SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

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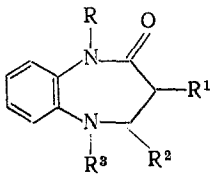
The 1,5-benzodiazepines are a class of substances which exhibit a variety of biological activities [5]. The purpose of the present work is to synthesize new N-substituted derivatives of 2,3,4,5-tetrahydro-1H,5-benzodiazepin-2-one (II, IV-VI, VIII, IX, and XIV-XX), and to study the biological activity of compounds IV-VI, VIII, IX, XI-XVII, and XX.



I—XX

I—XIV: R=H; XV: R=COEt; XVI, XVII, XX: R=Ac; XVIII: R=COPh; XIX: R=COPr; I, III—V, VII, VIII, X—XX: R^1—H; II, VI, IX: R^1=Me; I, II, IV—VI, VIII—XI, XIV—XIX: R^2=H; III, VII, XII, XIII, XX: R^2=Me; I—III: R^3=H; IV, VI, VII, XV, XVIII—XX: R^3=Ac; V: R^3=COEt; VIII, IX, XVII: R^3=CHO; X, XVI: R^3=NO; XI, XII: R^3=$CONH_2$; XIII: R^3=CONHMe; XIV: R^3=$COC_6H_2(OMe)_3$=3, 4, 5.

Compounds I [6], II, and III [8] were used as starting materials for the synthesis. Compound II was synthesized for the first time by fusing an equimolar mixture of o-phenylenediamine and methacrylic acid. The 5-N-acyl derivatives IV-VI were obtained by the reaction of the corresponding amines I-III with Ac_2O or $(EtCO)_2O$. The 5-N-formyl derivatives VIII and IX were obtained in yields of less than 30% from the reaction of I or II with HCOOH in dry benzene. Compound XIV was synthesized by the reaction of I with the acid chloride of 3,4,5,-trimethoxybenzoic acid. Compounds XI-XIII are reported in [6], and VII-X in [8].

Until now, no derivatives of 1,5-benzodiazepin-2-one with an acyl group at position 1 of the heterocyclic ring have been reported. Several methods were used to synthesize these compounds. The reaction of IV with PhCOCl in dry boiling $CHCl_3$ gave compound XVIII in 18% yield. Attempts to acylate the sodium salt of IV with the acid chloride using the method given in [9] also did not give a satisfactory result, and the derivative XVIII was isolated in low yield (20%). Compound XX was synthesized by refluxing VII with excess Ac_2O in toluene or pyridine [7] (yields were 46 and 54%, respectively). Derivatives XV, XVII-XIX were also prepared by this method. For the synthesis of compound XVI, which contains an unstable N-nitroso group, the reaction of X with Ac_2O was carried out in toluene.

Structures of the compounds synthesized were confirmed from elemental analysis and NMR spectral data (Tables 1 and 2).

The infrared spectra of compounds I-XIV display absorption bands at 1642-1680 cm^{-1} arising from the carbonyl group vibrations, and in the spectra of compounds XV-XX, which have an acyl group at position 1 of the heterocyclic ring, there are also bands at 1720-1730 cm^{-1}. The stretching vibrations of the associated NH group (in KBr pellets or in concentrated $CHCl_3$ solution) produce bands at 3150-3180 cm^{-1}, characteristic of the NHCO group in which the N—H and C=O bonds are in the s-cis-configuration [2]. Vibrations of the free NH-group (in dilute $CHCl_3$ solution) are observed at 3370-3380 cm^{-1}. In the infrared spectra of compounds XI-XIII, which also have an exocyclic NHCO-group, absorption bands at 3425-3500 cm^{-1}, due to the oscillation of the free NH group, are also observed. At 1500-1600 cm^{-1}, in addition to absorption

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TABLE 1. Date for Compounds II, IV-VI, VIII, IX, and XIV-XX

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
II	23	202—4	68,5	6,6	15,8	$C_{10}H_{12}N_2O$	68,2	6,9	15,9
IV	75	158—60	64.5	5,9	13,7	$C_{11}H_{12}N_2O_2$	64,7	5,9	13,7
V	65	135—7	65,9	6,5	12,9	$C_{12}H_{14}N_2O_2$	66,0	6,5	12,8
VI	82	163—5	66,3	6,3	12,7	$C_{12}H_{14}N_2O_2$	66,0	6,5	12,8
VIII	21	198—200	63.3	5,3	14,6	$C_{10}H_{10}N_2O_2$	63,2	5,3	14,7
IX	32	187—9	64,8	6,0	13,7	$C_{11}H_{12}N_2O_2$	64,7	5,9	13,7
XIV	75	116—8	64.4	5,7	7,5	$C_{19}H_{20}N_2O_5$	64,0	5,7	7,9
XV	61	153—5	64,6	6,4	10,8	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,8
XVI	35	121—3	56,4	4,8	17,7	$C_{11}H_{11}N_3O_3$	56,7	4,8	18,0
XVII	74	149—51	62,3	5,2	12,2	$C_{12}H_{12}N_2O_3$	62,1	5,2	12,1
XVIII	30	172—4	70,1	5,3	9,0	$C_{18}H_{16}N_2O_3$	70,1	5,2	9,1
XIX	55	84—6	65,5	6,6	10,1	$C_{15}H_{18}N_2O_3$	65,7	6,6	10,2
XX	54	100—3	64,8	6,2	11,0	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,8

Note. Compounds II and XIV were recrystallized from benzene, IV-VI, VIII, IX, and XVII from ethyl acetate, XV from CCl_4, XVI from AcOPr-iso, XVIII from PrOH, XIX and XX from ether.

