CONFORMATIONAL ANALYSIS OF AROMATIC DERIVATIVES OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE

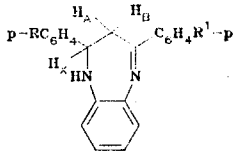
V. D. Orlov, N. N. Kolos, and A. F. Abramov

UDC 547.892:541.63:543.422.25'47

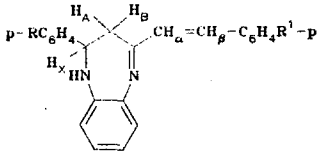
The PMR spectra and dipole moments of some 2,4-disubstituted 2,3-dihydro-1H-1,5-benzodiazepines have been examined. It is shown that seven-membered rings with an aromatic or heterocyclic substituent in the 2-position have the boat configuration, the substitutent preferentially being equatorially oriented. It has been found that the changes in the chemical shifts and spin coupling constants for the protons of the CH—CH_2 fragment in the dihydrobenzodiazepine ring are mainly due to differences in the electronegativity of the substituents in the 2- and 4-positions. Some dipole moment vectors have been calculated for the dihydrobenzodiazepine ring.

Literature information on the structure of 2,3-dihydro-1H-1,5-benzodiazepines is limited to a report [1] of the examination of the PMR spectra of some methyl derivatives. The spectrum of the 2,4-diphenyl derivative, which shows no inversion of the seven-membered ring, was also given. The object of this study was to examine the conformations of aromatic derivatives of dihydrobenzodiazepine (I-XXXII) by PMR spectroscopy and determination of dipole moments.

A general feature of the PMR spectra of (I-XXXII) (Table 1) is the presence, in addition to complex multiplets for the aromatic protons at 6.5-7.8 ppm, of an octet and a quartet (or triplet) for the protons of the CH—CH_2 moiety. Since any changes in the conformation of the bicyclic system will affect the PMR spectra primarily with respect to the chemical shifts and coupling constants of these protons, special attention was devoted to them. The appropriate values were calculated for the ABX system using the ITRCAL program.



I-XXI



XXII-XXXII

The PMR spectra of (III) were recorded over the temperature range −80-150°C in deuteroacetone, deuterochloroform, and naphthalene. The constancy of the shapes of the signals for the protons of the CH—CH_2 moiety and the insignificant changes in the chemical shifts of these protons (< 0.1 ppm), in addition to the multiplicity of the spectra noted above, indicate that a single conformer predominates in solution. Since the spectra of the other compounds contain signals of the same form, it is reasonable to suppose that the conformations of all the compounds are similar.

Although on average the chemical shifts of the methylene protons (protons A and B) vary little, these changes are regular. Thus, in compounds (I-VI), the values of δ_A and δ_B correlate with the σ_I constants of the substituents R^1 according to the equation $\delta = \delta_0 + \rho\sigma_I$ ($r_A = 0.92$; $\rho_A = -0.04$; $r_B = 0.95$; $\rho_B = -0.06$). This correlation with the inductive constants in all probability indicates the absence of conjugation of the methylene group with the substituent R^1. However, differing anisotropic screening of the aromatic nuclei in the 4-position of the heterocycle could play an important part in the changes in δ_A and δ_B. The effect of this factor is also apparent from the fact that the introduction of a trans-vinylene bridge into the 4-position of the dihydroazepine ring (the trans-structure follows from the values of the

A. M. Gor'kii Kharkov State University, Khar'kov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1662-1666, December, 1984. Original article submitted March 23, 1983; revision submitted May 10, 1984.

 0009-3122/84/2012-1370$08.50

TABLE 1. PMR Spectral Parameters and Dipole Moments of (I-XXXII)

