1,3-Dimethyl-5-anilinomethylenebarbituric Acid (IIb) was obtained in a similar way. The reaction was carried out in boiling butanol. Yield 91%, mp 198-199°C (ethanol). Found, %: C 60.2; H 5.0; N 16.4. $C_{13}H_{13}N_3O_3$. Calculated, %: C 60.2; H 5.1; N 16.2.

Sodium Salt of 1,3-Dimethyl-5-anilinomethylenebarbituric Acid. A 5.5 ml portion of a 2 M solution of sodium methoxide (0.011 mole) in absolute methanol was added at 20°C to 2.59 g (0.01 mole) of 1,3-dimethyl-5-anilinomethylenebarbituric acid. The suspension obtained was stirred for 30 min, the precipitate was filtered, washed with methanol, and dried in vacuo. The yield was practically quantitative.

5-Pyridinium-barbituric Acid (IV) was obtained by a method described in [11].

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SYNTHESIS AND STUDY OF STRUCTURE OF 5-FORMYL-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

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UDC 547.892:542.951:541.63:543.422.25

A series of 5-formyl derivatives was synthesized by formylation of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones with a mixture of formic acid and acetic anhydride. The structure of their rotation isomers was studied by PMR spectroscopy.

The restrained internal rotation around the noncyclic N—C bond in N-acylindolines and N-acyltetrahydroquinolines was studied by several groups of authors [1-3]. For the derivatives of seven-membered saturated nitrogen-containing heterocyclic compounds, this process has practically not been investigated.

The present work was devoted to the synthesis of 5-formyl derivatives of the 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones of the general formula I-XII and the study of their rotation isomerism by PMR spectroscopy. (See scheme on following page.)

In the first experiments, the 5-formyl derivatives I, II were obtained by reacting tetrahydrobenzodiazepinones XIII, XIV with 85% formic acid in benzene [4], in yields not exceeding 30%, and the amount of unreacted starting compounds reached 50%. Later, a mixture of 98% formic acid and acetic anhydride was used for the formulation. By carrying out the process at room temperature, the possible participation in the reaction of acetic anhydride

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 957-961, July, 1988. Original article submitted February 5, 1987; revision submitted June 9, 1987.

0009-3122/88/2407-0786$12.50

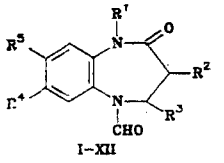
TABLE 1. Characteristics of 5-Formyl-Substituted 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepin-2-ones (III-VI, VIII-XI)

Compound	mp,* °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
III	245—247	64,7	5,9	13,5	$C_{11}H_{12}N_2O_2$	64,7	5,9	13,7	93
IV	199—201	72,2	5,5	10,6	$C_{16}H_{14}N_2O_2$	72,2	5,3	10,5	60
V	267—269	53,0	4,5	16,8	$C_{11}H_{11}N_3O_4$	53,0	4,5	16,9	61
VI	212—213	52,8	4,3	16,7	$C_{11}H_{11}N_3O_4$	53,0	4,5	16,9	71
VIII	128—130	64,7	6,0	13,6	$C_{11}H_{12}N_2O_2$	64,7	5,9	13,7	49
IX	97—99	73,0	5,6	9,7	$C_{17}H_{16}N_2O_2$	72,8	5,8	10,0	61
X	107—109	73,6	6,1	9,6	$C_{18}H_{18}N_2O_2$	73,5	6,2	9,5	75
XI	137—139	73,5	6,2	9,7	$C_{18}H_{18}N_2O_2$	73,5	6,2	9,5	70

*Compound III was recrystallized from methanol, IV, from propanol, V, from acetone, VI, from acetonitrile, VIII, from ethyl acetate, IX-XI, from a benzene—hexane mixture.

itself as an acylating agent is excluded. Thus, 5-formyl derivatives I-VI were obtained in yields of 60-70% from 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XIII), its 3-methyl- (XIV), 4-methyl- (XV) [4], 4-phenyl- (XVI) [5], 4-methyl-8-nitro- (XVII) [6] and 4-methyl-7-nitro- (XVIII) analogs (Table 1). Similarly, compound XII was synthesized from 1-isopropyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XIX) [7].

