The experimental results recorded 1, 3, and 24 h after administration, showed that in low concentrations (0.1-0.5%) the compounds do not exhibit a local irritant effect. In 1% concentrations a point necrosis and in 2% concentrations a strong necrosis is observed (in compounds XII, XIII – a point necrosis).

The compounds studied do not have anti-inflammatory or antibacterial activity.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-ALKYL DERIVATIVES OF 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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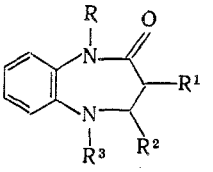
It is known that derivatives of the bicyclic system of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one are characterized by different kinds of physiological activity [9]. We have previously published [6] a study on the anti-inflammatory activity of N-acylderivatives of tetrahydrobenzodiazepinones. At the same time it was reported that 1-dialkylaminoalkyl substituted benzodiazepinones are prospective analgesics and antiphlogistics [13].

The aim of the present work was to synthesize derivatives of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (IV-XXII) containing alkyl substituents at the 1- and 1,5-positions of the heterocyclic ring, and to study their biological properties. We have developed for this purpose preparative methods for introducing the alkyl substituents into the 1-position of the benzodiazepine ring. Compounds IV-XVI were obtained by the alkylation of 5-acetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones (I-III) [6, 10, 11] under conditions of interphase catalysis.



I – XXII

R=H (I—III, XXI), CH_2Ph (IV, XV, XVI), Me (V, XIX, XX), Et (VI, XVII), Pr (VII), Pr-i (VIII), Bu (IX), Bu-i (X), Am-i (XI), $CH_2CH{=}CH_2$ (XII, XVIII), $(CH_2)_2NEt_2$ (XIII), $(CH_2)_3OPh$ (XIV), CH_2CH_2OH (XXII); R^1 = H (I—XVIII, XX—XXII), Me (XIX); R^2 = H (I, IV—XIV, XVII—XIX, XXI, XXII), Me (II, XV, XX), Ph (III, XVI); R^3 = H (XVII, XVIII), Ac (I—XVI, XXII), Me (XIX, XX), Et (XXI).

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TABLE 1. Physical Constants of 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepinones

Compound	X of alkylating agent	Yield by methods A and B, %	mp, °C	Empirical formula	Found, % / calculated, %		
					C	H	N
V	I	20 (A) 74 (B)	166—8	$C_{12}H_{14}N_2O_2$	65,9 66,0	6,3 6,5	12,9 12,8
VI	Br	65 (A)	146—7	$C_{13}H_{16}N_2O_2$	67,5 67,2	6,7 6,9	12,2 12,1
VII	Br	72 (A) 53 (B)	137—9	$C_{14}H_{18}N_2O_2$	68,2 68,3	7,4 7,4	11,4 11,4
VIII	I	20 (A) 20 (B)	123—5	[8]	—	—	—
	Br	36 (A) 0 (B)					
IX	I	40 (A) 90 (B)	88—9	$C_{15}H_{20}N_2O_2$	69,5 69,2	7,9 7,7	10,5 10,8
	Cl	48 (A) 0 (B)					
X	Br	65 (A) 20 (B)	143—5	$C_{15}H_{20}N_2O_2$	69,4 69,2	7,7 7,7	10,7 10,8
XI	Br	72 (A)	152—4	$C_{16}H_{22}N_2O_2$	70,1 70,0	8,0 8,1	10,2 10,2
XII	Br	73 (A)	123—5	$C_{14}H_{16}N_2O_2$	69,0 68,8	6,5 6,6	11,6 11,5
XIII	Cl	20 (A)	113—5	$C_{17}H_{25}N_3O_2$	67,3 67,3	8,3 8,3	13,8 13,9
XIV	Br	20 (A)	94—6	$C_{19}H_{20}N_2O_3$	70,1 70,4	6,3 6,2	8,4 8,6
XXII	Br	22 (A) 20 (B)	185—7	$C_{13}H_{16}N_2O_3$	62,7 62,9	6,4 6,5	11,5 11,3

Note. Compounds VI, VII, IX-XIII were crystallized from a benzene–hexane mixture, V from CCl_4, XIV from an ether–hexane mixture, XXII from acetonitrile.

The starting compounds I-III were treated with a double amount of the corresponding alkyl halide in a benzene-50% NaOH two-phase system in the presence of quaternary ammonium salts (method A). Triethylbenzylammonium chloride (TEBA Cl) or tetrabutylammonium bromide (TBA Br) served as catalysts. The nature of the catalyst has no noticeable influence on the course of the reaction. Thus, compound IV was obtained in 92% yield in the presence of TEBA Cl and in 95% yield when TBA Br was used. It should be noted that increase in the amount of the alkylating agent and the duration of the reaction does not lead to the formation of 1,3-dialkyl-substituted derivatives. From I with a fourfold excess of benzyl bromide only compound IV was obtained. Examination of the crude reaction product did not reveal the formation of an O-alkyl derivative, as has been noted in the series of dihydrobenzodiazepinones [12].