Compound	R	R¹	δ, ppm[a]				J, Hz			θ_{AX}	θ_{BX}	μ_{exp}, D	μ_{calc}, D
			H_A	H_B	H_X	N—H	AX	BX	AB				
I	H	OCH_3	2,92	3,10	5,07	3,62	3,86	8,79	13,25	46	168	3,14	3,29
II	H	CH_3	2,86	3,03	4,97	3,56	3,56	8,79	13,30	48	168	2,95	3,24
III	H	H	2,90	3,08	4,99	3,85	3,50	8,85	13,60	48	168	3,37	3,30
IV	H	Cl	2,96	3,11	5,04	3,80	3,68	8,35	13,50	47	162	3,93	3,96
V	H	Br	2,99	3,16	5,15	3,80	3,79	8,41	13,60	47	163	3,90	3,95
VI	H	NO_2	3,01	3,17	5,12	3,72	3,72	7,50	13,75	47	155	5,30	5,70
VII	H	C_6H_5	3,03	3,23	5,20	3,80	3,68	8,99	13,32	47	171	—	—
VIII	H	2-Thienyl[b]	2,99	3,18	5,09	3,77	3,65	8,65	13,55	47	166	—	—
IX	H	3-Pyridyl[b]	3,06	3,20	5,20	3,92	3,86	8,16	13,72	47	161	—	—
X	H	CH_3[b]	2,68	2,79	5,14	3,64	4,38	8,21	12,60	42	161	—	—
XI	OCH_3	H	2,97	3,15	5,13	3,68	3,98	8,62	13,00	45	165	3,24	3,50
XII	Cl	H	2,88	3,06	5,08	3,58	3,60	8,67	13,55	48	168	2,12	2,33
XIII	Br	H	3,00	3,18	5,16	3,43	3,68	8,50	13,12	47	164	2,55	2,33
XIV	NO_2	H	3,08	3,18	5,34	3,73	4,89	6,69	13,43	39	149	—	—
XV	2-NO_2	H	3,39	3,51	5,89	3,76	5,11	6,24	12,95	37	146	—	—
XVI	2-Thienyl[b]	H	2,93	3,19	5,49	3,64	4,15	9,80	13,40	44	180	—	—
XVII	Cl	Cl	2,81	2,96	4,97	3,56	5,65	6,95	13,55	33	151	2,98	2,96
XVIII	NO_2	CH_3[b]	2,57	2,78	5,32	3,73	4,91	6,09	12,75	33	145	—	—
XIX	NO_2	OCH_3	2,98	3,19	5,37	3,76	4,37	8,75	13,17	42	167	—	—
XX	Cl	2-Quinolinyl	3,11	3,94	5,03	3,77	3,70	9,29	13,17	47	180	—	—
XXI	2-Quinolinyl	Br	3,05	3,24	5,22	4,66	3,30	7,95	13,95	50	158	—	—
XXII	H	H	2,75	2,96	5,02	3,66	3,62	8,96	13,47	47	170	3,33	3,30
XXIII	H	OCH_3	2,88	3,13	4,98	3,64	3,96	8,67	13,12	45	166	—	—
XXIV	H	NO_2	2,71	2,90	5,09	3,70	4,02	8,61	13,72	45	165	—	—
XXV	H	2-Thienyl[b]	2,72	3,01	5,13	3,63	3,78	8,22	13,10	46	161	—	—
XXVI	Cl	H	2,75	2,91	5,25	3,63	3,91	7,71	13,27	45	157	2,68	2,33
XXVII	Br	H	2,74	2,91	5,11	3,62	3,93	7,22	13,05	45	153	2,58	2,33
XXVIII	OCH_3	OCH_3	2,62	2,85	4,82	3,65	3,98	8,66	13,30	45	166	3,62	—
XXIX	Cl	Cl	2,67	2,89	5,05	3,61	5,31	6,34	13,90	36	147	3,14	2,96
XXX	Br	Br	2,75	2,97	5,05	3,62	5,08	6,36	13,99	37	147	—	—
XXXI	2,4-Dichlo	2,4-Dichlo	2,81	2,95	5,65	3,70	5,29	4,31	14,25	36	134	2,45	—
XXXII	NO_2	NO_2	2,87	3,11	5,39	3,77	4,53	5,64	13,47	41	142	—	—

[a]The values of δ_{H_α} and δ_{H_β} for (XXV), (XXXI), and (XXXII) were 6.57-7.26 and 6.95-7.35 ppm, respectively (294 MHz); $J_{H_\alpha H_\beta}$ = 16.0-16.2 Hz for (XXII-XXXII). [b]Instead of C_6H_4R or $C_6H_4R^1$.

vicinal constants J = 16.0-16.2 Hz [2]), or replacement of the aromatic substituent by methyl, results in a shift of the methylene protons to higher field. Anisotropic screening of the substituent in the 4-position is most clearly apparent in (XX) ($C_6H_4R^1$ = 2-quinolinyl), in which the different orientations of the methylene protons relative to the R^1 substituent result in a large difference in the values of their chemical shifts.

