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INVESTIGATION OF 4H-3,1-BENZOXAZINES. 12.* N-SUBSTITUTION OF 1,2-DIHYDRO-4H-3,1-BENZOXAZINES

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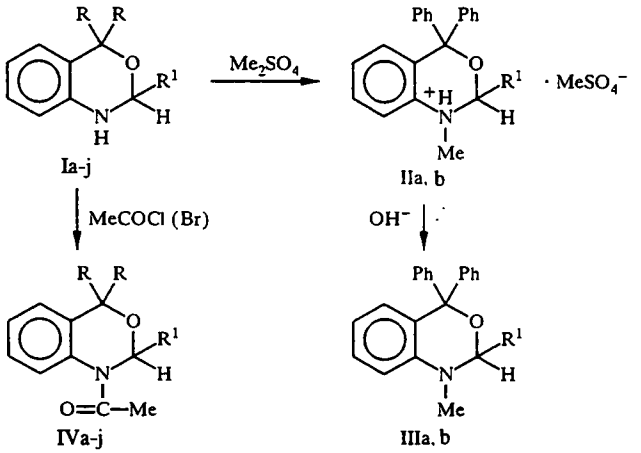
The alkylation and acylation of 2,4-disubstituted 1,2-dihydro-4H-3,1-benzoxazines were used to obtain N-methyl and N-acetyl derivatives of these compounds for the first time. ^1H NMR was used to reveal several conformational features of these compounds relative to their donor–acceptor properties at positions 2, 3, and 4 of the heterocycle.

In previous work, we have described the synthesis of 2,4-disubstituted 1,2-dihydro-4H-3,1-benzoxazines [2], their structure [3], and the mechanism for their formation [4]. Major attention in the study of dihydrobenzoxazines has been related to destruction of the heterocycle [5, 6]. Electrophilic substitution into the aromatic system is known to proceed with retention of the heterocycle [7].

In the present work, we were the first to study the substitution of dihydrobenzoxazines (Ia-Ij) in the heterocycle at the secondary nitrogen atom. Thus, the N-alkylation of Ia-Ic by dimethyl sulfate was investigated. This reaction was found to occur only for 2-alkyldihydrobenzoxazines Ia and Ib and leads to N-methyl derivatives IIIa and IIIb through the corresponding 1-methylhydrobenzoxazinium methyl sulfates (IIa and IIb). The structure of II was established in the case of methylation of dihydrobenzoxazine Ib, in which salt IIb was isolated. This salt was identified by PMR and IR spectroscopy and elemental analysis.

The corresponding 1-acetyldihydrobenzoxazines (IVa-IVj) were obtained by the acylation of dihydrobenzoxazines Ia-Ij by acetyl halides.



I—IV a—g R = C_6H_5; h-j R = CH_3; a R^1 = CH_3; b R^1 = *n*-C_3H_7; c, i R^1 = C_6H_5; d R^1 = 5-bromo-2-furyl e R^1 = CH=$CHCH_3$; f R^1 = CH=CHC_6H_5; g,h R = CCl_3; j R^1 = 5-nitro-2-furyl

*Communication 11, see [2].

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TABLE 1. Physical Indices of Products

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
IIIa	$C_{22}H_{21}NO$	83.46 83,80	6.53 6,66	4.90 4,44	86	0,65	51
IIIb	$C_{24}H_{25}NO$	83.79 83,90	7.68 7,30	4.15 4,08	112	0,68	55
IVa	$C_{23}H_{21}NO_2$	80.96 80,50	6.31 6,12	4.41 4,08	166	0,20	75
IVb	$C_{25}H_{25}NO_2$	80.65 80,80	6.26 6,75	3.97 3,77	131	0,25	73
IVc	$C_{28}H_{23}NO_2$	82.52 82,96	5.51 5,68	3.68 3,45	168	0,17	75
IVd	$C_{26}H_{20}BrNO_3$	65.54 65,90	4.34 4,23	2.62 2,96	163	0,28	62
IVe	$C_{25}H_{23}NO_2$	81.21 81,30	6.35 6,23	3.58 3,79	104...105	0,31	65
IVf	$C_{30}H_{25}NO_2$	83.71 83,53	5.52 5,80	3.38 3,25	135...137	0,18	70
IVg	$C_{23}H_{18}Cl_3NO_2$	61.62 61,81	4.29 4,03	3.31 3,13	223...225	0,32	75
IVh	$C_{13}H_{14}Cl_3NO_2$	51.10 50,90	4.61 4,57	4.42 4,57	190...191	0,41	68
IVi	$C_{18}H_{19}NO_2$	76.59 76,87	6.47 6,76	4.61 4,98	110...112	0,36	70
IVj	$C_{16}H_{16}N_2O_5$	60.88 60,76	5.25 5,06	8.52 8,86	118...120	0,23	65

