).

The torsion angles $N_{(3)}–N_{(4)}–C_{(15)}–C_{(17)}$ (174.1(3)°), $N_{(4)}–C_{(5)}–C_{(17)}–C_{(22)}$ (-8.5(6)°), and the bond lengths $C_{(5)}–N_{(4)}$ and $N_{(4)}–N_{(3)}$ (1.370(6) and 1.412(5) Å respectively) indicate the presence of conjugation between the π-electron systems of the phenyl substituent at $C_{(2)}$ and the $C_{(2)}=N_{(3)}–N_{(4)}$ unit. Nevertheless, the atom $N_{(4)}$ has a trigonal pyramidal configuration (the sum of the bond angles at this atom is 335.7(4)°).

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* The numbering of the toms in Fig. 1 and Tables 3 and 4 does not conform to the IUPAC rules for compounds III.

TABLE 4. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) of the Atoms in Molecule of Compound IIIa

Atom	x	y	z	$U_{(eq)}$
$O_{(1)}$	115(5)	2437(2)	3455(2)	53(1)
$C_{(2)}$	-981(8)	3305(4)	3455(2)	47(1)
$N_{(3)}$	-2274(6)	4119(3)	3692(3)	43(1)
$N_{(4)}$	-809(6)	4868(3)	3155(3)	50(1)
$C_{(5)}$	-1863(8)	5073(4)	2336(3)	45(1)
$C_{(6)}$	-4217(8)	4417(4)	2170(4)	56(1)
$C_{(6a)}$	-4128(7)	3535(3)	2984(3)	45(1)
$C_{(6b)}$	-3499(8)	2295(4)	2519(3)	42(1)
$C_{(7)}$	-5041(8)	1607(4)	1841(3)	57(1)
$C_{(8)}$	-4488(9)	485(4)	1378(3)	67(1)
$C_{(9)}$	-2368(9)	53(4)	1581(3)	69(1)
$C_{(10)}$	-842(9)	695(4)	2276(4)	63(1)
$C_{(10a)}$	-1448(8)	1818(4)	2749(3)	47(1)
$C_{(11)}$	-2456(7)	2645(4)	4931(3)	44(1)
$C_{(12)}$	-1870(8)	1536(4)	5171(3)	56(1)
$C_{(13)}$	-3252(9)	937(4)	5828(4)	73(1)
$C_{(14)}$	-5227(9)	1426(4)	6234(3)	72(1)
$C_{(15)}$	-5801(8)	2535(4)	6017(3)	61(1)
$C_{(16)}$	-4424(8)	3141(4)	5368(3)	56(1)
$C_{(17)}$	-876(7)	5918(3)	1661(3)	43(1)
$C_{(18)}$	-1834(9)	5984(4)	690(4)	72(1)
$C_{(19)}$	-868(9)	6742(4)	31(4)	80(1)
$C_{(20)}$	1071(9)	7435(4)	336(4)	71(1)
$C_{(21)}$	2048(9)	7392(4)	1303(4)	68(1)
$C_{(22)}$	1072(8)	6640(4)	1948(3)	54(1)

EXPERIMENTAL

The IR spectra of compounds IIIa-l were measured in KBr disks on a Specord IR-75 spectrophotometer. Electronic spectra of methanol solutions were recorded with a Specord M-40 instrument (c = 2-4$\times 10^{-3}$ mol/liter). ^1H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were measured with a Bruker AM-400 instrument. Purity of compounds was monitored by TLC on Silufol UV-254 strips with chloroform and ethyl acetate as eluents.

X-ray Diffraction Study of Compound IIIa. Crystals of compound IIIa are triclinic. At 20°C, a = 5.767(2), b = 11.264(3), c = 13.037(4) Å, α = 97.14(2)°, β = 90.20(2)°, γ = 92.94(2)°, V = 839.2(4) $Å^3$, Z = 2, d_{calc} = 1.292 g/cm^3, space group P_1. Lattice parameters and the intensities of 4073 independent reflexions with $F > 6.0\sigma(F)$ were measured on a Siemens P3/PC four-circle automatic diffractometer with a graphite monochromator with MoKα radiation ($\theta/2\theta$ scanning, $2\theta < 50°$). The structure was solved by direct methods using the SHELXTL PLUS, 4.2 suite of programs. Refinement on F in the anisotropic approximation led to R = 0.055 (R_w = 0.061). Positions of hydrogen atoms were calculated geometrically and they were refined *via* the "riding" model. Coordinates of the nonhydrogen atoms and their equivalent isotropic thermal parameters are given in Table 4.

2,5-Diphenyl-1,10*b*-dihydro-5H-pyrazolo[1,5-c]-1,3-benzoxazine (IIIa). A. A mixture of compound I (0.24 g, 1 mmol) and benzaldehyde IIa (0.11 g, 1 mmol) were boiled in methanol (10 ml). After compound I had completely dissolved (30 min) the mixture was cooled to 20°C and filtered to give compound IIIa (0.22 g); mp 152°C (methanol). Lit. mp 152°C [2].

Compounds IIIb-g were prepared analogously from the corresponding aldehydes.

B. The synthesis was analogous to method A but using isopropanol as the solvent. Yield of IIIa 0.21 g. Compounds IIIh-k were prepared analogously.

C. A mixture of compound I (0.24 g, 1 mmol) and benzaldehyde IIa (0.11 g, 1 mmol) were boiled in pyridine (0.5 ml), the solution was cooled to 20°C, mixed with hexane (20 ml), and filtered to give compound IIIa (0.24 g).

Compounds IIIh-l were prepared analogously.

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