The course of the reactions depends mainly on the nature of the alkyl halide (Table 1). When benzyl bromide is used as the active alkylating agent, capable of forming a stable carbocation in nucleophilic substitution reactions, 1-benzyl derivatives IV, XV, XVI [8] are obtained in high yields (95-72%). The reaction of I with methyl iodide is an exception; the yield of the 1-methyl-substituted compound V does not exceed 20%. However, V is formed in 74% yield in the reactions of the same starting materials in absolute acetone in the presence of solid KOH (method B). 1-n-Butyl-5-acetyltetrahydrobenzodiazepinone IX was also obtained by a reaction of I with n-butyl iodide by method B in a higher yield, while under the same conditions, the reaction with n-butyl chloride did not proceed. It is possible that the activity of the halide anion used in the reaction plays a decisive role under these conditions. Under the catalysis conditions, the presence of the halide anion does not substantially affect the yields of the products. The steric hindrances occurring during the introduction of branched radicals, for example isopropyl, cause a decrease in the yield (up to 20%) when both methods A and B are used (compound VIII).

TABLE 2. Data on PMR Spectra of 2,3,4,5-Tetrahydro-1H-1,5-Benzodiazepin-2-one Derivatives

Compound	PMR spectrum, δ, ppm, solvent $CDCl_3$
V	1,76 (3H, s, $COCH_3$), 2,41 (2H, m, $COCH_2$), 3,26 (3H, s, 1-CH_3 overlaps with 1H,m, 4-NCH_2), 4,86 (1H,m, 4-NCH_2), 7,07 and 7,45 (4H, Ar)
VI	1,04 (3H, t, CH_3), 1,79 (3H, s, $COCH_3$), 2,41 (2H,m, $COCH_2$), 3,44 (1H,m, 1-NCH_2 and 1H,m, 4-NCH_2), 4,27 (1H,m, 1-NCH_2), 4,87 (1H,m, 4-NCH_2), 7,07—7,53 (4H, Ar)
VII	0,76 (3H, t, CH_3), 1,38 (2H, m, CH_2), 1,79 (3H, s, 5-$COCH_3$), 2,41 (2H, m $COCH_2$), 3,37 (1H, m, 1-NCH_2 and 1H,m, 4-NCH_2), 4,19 (1H,m, 1-NCH_2), 4,84 (1H, m, 4-NCH_2), 7,07—7,50 (4H, Ar)
IX	0,78 (3H, t, CH_3), 0,98—1,47 (4H,two CH_2), 1,73 (3H, s, $COCH_3$), 2,39 (2H, m $COCH_2$), 3,37 (1H, m, 1-NCH_2 1H, m, 4-NCH_2), 4,20 (1H, m, 1-NCH_2), 4,78 (1H, m, 4-NCH_2), 7,06—7,50 (4H, Ar)
X	0,76 (6H, br. d, two CH_3), 1,80 (3H, s, $COCH_3$ overlaps with s. 1H, m, CH), 2,40 (2H,m, $COCH_2$), 3,04—3,56 (1H, m, 1-NCH_2 and 1H, m, 4-NCH_2), 4,16 (1H, m, 1-NCH_2), 4,73 (1H, m, 4-NCH_2), 7,09—7,51 (4H, Ar)
XI	0,73 and 0,81 (6H, two d, twoCH_3), 1,29 (3H, m CH_2CH), 1,78 (3H, s, $COCH_3$), 2,40 (2H, m, $COCH_2$), 3,38 (1H, m, 1-NCH_2 and 1H, m, 4-NCH_2), 4,29 (1H,m, 1-NCH_2), 4,82 (1H, m, 4-NCH_2), 7,02—7,42 (4H, Ar)
XII	1,76 (3H, s, $COCH_3$), 2,42 (2H, m, $COCH_2$), 3,38 (1H, m, 4-NCH_2), 4,09 (1H, m, 1-NCH_2), 4,50—5,36 (1H, 1-NCH_2, 1H, 4-NCH_2, 2H, $=CH_2$), 5,76 (1H m, CH), 7,04—7,50 (4H, Ar)
XIII	0,71—0,98 (6H, two t, twoCH_3), 1,78 (3H, s, $COCH_3$), 2,24—2,84 (8H, $COCH_2$ and three NCH_2), 3,44 (1H, 1-$NCH_2$and 1H, 4-NCH_2), 4,20 (1H,m, 1-NCH_2), 4,89 (1H, m, 4-NCH_2), 7,00—7,53 (4H, Ar)
XIV	1,52 (3H,s, $COCH_3$), 2,40 (2H,m, $COCH_2$), 3,39 and 4,82 (2H, two m, 4-NCH_2), 3,37—4,42 (4H, CH_2CH_2O), 6,67—7,31 (9H, Ar)
XXII[a]	1,62 (3H, s, $COCH_3$), 2,29 (2H,m, $COCH_2$), 3,11—4,02 (1H, 4-NCH_2, 5H, 1-CH_2CH_2OH), 4,60 (1H, m, 4-NCH_2), 7,24—7,66 (4H, Ar)

