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CHEMICAL PROPERTIES OF 2,2,4-TRISUBSTITUTED 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES

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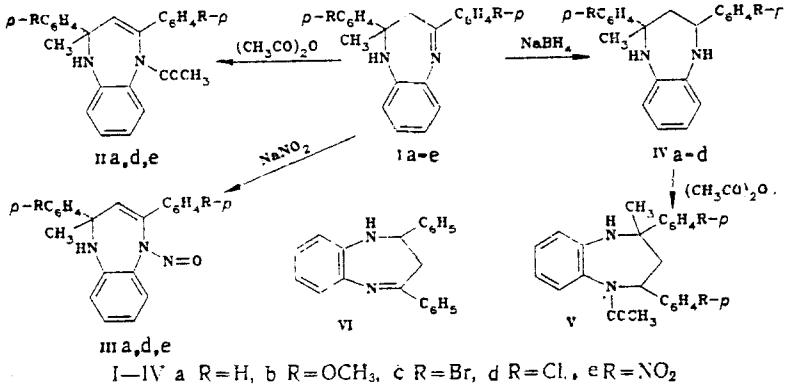
Acetylation and nitrosation of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines take place at the azomethyne nitrogen. Reduction is stereoselective.

2,4-Diaryl-2,3-dihydro-1H-1,5-benzodiazepines are not stable in acid medium [1]. On the other hand their 2,2,4-trisubstituted derivatives are resistant to acid, as evidenced by the use of an acid catalyst ($BF_3 \cdot Et_2O$ or HCl) [2, 3] in their synthesis. Thus the presence of the second substituent at position 2 of the heterocycle causes a drastic change in the chemical stability of the dihydrobenzodiazepine system. The present work presents a broader investigation of the effect of this substituent on dihydrobenzodiazepine properties. For this purpose acetylation, nitrosation, and reduction of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines (Ia-e) were carried out, and methylation and oxidation were attempted.

Scheme 1



I—IV a R=H, b R=OCH_3, c R=Br, d R=Cl, e R=NO_2

Acetylation of compounds Ia, d, e could be carried out by brief boiling of their solution in acetic anhydride. Previous attempts to acetylate compound Ia [3] under milder conditions (in methanol, pyridine, dioxane) were unsuccessful. In the present case 5-acetyl-2,4-diaryl-2-methyl-1,2-dihydro-5H-benzodiazepines (IIa, d, e) were obtained in good yield (Table 1). Data from the IR and UV spectroscopes are proof of the formation of 5-acetyl derivatives (Table 1). Thus in the IR spectrum of compounds IIa, d, e the C=N valence vibration band (1608-1612

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TABLE 1. Properties of Compounds II-V

Compound	T_{mp}, °C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Found, % N	Empirical formula	Calculated, % N	Yield, %
		$\nu_{C=C}$ ($\nu_{C=O}$)	ν_{NH} ($\nu_{N=O}$)					
IIa	128	1625 (1694)	3375	256 (31,0)	7,8	$C_{24}H_{22}N_2O$	7,9	75
IId	142—143	1628 (1702)	3388	260 (30,2)	6,8	$C_{24}H_{20}Cl_2N_2O$	6,6	70
IIe	186—188	1629 (1689)	3376	264 (31,2)	12,4	$C_{24}H_{20}N_4O_5$	12,6	54
IIIa	80—83 (decomp.)	1638	3361 (1442)	253*	12,6	$C_{22}H_{17}N_3O$	12,3	75
IIId	105—108 (decomp.)	1642	3394 (1440)	255*	10,4	$C_{22}H_{17}Cl_2N_3O$	10,2	77
IIIe	76—79 (decomp.)	1638	3381 (1448)	269*	16,4	$C_{22}H_{17}N_5O_5$	16,2	62
IVa	122—127	—	3355	250 (9,3), 296 (4,1)	8,9	$C_{22}H_{22}N_2$	8,9	94
IVb	130	—	3340	248 (9,1), 296 (3,6)	7,4	$C_{24}H_{26}N_2O_2$	7,5	90
IVc	165	—	3348	249 (9,5), 295 (4,0)	5,9	$C_{22}H_{20}Br_2N_2$	5,9	95
IVd	171	—	3361	249 (9,9), 294 (3,9)	7,5	$C_{22}H_{20}Cl_2N_2$	7,3	90
V	150—151	(1695)	3398	257 (13,1), 298 (2,8)	7,9	$C_{24}H_{24}N_2O$	7,9	85

*Determination of ε hindered by instability of compounds IIIa, d, e.

cm^{-1} [3]) disappears; the NH vibration band (3375-3388 cm^{-1}) is retained; and the C=O (1689-1702 cm^{-1}) and C=C (1625-1629 cm^{-1}) vibration bands appear. The electron absorption spectra of compounds IIa, d, e lack the long-wave band in the 360-420 nm region that is typical of the initial dihydrobenzodiazepine systems. Since that band is due to an electron transition that is localized at the $N{-}C_6H_4{-}N{=}C{-}C_6H_4R$ segment [3], its disappearance can be ascribed to the disruption of conjugation in the π-electron system of this chromophore when acylation takes place (see Scheme 1).