1-Methyl- and 1-benzyl-5-formyl derivatives VIII-XI were synthesized in yields of 50-70% by boiling the corresponding 5-formyl derivatives I-III with methyl iodide or benzyl bromide in absolute acetone in the presence of potassium hydroxide. Under these conditions, in contrast to the method that we had already worked out of alkylation of tetrahydrobenzodiazepinones under conditions of interphase catalysis [7], there is no hydrolytic splitting of the formyl group. For the synthesis of compounds VIII-XI, areverse order of the introduction of substituents (the synthesis of XII) cannot be used, since, as we have already shown [8], the corresponding 1-methyl- and 1-benzyltetrahydrobenzodiazepinones are not formed. 1-Acetyl-5-formylbenzodiazepinone VII was synthesized by acylation of compound I according to [4].



I-XII

I—VI R^1=H; VII R^1=$COCH_3$; VIII R^1=CH_3; IX—XI R^1=$CH_2C_6H_5$; XII R^1=i-$CH(CH_3)_2$; I, III—IX, XI, XII R^2=H; II, X R^2=CH_3; I, II, VII—X, XII R^3=H; III, V, VI, XI R^3=CH_3; IV R^3=C_6H_5; I—IV, VI—XII R^4=H; V R^4=NO_2; I—V, VII—XII R^5=H; VI R^5=NO_2

In the PMR spectra of 5-formyl-substituted benzodiazepinones I-XII at 34°C (Table 2), besides the main signal (according to intensity), there was another less intense signal of the formyl proton, and also two signals of the NHCO proton in compounds I-VI. For compounds III, V, VI and XI, containing a methyl group at the 4 position of the heterocyclic ring, signals of its protons of different intensities with $\Delta\delta$ 0.1 ppm were observed. This indicates that the 5-substituted derivatives I-XII exist in the form of two rotamers present in equilibrium. This has been confirmed by investigation of the temperature dependence of the spectra. With increase in temperature, a broadening of the proton signals of the formyl, amide and methyl groups was observed, as well as their merging, contraction on further increase in temperature, and restoration to the initial spectrum on cooling. The ratio of the endo- and exo-conformers, which is slightly dependent on changes in the structure of the molecules, i.e., on the introduction of various substituents at the 1, 3, and 4 positions of the heterocyclic ring and 7, 8 positions of the aromatic ring, was determined by integration of signals under the stereochemical rigidity conditions (Table 2).

Assignment of the conformers to the exo- or endo-rotamers poses quite a complex problem. One of the criteria is an anisotropic descreening of the o-aromatic proton by the carbonyl group of the substituent. It was shown [2] that in N-acetyltetrahydroquinolines, the descreening of the 8-H aromatic proton for the exo- and endo-rotamers is equal to 0.4-0.8 and 1.1-1.65 ppm, respectively, i.e., for the cis-disposition of the 8-H proton and the CO group it is more strongly pronounced. This was confirmed also in an investigation of the PMR spectra of N-formyl derivatives of tetrahydroquinoline [3].

TABLE 2. PMR Spectral Data* for 5-Formyl Derivatives I-XII

Compound	δ, ppm (J, Hz)						Ratio of isomers, %
	3-CH_2 or 3-CH	4-CH_2 or 4-CH	3-C—CH_3 or 4-C—CH_3	NHCO	CHO	other protons	
I	2,67	4,09	—	9,82 9,69	8,18 8,35	Ar 6,90—7,45	93 7
II	2,94	3,65 (^3J 5,6) 4,27 (^3J 12,9) (^2J 12,9)	1,17	9,84 9,69	8,21 8,35	Ar 7,00—7,45	97 3
III	2,43 (^3J 13,6) 2,53 (^3J 4,1) (^2J 12,9)	5,10	1,08 1,17	9,82 9,68	8,03 8,38	Ar 7,00—7,50	89 11
IV	2,68 (^3J 4,4) 3,06 (^3J 13,7) (^2J 13,3)	6,01	—	9,99 9,86	8,14 8,45	Ar 7,05—7,55	93 7
V	2,49 †	4,85	1,15 1,27	10,40 10,28	8,19 8,44	H_6, H_8 8,10—8,35; H_9 7,30	86 14
VI	2,49†	4,85	1,13 1,22	10,16 10,02	8,12 8,46	H_6 7,52; 7,58; H_7 7,96; H_9 8,10 ($^3J_{67}$ 8,0), ($^3J_{79}$ 2,8)	89 11
VII	2,61	4,00	—	—	8,33	Ar 7,10—7,45; 1-$COCH_3$ 2,60	
VIII	2,63	4,12	—	—	8,22 8,31	Ar 7,00—7,45; 1-CH_3 3,34	92 8
IX	2,69	4,09	—	—	7,75 8,27	Ar 6,90—7,40; 1-CH_2 4,97	93 7
X	2,88	3,38 (^3J 6,0) 4,33 (^3J 12,9) (^2J 12,6)	1,17	—	7,67 8,23	Ar 6,75—7,35; 1-CH_2 4,55, 5,52 (^2J 14,9)	95 5
XI	2,48 (^3J 13,6) 2,58 (^3J 4,1) (^2J 12,9)	5,15	1,12 1,23	—	7,58 8,27	Ar 6,75—7,35; 1-CH_2 4,56, 5,46 (^2J 14,6)	95 5
XII	2,53	3,1—4,6	—	—	8,22 8,29	Ar 6,90—7,50; 1-CH 4,61; $(CH_3)_2$ 1,17	93 7