[a]The spectrum was run in DMSO-d_4.

Note. c = s, A = d, M = m.

It should be noted that in the reaction of I with dibromoethane, instead of the expected 1-bromoethyl derivative, only 1-(2-hydroxyethyl)-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XXII) was obtained in a 20% yield. It is possible that by the action of alkalies, hydrogen bromide is eliminated in the alkylating agent. The structure of XXII was confirmed by IR and PMR spectra (Table 2). In the IR spectrum of XXII (a KBr tablet), a stretching vibrations band of the C=O group is observed at 1653 cm^{-1} (amide I) and a broad stretching vibrations band of the associated OH group at 3330 cm^{-1}, whose intensity decreases in a dilute solution (3440 cm^{-1}), and a new narrow band appears at 3625 cm^{-1} of the free OH group [2].

Compounds XVII-XX were synthesized by methods A and B from 5-tetrahydrobenzodiazepinones unsubstituted at the 5-position [7]. Compound XXI was described in [5].

EXPERIMENTAL (CHEMICAL)

The PMR spectra were run on a "Hitachi R-22" spectrophotometer (90 MHz, Japan), using HMDS as an internal standard. The IR spectrum of compound XXII was recorded on a "Specord 711 R" spectrophotometer (GDR) in a KBr tablet in solution ($CHCl_3$). The purity of the compounds and the course of the reactions was monitored chromatographically on Silufol UV-254 plates (CSSR) in a $CHCl_3$–ethyl acetate–methanol (14:7:1.5) system.

1-Methyl-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (V). A. A 4.29 g portion (30 mmoles) of MeI is added with stirring to a mixture of 3.06 g (15 mmoles) of I, 0.34 g (1.5 mmoles) of TEBA Cl, 200 ml of benzene and 11.3 ml of 50% NaOH. The reaction mixture is boiled for 2-4 h, while monitoring the completion of the reaction by TLC. After cooling, the aqueous layer is separated, and the benzene layer is washed with water to a neutral reaction of the washings. The solvent is evaporated, and the residue is recrystallized.

In a similar way, from I and ethyl and isopropyl bromides, n-butyl iodide and n-butyl chloride, isobutyl-, isoamyl- and allyl bromides, diethylaminoethyl chloride, phenylethyl bromide, and dibromoethane, compounds VI, VIII, IX-XIV, and XXII, respectively, are obtained.

B. A mixture of 3.06 g (15 mmoles) of I, 4.29 g (30 mmoles) of MeI, 4.2 g (75 mmoles) of KOH, and 75 ml of absolute acetone is boiled, with stirring, for 2-4 h, monitoring the

course of the reaction by TLC. After cooling, the reaction mixture is filtered, the solvent is evaporated, and the residue is dissolved in $CHCl_3$ and washed with water. The solvent is evaporated, and the residue recrystallized.

In a similar way, from I and n-propyl bromide, n-butyl iodide and n-butyl chloride, isobutyl bromide, and dibromoethane, compounds VII, IX, X, and XXII, respectively, are obtained.

EXPERIMENTAL (BIOLOGICAL)

The acute toxicity of the compounds was determined on white mice by the Kerber method [1] with intraperitoneal administration.

The anti-inflammatory activity was characterized by means of an agar model of inflammation [4], produced by subplantary administration of 0.15 ml of 0.15% "Difco" agar into posterior paws of rats. The degree of inhibition of inflammation (in percent) was calculated from the formula

$$\frac{X_{control} - X_{experiment}}{X_{control}} \cdot 100,$$

where X is the volume of the inflamed paws, measured oncometrically..

In the evaluation of the general and neutropic action of the compounds tested, the methods of "open field," actography (orientational and motor activity), "hot plate" [14] (anaesthetizing action), horizontal rotating rod [3] (state of coordinational mechanisms) were selectively used, the influence on the hexenal- and sombrevin-induced sleep was studied, and the thermometry of the animals was carried out. The antispasmodic activity was evaluated from the maximal electric shock test [3]. The compounds were administered intraperitoneally in a starch mucilage.