Attempts to alkylate dihydrobenzodiazepines Ia, d, e in various solvents (ether, benzene, methanol, acetonitrile) with $(CH_3)_2SO_4$ or CH_3I were ineffectual. In all cases the starting compounds were recovered with resinous impurities.

Nitrosation of Ia, d, e with sodium nitrite in glacial acetic acid gives the mononitroso derivatives IIIa, d, e. In the IR spectra of these compounds the band at 1608-1612 cm^{-1} (C=N) has disappeared, but the NH band (3361-3394 cm^{-1}) is retained, and a new band appears at 1638-1642 cm^{-1} (C=C). The electron absorption spectra undergo the same changes as upon alkylation (Table 1). Consequently, nitrosation is also directed at position 5 of the heterocycle. It has previously been established [1] that 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (VI) is acylated and nitrosated like a secondary amine, i.e., at the $N_{(1)}$ atom. Compound VI differs from Ia only in the absence at heterocycle position 2 of a methyl group, the electronic effect of which is small in this case. Hence it can be presumed that the change in the course of electrophilic attack in the case of Ia, d, e as compared with VI is to be attributed to the shielding of imine nitrogen by the two bulky groups at heterocycle position 2.

It should also be noted that the yields of compounds IIe and IIIe in acetylation and nitrosation are appreciably lower than those of compounds IIa, d and IIIa, d (see Table 1). This is probably due to the presence of the electron-acceptor nitro group in the aromatic ring bonded to the azomethyne group; this favors an increase in thermodynamic stability for the 2,3-dihydrobenzodiazepines [3].

The presence at heterocycle position 2 of two substituents should hinder the oxidation of compounds Ia-e to 2,4-diaryl-3H-benzodiazepines [1]. Indeed, the mild oxidant $K_2S_2O_5$ does not oxidize the test compounds. Attempts to oxidize compounds Ia-e with SeO_2 or peracids give unidentifiable resinous products.

Reduction of dihydrobenzodiazepines Ia-d with sodium borohydride in methanol gives the tetrahydro derivatives IVa-d in 90-95% yield. The process is accompanied by the disappearance from the IR spectra of the C=N band, and from the electron spectra of the bands in the 360-420 nm region (Table 1). Tetrahydrodiazepines IVa-d are characterized by two chiral centers; this offers the possibility of the preferential formation of one diastereomer or of a mixture. The published data on the stereoselectivity of the reduction of the dihydrodiazepine ring

TABLE 2. PMR Spectra of Compounds IVa-d, V

Compound	δ, ppm						SSCC, Hz		
	CH_3, s	CH_2		CH (H_X), dd	NH, s	arom. protons, m	J_{AB}	J_{AX}	J_{BX}
		H_A, dd	H_B, dd						
IVa	1,56	1,81	2,37	4,15	3,71	6,57—7,69	13,5	1,8	11,4
IVb	1,53	1,75	2,35	4,06	—*	6,30—7,60	13,5	1,5	11,3
IVc	1,52	1,74	2,28	4,12	3,63	6,54—7,61	13,2	1,9	11,2
IVd	1,53	1,74	2,29	4,13	3,64	6,54—7,63	13,5	1,8	11,2
V	1,71 1,74	1,83	2,34	5,88	3,76	6,77—7,44	15,0	4,3	12,4

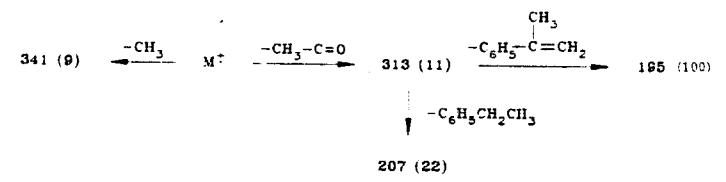
*The signal of this proton is overlapped by the signals of the methoxy protons with δ 3.73 and 3.72 ppm.

with sodium borohydride are contradictory. Thus when 5,7-diphenyl-2,3-dicyano-6,7-dihydro-1H-1,4-diazepine is reduced with $NaBH_4$, the cis isomer of the respective tetrahydro derivative is formed exclusively [4], whereas reduction of compound VI under analogous conditions gives an equimolar mixture of cis and trans isomers. This is demonstrated unequivocally by PMR spectroscopy [1]; the signals of the tetrahydrodiazepine rings of the two isomers are appreciably different both in chemical shifts and in the nature of the spin-spin couplings. The PMR spectra that we measured are unequivocal evidence of the individuality of compounds IVa-d. They show (Table 2) a methyl singlet, two quartets of nonequivalent CH_2 protons, a quartet of CH protons, a broadened imino proton singlet, and an aromatic proton multiplet. None of the proton signals of the tetrahydrodiazepine rings of IVa-d show any sign of additional splitting as a result of belonging to two different diastereomers.