The substituent R also influences δ_A and δ_B. The introduction of an o-nitro group has the greatest effect (shifts of 0.49 and 0.43 for (XV)), probably because it may be sterically close to the methylene protons. The group R has an even greater effect on the value of δ_X, the maximum effect being reached in ortho-substituted compounds (XV and XXXI), and also with the introduction of strongly electronegative substituents (XIV, XVIII, XIX, XXXII). The considerable increase in δ_X for (XVI) is unexpected, and could be due to descreening of the methine protons by the sulfur atom of the thienyl group. A Dreiding model of 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (III) was constructed [3] (Fig. 1), which predicts a somewhat distorted boat conformation for the seven-membered ring.* Projections of the model in two mutually perpendicular planes enabled the atom coordinates to be calculated (Table 2) and the dihedral angles to be evaluated. The methine proton in the heterocycle is nearly axial, and the C_6H_5 group is consequently equatorial. This conclusion is confirmed by the PMR spectrum of (III), in which one of the constants for its value (8.85 Hz) is to be considered as a J_{aa} type constant. In Table 1, the designation A refers to an equatorial proton, and B to an axial proton.

Axial protons in carbocycles usually resonate at higher fields than equatorial protons [5]. In the PMR spectra of dihydrobenzodiazepines (I-XXXII), however, the methylene proton

*In the course of joint researches with Prof. Z. Kaluzki and É. Gzhisyak (Poznan University), compound (III) has been subjected to x-ray structural analysis, according to which the heterocycle in this compound does in fact exist in the boat conformation [4].

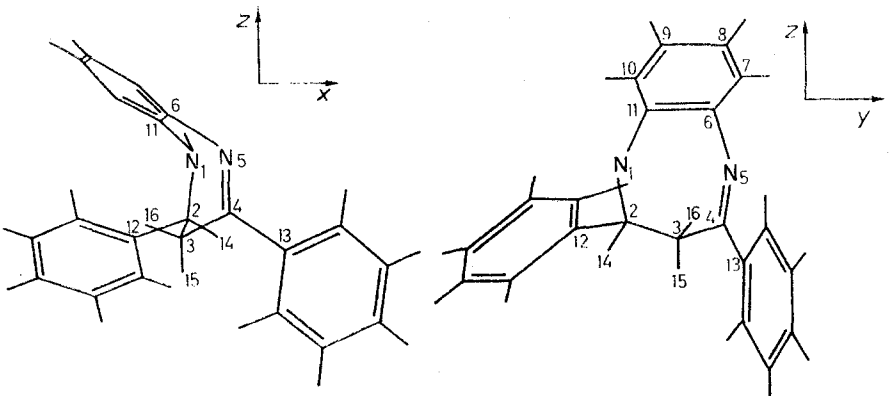
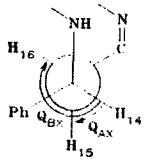


Fig. 1. Projection of a Dreiding model of (III) on planes of xz and yz.



possessing the greater chemical shift corresponds to the higher vicinal constant (typical in values for J_{aa}). It may be assumed that in this series of compounds an effect is observed which is similar to the behavior of the protons in cyclohexanone [5], in which, under the influence of the electric field of the carbonyl group, the signals for the axial protons appear at lower field than those for the equatorial protons. In the dihydrobenzodiazepine series, the reason for this anomalous behavior could be screening by the endo-C=N bond or by the aromatic rings.

One of us [6] has shown, taking 2-arylidene-4-phenyl-1-tetralones as examples, that electronic effects and, primarily, conjugation effects, in the conjugated system which is partially incorporated into the six-membered ring have an effect on its conformation. It would be expected that changes in the electronic character of the substituent R^1, and correspondingly also in the extent of polarization in the system R^1—C_6H_4—C=N—C_6H_4—N would also modify the conformation of the seven-membered ring [6]. However, in (I-VII) and (XXII-XXIV), the spin coupling constants vary only in proportion to the inductive σ_I constants of the substituents. Similar behavior is observed when R is varied (III, XI-XV). This dependence shows that the decisive factor in changes in the spin coupling constants in the dihydrobenzodiazepines is the electronegativity of R and R^1. This probably also explains the fact that the greatest changes in the vicinal constants are found in cases in which both substituents are strongly electronegative (XV, XIV, XVII, XXIV, XXIX-XXXII; Table 1).

The values of the dihedral angles θ_{AX} and θ_{BX}, calculated using the Karplus equation [7], are shown in Table 1. A definite criterion of their correctness is the fact that the difference $\Delta\theta = \theta_{BX} - \theta_{AX}$ is in most instances close to 120°, that is, the angle which would be expected if the valence angles in the heterocycle were close to the standard values [8]. Marked deviations from 120° are seen in those compounds in which R and R^1 are nitrophenyl or heterocyclyl, and in (XXIX-XXXI). It is probable that in these cases the approximate nature of the Karplus equation is apparent, since it does not take full account of the high electronegativity of these radicals.