*Spectra of compounds I-IV, VII-XII were taken in $CDCl_3$, V, VI in DMSO-D_6, the chemical shifts of NHCO are everywhere given in DMSO-D_6.

†The signals overlap with those of the solvent.

For most of the derivatives synthesized, the signals of the aromatic protons were not assigned because of the strong coupling of this spin system. Only for 7(8)-nitro derivatives V, VI, signals are observed in the aromatic protons region, which correspond to the AMX system with characteristic o-, m-, and p-values of SSCC (Table 2). In the spectrum of compound VI, the aromatic 6-H proton gives rise to chemical shifts for the exo- and endo-rotamers at 7.58 ppm (the more intense) and 7.52 ppm (Δδ 0.06 ppm). A comparison of the chemical shifts of the aromatic 6-H proton in the spectrum of 4-methyl-8-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (VIII) and its formyl derivative shows that the descreening is equal to 0.72 and 0.78 ppm. We can thus conclude that in compound VI, the anisotropic influence of the formyl group on the screening of the aromatic protons is weakly pronounced. Thus an appreciable divergence from coplanarity between the planes of the carbonyl group of the substituent and the atomatic ring can be assumed.

The disturbance of coplanarity can also be estimated from the UV spectra of the model compounds: N,N'-diacetyl-o-phenylenediamine (XX), 4-acetyltetrahydroquinoxalin-2-one (XXI) [9], and 5-formyl- (I) and 5-acetyltetrahydrobenzodiazepin-2-ones (XXII) [4] (Table 3). The long-wave ^1L_a-band (259 nm) in the spectrum of compound XXI, containing a six-membered ring, is bathochromically shifted compared with the band (242 nm) for the noncyclic compound XX, while in the spectra of 5-formyl- and 5-acetyl derivatives of benzodiapines (I and XXII), this shift is absent. Similar regularities were also observed during an examination of the UV spectra of N-acyl substituted indolines and tetrahydroquinolines [2]. If the characteristics of the absorption spectra of the model compounds are compared, we can conclude that the deviations from coplanarity between the aromatic ring and the carbonyl group of the

TABLE 3. UV Spectra of Compounds I, XX-XXII

Compound	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$, liter · mole^{-1} · cm^{-1})
I	221 (30,2), 246 (11,5)
XX	214 (20,0), 242 (11,7)
XXI	229 (26,8), 259 (7,5)
XXII	223 (27,5), 243 (12,0)

substituents in compounds containing six- and seven-membered heterocyclic rings are not the same. This is shown by different descreening effects on the o-aromatic protons in the two heterocyclic systems being compared.