This reaction proceeds upon heating I in benzene at reflux with a two-fold excess of acetyl halide for 1 h. Acylation with acetyl chloride gives N-acetyl derivatives IVa-IVe, IVi, and IVj in 62-75% yield (Table 1). Products Ig and Ih, which have an electron-withdrawing CCl_3 group, react slowly with acetyl chloride and this reaction is not complete even after 48 h. The use of more active acetyl bromide permits the preparation of their acylation products IVg and IVh in high yield in 30 min (see Table 1).

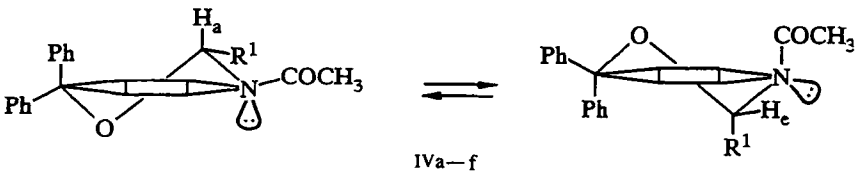
Thus, the N-substitution reaction in dihydrobenzoxazines is a function of structural factors, basicity of the nitrogen atom, and activity of the electrophilic reagent.

Products IIIa, IIIb, and IVa-IVj are crystalline compounds, which are insoluble in water but dissolve in organic solvents. Their structure was established by PMR and IR spectroscopy and mass spectrometry.

The IR spectra of all the products lack N–H stretching bands at 3400-3200 cm^{-1}. Evidence for the presence of an acyl group in IVa-IVj is found in the amide carbonyl stretching band (amide I) at 1660-1710 cm^{-1}. The shift of this band towards higher frequency for IVg (1695 cm^{-1}) and IVh (1710 cm^{-1}) is a consequence of the electron-withdrawing effect of the CCl_3 group at $C_{(2)}$ of the heterocycle [8].

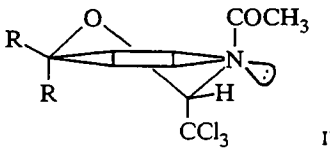
Analysis of the PMR spectra showed that the presence of the N-acyl group causes a significant downfield shift of the signal for 2-H in acyl derivatives IVa-IVj relative to this signal in the starting dihydrobenzoxazines Ia-Ij ($\delta_{IV} - \delta_I = \Delta\delta$ = 1.12-1.35 ppm) [2, 3].

Dihydrobenzoxazines Ia-Ij [2, 3] have predominantly half-chair conformation. The replacement of hydrogen in these compounds by an acyl group leads to a decrease in the basicity of the nitrogen atom, weakening of the $p-\pi$ interaction between this atom and the aromatic ring, and, as a consequence, a decrease in the conformational rigidity and inversion of the heterocycle as indicated by the singlet nature of the protons of the *gem*-diphenyl groups at $C_{(4)}$ of the heterocycle in IVa-IVf.