The Dreiding models of IVa were analyzed, and the possible spatial orientations of the H_A, H_B, and H_X protons with vicinal SSCC (J_{AX} and J_{BX}, Table 2) were compared. The seven-membered heterocycle exists predominantly in the quasiboat conformation, in which the H_B and H_X protons occupy pseudoaxial location; the J_{BX} constant is typical of J_{aa} type constants [5]. It also follows from this analysis that in the spectra of IVa-d the axial proton resonates in a weaker field region than does the equatorial H_A proton (by 0.50-0.56 ppm, Table 2). Unfortunately, the SSCC measured for the tetrahydrodiazepine ring protons do not unequivocally answer the question of the relative orientation of the substituents at $C_{(2)}$ and $C_{(4)}$; i.e., do IVa-d belong to the cis or trans series of isomers.

Acetylation of IVa with acetic anhydride gave the monoacetyl derivative V. Its structure was confirmed by elemental analysis and spectral analysis (Tables 1 and 2). Thus, the location of the acetyl group was established by NMR spectroscopy. Comparison of the spectra of compounds IVa and V reveals an appreciable (1.73 ppm) weak-field shift of the $C_{(4)}$ proton signal after acetylation (Table 2). Such a shift is due to the effect of the carbonyl group and is typical of the $>CH-\overset{|}{N}-CO-CH_3$ grouping [5]. The appearance of the same effect in the case of acetylation of the imino group at heterocycle position 1 is unlikely, due to the remoteness of the C=O and $C_{(4)}H$ groups. Thus, acetylation of IVa takes place at the spatially more accessible position 5 of the heterocycle.

Along with the peaks of the molecule ion (m/z 356, 40%) and the $M-CH_3$ (19) and $M-(CH_3-C=O)$ (11) ions, the mass spectrum of compound V shows ion peaks at 207 (22) and 195 (100). These form by cleavage of the diazepine ring at the $N_{(1)}-C_{(2)}$ and $C_{(2)}-C_{(3)}$ or $C_{(3)}-C_{(4)}$ bonds, with loss of a molecule of ethylbenzene or α-methylstyrene, respectively:



The formation of ions with m/z 195 and 207, which probably have the structures of 2-phenylbenzimidazolinium and 2-phenylquinoxalinium ions, respectively, is typical of the mass spectral decomposition of benzodiazepine derivatives [6].

Thus the introduction of a methyl group at position 2 of the dihydrobenzodiazepine heterocycle (i.e., going from compound VI to Ia) substantially affects the chemical properties of the compounds. Besides the previously noted [3] loss by Ia of the ability to undergo benzimidazole rearrangement, its oxidation is hindered, the course of acetylation and nitrosation is changed, and the stereoselectivity of dihydrobenzodiazepine ring reduction sharply increases.

EXPERIMENTAL

IR spectra were measured in KBr tablets with a Specord IR-75 spectrophotometer. Electron spectra were measured in methanol solution at concentrations of $(2\text{-}4)\cdot10^{-5}$ mole/liter with a Specord UV-vis instrument. PMR spectra of compounds IVa-d and V were obtained in $CDCl_3$ solution with a Brucker WP-200 instrument, with HMDS internal standard. Mass spectra were recorded with a Varian MAT-212 instrument at 70 eV ionization voltage. The individuality of compounds and the composition of reaction mixtures were monitored by TLC on Silufol UV-254 plates, with chloroform as eluent.

The synthesis of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines (Ia-e) has been described in [3].

5-Acetyl-2,4-diphenyl-2-methyl-1,2-dihydro-5H-benzodiazepine (IIa). A solution of 2 g (6.4 mmole) of 2-methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (Ia) in 5 ml of acetic anhydride was boiled for 30 min and left overnight at 20°. Then acetic anhydride was distilled off in vacuum. The residue was dissolved in 5 ml of ether with heating, cooled, and the crystalline precipitate was filtered off. Yield 1.7 g (75%), mp 128° (from methanol).

Compounds IId, e and V were obtained analogously.

2,4-Diphenyl-2-methyl-5-nitroso-1,2-dihydro-5H-benzodiazepine (IIIa). To a solution of 0.6 g (1.6 mmole) of compound Ia in 5 ml of glacial acetic acid was added 0.14 g (1.6 mmole) of $NaNO_2$. The mixture was stirred for 10 min, then poured into 40 ml of H_2O, and 0.4 g (75%) of IIIa crystals was filtered off, mp 80-83° (with decomp.).

Compounds IIId, e were obtained analogously.

2,4-Diphenyl-2-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (IVa). To a solution of 2 g (6.4 mmole) of compound Ia in 50 ml of methanol was added 1 g (26.3 mmole) of $NaBH_4$ portionwise. The mixture was boiled for 1 h, treated with 100 ml of water, and left overnight. Crystals of IVa, 1.9 g (94%) were filtered off; mp 125-127° (from methanol).

Compounds IIIc, d were obtained analogously.

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