Hence, the values of the dihedral angles calculated from the PMR spectra are in good agreement with the angles obtained from the Dreiding model, and they confirm that the dihydrobenzodiazepine ring exists in the boat form, which is of low sensitivity to the electronic effects of the radicals introduced into the heterocycle.

This conformation for dihydrobenzodiazepines is also in agreement with dipole moment studies. Table 1 shows values for μ_{exp} measured in benzene at 25°C, and for μ_{calc} obtained by the vector addition method [9]. The directions and value of the dipole moment vector for the dihydrobenzodiazepine ring were determined by breaking down the μ_{exp} vectors for mono- and dihalo-derivatives (IV, XII, XVIII) into their components, taking into account the atom

TABLE 2. Atom Coordinates for the Dihydrobenzodiazepine Ring in (III) (Å), Calculated from the Dreiding Model

Atom	x	y	z
1	0,4	−1,52	1,94
2	0,16	−1,48	0,48
3	0	0	0
4	1,16	0,93	0,52
5	1,16	1,28	1,8
6	−0,08	0,8	2,68
7	−0,74	1,66	3,40
8	1,84	1,20	4,18
9	−2,12	−0,16	4,20
10	−1,44	−0,84	3,48
11	−0,4	−0,56	2,72
12	−1,08	−2,38	−0,08
13	2,32	1,36	−0,44
14	1,00	−1,88	−0,1
15	0	0	−0,88
16	−0,96	0,32	0,4

TABLE 3. Properties of New 2,3-Dihydro-1H-1,5-benzodiazepines

Compound	Mp, °C	λ_{max}, nm(ε · 10⁻³)	ν, cm⁻¹ C=N	ν, cm⁻¹ N–H	Found, N %	Empirical formula	Calculated, N, %	Yield, %
VII	179—180	287 (28,6), 374 (9,1)	1602	3356	7,5	$C_{27}H_{22}N_2$	7,5	45
VIII	129—130	263 (25,4), 384 (6,9)	1601	3305	9,1	$C_{19}H_{16}N_2S$	9,2	75
IX	108—109	250 (21,0), 391 (4,8)	1607	3260	13,9	$C_{20}H_{17}N_3$	14,0	48
XII	144—145	256 (19,2), 370 (4,6)	1615	3368	8,3	$C_{21}H_{17}ClN_2$	8,4	64
XVI	128—129	246 (26,7), 367 (5,8)	1609	3345	9,0	$C_{19}H_{16}N_2S$	9,2	33
XVII	120—121	261 (25,1), 375 (7,5)	1608	3376	7,8	$C_{21}H_{16}Cl_2N_2$	7,6	45
XVIII	169—171	258 (14,4), 321 sh.	1647	3362	14,8	$C_{16}H_{15}N_3O_2$	14,9	32
XIX	186—187	270 (27,9), 361 (7,2)	1603	3372	11,1	$C_{22}H_{19}N_3O_3$	11,3	86
XX	164—165	248 (26,5), 388 (8,8)	1614	3300	10,5	$C_{24}H_{18}ClN_3$	11,0	62
XXI	139—140	264 (25,3), 380 (5,7)	1609	3356	9,7	$C_{24}H_{18}BrN_3$	9,8	70
XXV	139—141	233 (20,1), 391 (8,9)	1608	3327	8,6	$C_{21}H_{18}N_2S$	8,5	65

coordinates given in Table 2. The dipole moment of the heterocycle was 3.30 D, and the values of its individual vectors μ_x, μ_y, and μ_z were −0.94, 0, and 0.34. The calculated value for the moment was close to the experimental value for (III), and was equal to the sum of the moments of benzalaniline (1.6 D) and N-methylaniline (1.7 D) [9], on condition that these are oriented in parallel. The validity of this effect is in our opinion justified by the fact that the value of μ for each of these fragments already takes into account an interaction of the substituent group with the aromatic nucleus. In calculating the moments of (XXVI, XXVII, and XXIX), allowance was made for the trans-structure of the vinylene group noted above. The good general agreement between μ_{calc} and μ_{exp} shows that the Dreiding model on the whole correctly represents the actual geometry of the dihydrobenzodiazepines.