In the spectra of compounds I, VII-IX with no substituents at the $C_{(3)}$ and $C_{(4)}$ atoms, the protons of the two methylene groups of the heterocyclic ring are represented by two averaged signals. For compounds II-IV, X, and XI, containing substituents at the $C_{(3)}$ or $C_{(4)}$ atoms, the proton signals of the $-CH_2CH-$ fragment of the heterocyclic ring represent an ABX spin system. The protons interacting with a vicinal SSCC $^3J_{HH}$ 12.9-13.7 Hz have been assigned as pseudoaxial, and those with $^3J_{HH}$ 4.1-6.0 Hz as axially-equatorial protons. In compounds II and X, we can evaluate the influence of the carbonyl group on the screening of the axial and equatorial protons at the $C_{(4)}$ atoms. The data in Table 2 show that the pseudo-equatorial ones ($\Delta\delta$ ~ 1.0 ppm). Thus, in the heterocyclic ring, there is an anisotropic screening of the pseudoequatorial and descreening of the pseudoaxial protons. It should be noted that in the spectra of compounds II and X, there exist far-range SSCC of the formyl proton with protons at the $C_{(4)}$ atom – $^4J_{HH}$ 1.2 and 0.5 Hz with pseudoequatorial and pseudo-axial protons, respectively; in compounds III and XI $^4J_{HH}$ 0.5 Hz.

To understand better the steric disposition of the carbonyl group of the formyl substituent, we analyzed thoroughly the PMR spectra of compounds IX-XI containing a benzyl group at the 1 position of the benzene ring. It was found that under the influence of the benzene ring of this group, the signals of the formyl protons are shifted to a stronger field: the more intense signal is shifted by 0.43-0.54 ppm, and the less intense signal by 0.08-0.12 ppm only.

These facts, and also the examination of the EUGON spherical models indicate that the benzodiazepine ring possibly has a pseudo-boat conformation and that the carbonyl group of the formyl substituent of the main rotamer (not less than 86%) is present at the exo-position relative to the benzene ring of the bicyclic system.

EXPERIMENTAL

The UV spectra were run on a Specord UV-vis spectrophotometer in ethanol. The PMR spectra were recorded on a Hitachi R-22 spectrometer (90 MHz), using HMDS as internal standard. The chemical shifts were converted relative to TMS. The ABX and AMX spin systems were calculated out according to a program LAOCN3 [10]. The course of the reaction and the purity of the compounds were controlled by the TLC method on Silufol UV-254 plates in a chloroform–ethyl acetate–methanol system (14:7:1.5).

5-Formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (I). A mixture of 31 ml of $(CH_3CO)_2O$ and 1.31 ml (30 mmoles) of 98% HCOOH is held for 2 h at 50°C. A solution of 4.8 g (30 mmoles) of benzodiazepinone XIII in 60 ml of absolute $CHCl_3$ is added, and the mixture is left to stand at 20°C for 20 h. After evaporation of the solvent, the residue is recrystallized.

Compounds II-VI are obtained in a similar way from XIV-XVIII, but solutions of the starting compounds in absolute tetrahydrofuran are used.

1-Methyl-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (VIII). A mixture of 3.8 g (20 mmoles) of compound I, 2.5 ml (40 mmoles) of CH_3I, and 5.6 g (100 mmoles) of KOH in 70 ml of absolute acetone is boiled, with stirring, with TLC control of the completion of the reaction. When cool, the reaction mixture is filtered, the solvent is evaporated, and the residue is dissolved in $CHCl_3$. The solution is washed with water to a neutral reaction in the washings. The $CHCl_3$ is then evaporated and the residue is recrystallized.

Derivatives IX-XI are obtained in a similar way from compounds I-III and benzyl bromide, respectively.

4-Methyl-7-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XVII). A mixture of 2.2 g (10 mmoles) of 4-methyl-7-nitro-2,3-dihydro-1H-1,5-benzodiazepin-2-one [11] and 0.5 g (13 mmoles) of $NaBH_4$ is boiled for 3 h in 50 ml of absolute ethanol. The solution is filtered, the filtrate is concentrated to half its volume, and cooled. The precipitate is separated and recrystallized. Yield 1.1 g (50%) of XVII, mp 243-245°C (from ethanol). Found, %: C 54.4; H 4.8; N 18.9. $C_{10}H_{11}N_3O_3$. Calculated, %: C 54.3; H 5.0; N 19.0. PMR spectrum (DMSO-D_6): 1.20 (3H, d, 4-CH_3), 2.1-2.7 (2H, overlaps with a signal of the solvent, 3-CH_2), 3.82 (1H, m, 4-CH), 10.08 (1H, s, NHCO), 7.74 (1H, Ar, H_6), 7.50 (1H, Ar, H_8), 7.04 (1H, Ar, H_9), 6.12 ppm (1H, s, NH), $^3J_{H_6H_8}$ 2.8 Hz; $^3J_{H_8H_9}$ 9.0 Hz.

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