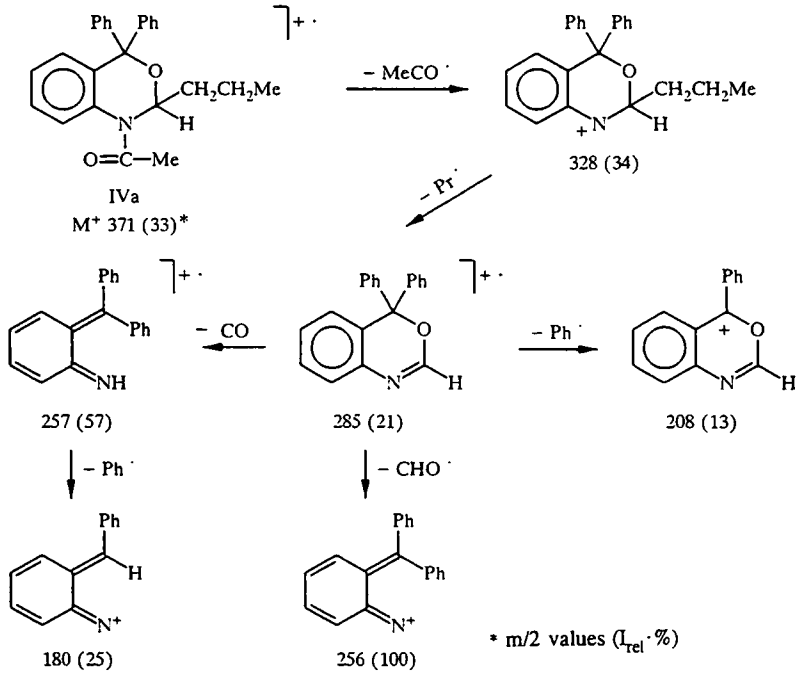
IVa—f

Inversion is not observed for IVg-IVj. The signals of the geminal methyl or phenyl substituents at $C_{(4)}$ in the ring appear as two singlets (Table 2). A stable half-chair conformation for IVg and IVh is possible with diaxial orientation of the 2-CCl_3 and 1-$COCH_3$ groups due to an anomeric effect [9].



IV g-i

The presence of a methyl group at the nitrogen atom in dihydrobenzoxazines IIIa and IIIb ($\delta_{(N\text{-}CH_2)}$ = 2.75 and 2.80 ppm, respectively) does not alter the conformation of the heterocyclic fragment of these molecules.



The mass spectrum of 1-acyl-2-*n*-propyl-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine IVb shows the molecular ion (M^+), whose initial fragmentation entails loss of acyl and alkyl radicals and then destruction of the ring. The decomposition of IVb supports its assigned structure and is in accord with the general scheme for fragmentation of 4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazines upon electron impact, in which the cation peak with *m/z* 256 is the maximum [3].

EXPERIMENTAL

The IR spectra were taken on a Specord-71 spectrometer for Vaseline mulls at room temperature. The PMR spectra were taken on a Tesla BS-467 spectrometer at 60 MHz in $CDCl_3$ with HMDS as the internal standard. The mass spectrum was taken on a Varian MAT CH-6 mass spectrometer with direct inlet into the ion source. The ionization voltage was 70 eV and the temperature was 50°C. The reaction course and purity of the products were monitored on Silufol UV-254 plates with benzene as the eluent and development by iodine vapor. Dihydrobenzoxazines Ia-Ij were prepared according to reported procedures [2, 3, 10].

1-Methyl-2-*n*-propyl-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazinium Methyl Sulfate (IIb). A sample of 5.7 g (0.045 mole) dimethyl sulfate Ib in 10 ml water was added gradually to a suspension of 1.98 g (0.006 mole) dihydrobenzoxazine Ib in 10 ml water at 10°C. The mixture was stirred at this temperature for 3 h and then extracted with