EXPERIMENTAL

Compounds (VII-IX), (XII), and (XVI-XXI) (Table 3) were obtained as described in [10], and the remaining compounds are described in [10] and [11]. PMR spectra were measured in $CDCl_3$ at a concentration of 0.3-0.4 mmole/liter on a Varian XL-100 (100 MHz) and on a spectrometer with a superconducting solenoid, operating frequency 294 MHz (X, XV, XXV, XXXI, XXXII) developed in the Institute of Chemical Physics, Academy of Sciences of the USSR (internal standard, TMS). Values of δ and J were calculated for the ABX system using the ITRCAL program (Bruker), mean square deviations not exceeding 0.08. The temperature dependence of the PMR spectra of (III) was examined in 20°C steps in deuteroacetone (from −80 to −40°C), deuterochloroform (from −20 to 40°C), and naphthalene (90-150°C). Dipole moments were measured in benzene by the dilute solution method of Debye, as described in [12]. UV spectra were obtained for solutions in ethanol, concentration $2 \cdot 10^{-5}$ mole/liter, on a Specord UV-VIS spectrophotometer. IR spectra were obtained on a UR-20 in KBr disks.

LITERATURE CITED

1. P. W. W. Hunter and G. A. Webb, Tetrahedron, 29, 147 (1973).
2. A. Zhunke, Nuclear Magnetic Resonance in Organic Chemistry [Russian translation], Mir, Moscow (1974), p. 75.
3. M. Yu. Kornilov and T. A. Tolstukha, Computer and Chem., 6, 193 (1982).
4. N. N. Kolos, Diss. Cand. Chem. Sci., Khar'kov (1982).
5. B. I. Ionin and B. A. Ershov, NMR Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1967), pp. 221-222.
6. V. D. Orlov, P. A. Grigorov, and L. B. Klisenko, Zh. Obshch. Khim., 51, 457 (1981).
7. Yu. Yu. Samitov, Khim. Geterotsikl. Soedin., No. 12, 1587 (1978).
8. V. M. Potapov, Stereochemistry [Russian translation], Mir, Moscow (1976), p. 316.
9. V. I. Minkin, I. A. Osipov, and Yu. A. Zhdanov, Dipole Moments in Organic Chemistry [in Russian], Khimiya, Leningrad (1968), pp. 79, 81, 99.
10. V. D. Orlov, N. N. Kolos, F. G. Yaremenko, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 5, 697 (1980).
11. D. V. Orlov, N. N. Kolos, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 6, 827 (1981).
12. S. V. Tsukerman, V. D. Orlov, Yu. N. Surov, and V. F. Lavrushin, Zh. Strukt. Khim., 9, 67 (1968).

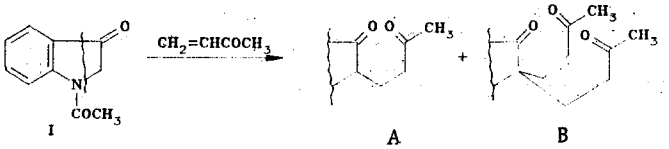
NEW METHOD OF SYNTHESIS OF QUINDOLINES FROM 1,5-DIKETONES OF THE INDOLINONE SERIES

V. P. Sevodin, V. S. Velezheva, Yu. V. Erofeev, and N. N. Suvorov

UDC 547.837.2'756'384.07

By the action of ammonium acetate and α,β-unsaturated carbonyl compounds, 1,5-diketones of the indolinone series undergo not yet known transformations into difficultly accessible 1,2-dihydro-10H-quinodolines. Under these conditions, 11-phenyl-1,2,3,4-tetrahydro-10H-quindoline was obtained from 1-acetyl-2-(benzylcyclohexan-1-on-α-yl)indolin-3-one. Dihydroquindolines with identical aryl substituents in the 1- and 11-positions were obtained from 1-acetylindolin-3-one by the action of an excess of certain α,β-unsaturated ketones and ammonium acetate. Dehydrogenation of dihydroquindolines proceeds smoothly on heating with sulfur. The possible paths of the formation of dihydroquindolines are discussed.

By analyzing previous publications [1, 2], we concluded that the result of the Michael reaction between 1-acetylindolin-3-one (I) and α,β-unsaturated carbonyl compounds depends on the nature of the substituent at the β-carbon atom. Thus, in absence of a substituent, mono- and diadducts A, B are simultaneously formed from indolinone I.



I A B

In the presence of a substituent (alkyl, aryl) in the reagent, only monoadducts, e.g., IIa, are formed from indolinone I.

We assumed that under given conditions, compounds of type IIa will also enter into the Michael reaction, but not with the participation of the sterically hindered α-methine group, but with the participation of one of the methylene groups α^1 or α^2 in the side chain. Because of the participation of these groups in the Michael reaction with unsaturated ketones, it was

D. I. Mendeleev Moscow Chemical Engineering Institute, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1667-1673, December, 1984. Original article submitted December 14, 1983.

 0009-3122/84/2012-1374$08.50