The toxicity of the compounds studied fluctuates within wide limits – LD_{50} from 50 to 1000 mg/kg. Compound XVI containing a phenyl radical at the 4-position has the lowest toxicity (LD_{50} 1000 mg/kg). Several compounds in toxic doses cause increased excitation, tremor, a spasmodic disposition (XVIII, LD_{50} 250 mg/kg), or spasms of the clonically-tonic character, interchangeable adynamia, general depression, disturbance of coordinational mechanisms (IV, VI, XII, XV, XVI, and XVII, the LD_{50} of which are 300, 100, 50, 75, 1000, and 75 mg/kg, respectively).

Compounds XIX, XX, and XXI (LD_{50} 250, 550, and 100 mg/kg, respectively) in doses of the order of magnitude of 1/10 LD_{50} induce cramps in the animals, indicating the irritant effect, while in toxic doses lead to depression, ataxia, and side position with attentuation of the reflexes, pain reaction, and curtailment of respiration. Thus, displacement of the alkyl radical to the 5-position qualitatively changes the character of the central action of the compounds in the series studied.

The compounds studied did not exhibit any anti-inflammatory activity.

At the same time, the alkyl derivatives in toxic doses induced several neutropic effects. Thus, while having no specific analgetic properties, compound XII considerably intensified the anaesthetic action of amidopyrine (the latent period of the increased defensive reaction from 30 ± 4.7 to 54 ± 3.5 sec). The same compound increased by more than twofold the duration of hexenal- (but not sombrevin)-induced sleep, and decreased the rectal temperature of the mice by 2.9°C. Almost the same decrease in temperature was also induced by compound XX, which together with XIX and XXI exhibited weak anaesthetic activity.

Of all the compounds tested, only compound XVIII (LD_{50} 250 mg/kg) exhibited an antispasmodic effect in a dose equal to 1/4 LD_{50}. Decrease in the dose led to a disappearance of the antispasmodic effect.

Thus, in contrast with the previously studied N-acyl derivatives of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one, having anti-inflammatory activity [6]. The N-alkyl compounds have no such activity, but, depending on structure, cause variably directed changes in the CNS.

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SYNTHESIS AND DIURETIC ACTIVITY OF 3-SULFAMOYL-4-CHLOROBENZOYL HYDRAZONES OF AROMATIC ALDEHYDES

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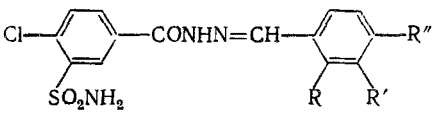
Hydrazides of 3-sulfamoyl-4-chlorobenzoic acid have been found to exhibit diuretic activity [3-9]. Compounds of that class which include N-(cis-2,6,-dimethylpiperidino)-3-sulfamoyl-4-chlorobenzamide – clopamide [2], and N-(3-sulfamoyl-4-chlorobenzoyl)-1-amino-2-methylindoline – indapamide [7], exhibit a high degree of natriuretic activity and antihypertensive action and have been employed in medical practice. At the same time practically no studies have been made of the 3-sulfamoyl-4-chlorobenzoyl hydrazones. The literature has some information about the diuretic action only of 3-sulfamoyl-4-chlorobenzoyl hydrazones of acetone (I) and benzaldehyde (II).

We felt it would be of interest to establish how diuretic activity would be affected by various substituents in the benzene ring of the aldehyde component of compound II. To that end we synthesized 3-sulfamoyl-4-chlorobenzoyl hydrazones of benzaldehyde and its derivatives (II-XI) and investigated their diuretic and saluretic activity. Compounds II-XI were obtained by boiling a solution of 3-sulfamoyl-4-chlorobenzoic hydrazide (XII) and an appropriate aldehyde in 2-propanol in the presence of acetic acid.



II – XI

R = H (II – VI, IX, X), OH (VII), OCH_3 (VIII, XI);
R′ = H (II – VIII, XI), Cl (IX), NO_2 (X);
R″ = H (II, VII – X), Br (III), NO_2 (IV), N $(C_2H_5)_2$ (V), OCH_3 (VI, XI).

The structures of II-XI were confirmed by element analysis and IR-spectroscopy. The IR-spectra of II-XI had the following absorption bands: 1665-1680 cm^{-1} (C=O, amide I), 1625-1660 cm^{-1} (C=N), 1329-1344 and 1160-1185 cm^{-1} (SO_2NH_2).

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