TABLE 2. Spectral Parameters for Products

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum	
	N—C—O	C=CH arom	CH_3CON	δ, ppm	Coupling constant, Hz
IIIa	1145 1090 1060	3030 1600 1580		1,40 (3H, d, 2-CH_3); 2,80 (3H, s, N—CH_3); 4,45 (1H, q, 2-H); 6,70 (4H, m, C_6H_4); 7,15and7,30 (10H, 2s, $2C_6H_5$)	$^3J_{CHCH_2}$ = 6,0
IIIb	1150 1100 1070	3030 1610 1590		0,70 (3H, t, γ-CH_3); 1,60 (4H, m, α- and β-CH_2); 2,75 (3H, s, N—CH_3); 4,25 (1H, t, 2-H); 6,60 (4H, m, C_6H_4); 7,10and7,15 (10H, 2c, $2C_6H_5$)	$^3J_{CHCH_2}$ = 6,0
IVa	1150 1080 1050	3030 1605 1580	1680	1,35 (3H, d, 2-CH_3); 1,65 (3H, s, $COCH_3$); 5,80 (1H, q, 2-H); 6,65 (4H, m, C_3H_4); 7,10 (10H, s, $2C_6H_5$)	$^3J_{CHCH_2}$ = 6,0
IVb	1140 1060 1040	3030 1610 1590	1670	0,85 (3H, t, γ-CH_3); 1,50 (4H, m, α-CH_2andβ-CH_2); 1,63 (3H, s, $COCH_3$); 5,50 (1H, t, 2-H); 6,50 (4H, m, C_6H_4); 7,16 (10H, s, $2C_6H_5$)	
IVc	1110 1080 1060	3030 1590 1580	1660	1,65 (3H, s, $COCH_3$); 6,70 (1H, s, 2-H); 6,95 (4H, m, C_6H_4); 7,15 (15H, s, $3C_6H_5$)	
IVd	1120 1080 1050	3110 3030 1590	1680	1,67 (3H, s, $COCH_3$); 6,13 (1H, s, 2-H); 5,96and6,17 (2H, d.d, H_{for}); 6,77 (4H, m, C_6H_4); 7,18 (10H, s, $2C_6H_5$)	$^3J_{3,4}$ = 3,5
IVд	1130 1050 1010	3030 1600 1590	1680	1,55 (3H, s, CH_3); 1,66 (3H, s, $COCH_3$); 5,56 (1H, d, β-CH); 6,21 (2H, m, α-CHand2-H); 6,75 (4H, m, C_6H_4); 7,30 (10H, s, $2C_6H_5$)	$^3J_{\alpha\beta}$ = 6,0
IVf	1140 1090 1020	3030 1610 1590	1690	1,70 (3H, s, $COCH_3$); 6,42 (1H, t, α-CH); 6,75 (4H, m, C_6H_4); 6,82 (1H, d, 2-H); 7,06 (1H, d, β-CH); 7,32 (15H, s, $3C_6H_5$)	$^3J_{HaCH\alpha}$ = 6,0 $^3J_{\alpha\beta}$ = 6,0
IVg	1120 1070 1020	3030 1590 1575	1695	1,60 (3H, s, $COCH_3$); 6,50 (1H, s, 2-H); 6,77 (4H, m, C_6H_4); 7,23and 7,30 (10H, 2s, $2C_6H_5$)	
IVh	1150 1080 1050	3030 1620 1600	1710	1,38and1,66(6H, 2s, $2CH_3$); 2,15 (3H, s, $COCH_3$); 6,62 (1H, s, 2-H); 7,25 (4H, m, C_6H_4)	
IVi	1110 1030 1020	3030 1600 1580	1670	1,46and1,56 (6H, 2s, $2CH_3$); 2,11 (3H, s, $COCH_3$); 6,76 (1H, s, 2-H); 7,10 (4H, m, C_6H_4); 7,18 (5H, s, C_6H_5)	
IVj	1110 1080 1020	3110 3030 1090	1680 1370* 1550*	1,43and1,50(6H, 2s, $2CH_3$); 2,20 (3H, s, $COCH_3$); 6,19and7,08 (2H, d. d, H_{for}); 6,98 (1H, s, 2-H); 7,21 (4H, m, C_6H_4)	$^3J_{3,4}$ = 4,0

*νNO_2.

chloroform. The product was precipitated from the extract by adding ether. The crystalline precipitate was filtered off, washed with petroleum ether, and dried in the air to give 1.01 g (37%) IIb, mp 167°C. IR spectrum: 2380, 1600, 1510, 1270, 1230, 1150, 1070, 1020, 830, 740 cm^{-1}. PMR spectrum: 0.70 (3H, t, γ-CH_3), 2.15 (4H, m, α-CH_2, β-CH_2), 3.70 (3H, s, N—CH_3), 3.80 (3H, s, O—CH_3), 5.40 (1H, t, 2-H), 7.18 ppm (14H, m, H_{arom}). Found: C, 65.51; H, 6.48; N, 2.74%. Calculated for $C_{25}H_{29}SNO_5$: C, 65.93; H, 6.37; N, 3.08%.

1-Methyl-2-*n*-propyl-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (IIIb). A. A sample of 4.55 g (0.01 mole) salt IIb was heated in 25 ml 10% aq. NaOH at reflux for 1 h. After cooling, the reaction mixture was extracted with ether. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off. Crystalline product IIIb was purified by chromatography on a silica gel L40/100 column using benzene as the eluent to give 2.47 g (72%) IIIb.

B. The synthesis was carried out analogously to the preparation of salt IIb until the chloroform extraction step. Aqueous sodium hydroxide was added until the solution became alkaline and the solution was then heated at reflux for 1 h. The product was isolated and purified as in procedure A to give 1.13 g (55%) IIIb.

Product IIIa was obtained analogously from dihydrobenzoxazine Ia using procedure B.

1-Acetyl-2-(5-bromo-2-furyl)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (IVd). A sample of 0.75 g (0.0096 mole) acetyl chloride was added gradually to a solution of 2.05 g (0.0048 mole) 2-(5-bromo-2-furyl)-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine Id in 10 ml absolute benzene at reflux. The mixture was heated at reflux until hydrogen chloride was no longer released (1-1.5 h) The cooled reaction mixture was filtered and the filtrate was evaporated. The residue was crystallized from petroleum ether to give 1.4 g (62%) IVd.

Analogously, products IVa-IVc, IVe, IVf, IVi, and IVj were obtained from dihydrobenzoxazines Ia-Ic, Ie, If, Ii, and Ij, respectively. Products IVg and IVh were obtained from dihydrobenzoxazines Ig and Ih according to the indicated procedure but using acetyl bromide.

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