TABLE 2. PMR-Spectral Data for 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepin-2-one Derivatives

Compound	PMR-spectra, δ, ppm
I	2,66 t ($3\text{-}CH_2$), 3,61 ($4\text{-}CH_2$), 6,55—6,97 (Ar, 4H), 8,82 (NH)
II	1,11 d (CH_3), 2,0 m (3-CH), 2,82 (5-NH), 3,42 m ($4\text{-}CH_2$), 6,55—6,85 (Ar, 4H), 7,42 (NH)
IV	1,75 s ($COCH_3$), 2,5 m ($3\text{-}CH_2$), 3,4 and 4,85 two m ($4\text{-}CH_2$), 7,0—7,4 (Ar, 4H), 9,7 (NH)
V	0,92 t (CH_3), 1,9 m ($COCH_2$), 2,5 m ($3\text{-}CH_2$), 3,4 and 4,8 two m ($4\text{-}CH_2$), 7,0—7,45 (Ar, 4H), 9,3 (NH)
VI	0,95 d (CH_3), 1,78 s ($COCH_3$), 2,76 m (3-CH), 3,51 and 4,57 two m ($4\text{-}CH_2$), 7,10—7,50 (Ar, 4H), 9,6 (NH)
VII	1,08 d (CH_3), 1,65 s ($COCH_3$), 2,3 m ($3\text{-}CH_2$), 5,25 m (4-CH), 7,0—7,4 (Ar, 4H), 9,3 (NH)
VIII	2,51 ($3\text{-}CH_3$), 3,94 ($4\text{-}CH_2$), 6,9—7,45 (Ar, 4H), 8,18 and 8,35 two s (CHO), 9,69 s, 9,82 two br s (NH)
IX	1,17 d (CH_3), 2,91 m (3-CH), 3,65 and 4,27 two m ($4\text{-}CH_2$), 7,45—7,0 (Ar, 4H), 8,21 8,35 two s (CHO), 9,24 (NH)
XIV	2,62 ($3\text{-}CH_2$), 3,5 s ($3,5\text{-}OCH_3$), 3,61 s ($4\text{-}OCH_3$), 3,4—5,0 ($4\text{-}CH_2$), 6,36 s (Ar, 2H), 6,6—7,2 (Ar, 4H), 9,76 (NH)
XV	1,1 t (CH_3), 1,8 s ($COCH_3$), 2,47 m ($3\text{-}CH_2$), 3,05 q ($COCH_2$), 3,27 and 4,77 two m ($4\text{-}CH_2$), 7,1—7,45 (Ar, 4H)
XVI	2,5 s ($COCH_3$), 2,7 t ($3\text{-}CH_2$), 4,02 t ($4\text{-}CH_2$), 7,22—7,5 (Ar, 4H)
XVII	2,45—2,68 ($3\text{-}CH_2$), 2,55 s ($COCH_3$), 3,95 ($4\text{-}CH_2$), 7,1—7,44 (Ar, 4H), 8,26 and 8,35 two s (CHO)
XVIII	1,8 s ($COCH_3$), 2,45 m ($3\text{-}CH_2$), 3,32 and 4,8 two m ($4\text{-}CO_2$), 7,1—7,7 (Ar, 9H)
XIX	0,88 t (CH_3), 1,6 m (CH_2), 1,76 s ($COCH_3$), 2,4 m ($3\text{-}CH_2$), 2,94 t ($COCH_2$), 3,24 and 4,8 two m ($4\text{-}CH_2$), 7,0—7,5 (Ar, 4H)
XX	1,0 d (CH_3), 1,64 s ($5\text{-}COCH_3$), 2,1 m ($3\text{-}CH_2$), 2,5 s ($1\text{-}COCH_3$), 5,0 q (4-CH), 7,0—7,4 (Ar, 4H)

bands arising from the benzene ring, compounds XI-XIII display strong amide-II bands at 1515-1580 cm^{-1}, which are absent in the spectra of compounds I-X. Absence of bands in this region due to the amide-II, agree with data reported in [1, 3] and confirm that the amide group of the diazepine ring has the cis-configuration.

The PMR spectrum of compound I shows that protons of the two methylene groups, at C_3 and C_4, form the spin system AA_1XX_1, and resonate as two triplets (see Table 2). The spectrum is typical of a system in an unstable state. With different substituents on the nitrogen atom at position 5 (compounds IV-VI, XI, XIV, XVIII, and XIX) the protons of the two CH_2-groups form an ABMX-system. This shows that the CH_2-protons become less equivalent on substitution, an effect due to the inversion of the molecule. The intramolecular mobility of the molecule also depends on the structure of the substituent (compare the spectra of compounds IV and VIII, XI, XIV).

TABLE 3. Toxicity and Effect on Agar Inflammation of Compounds IV-VI, VIII, IX, XI-XVII, and XX

Compound	LD_{50} mg/kg	Dose, mg/kg	Inhibition of edema, %	
			after 3 hours	after 5 hours
IV	108	15	47*	46*
		5	20	29*
V	470	60	29*	28
VI	<1000	100	25	31*
VIII	10	1	0	0
IX	50	5	54*	51*
XI	>1000	100	14	16
XII	708	70	0	10
XIII	>1000	100	16	16
XIV	>1000	100	35*	36*
XV	100	10	0	0
XVI	200	20	0	0
XVII	10	1	46*	58*
XX	250	25	53*	48*

Note. Asterisks indicate results with $P \leq 0.05$.

EXPERIMENTAL (CHEMICAL)

Infrared spectra of the compounds in KBr pellets and in $CHCl_3$ solution were taken on a Specord 71 IP (GDR), PMR spectra on a Hitachi P-22 spectrophotometer (Japan) at 90 MHz; internal standard HMDS, solvent $CDCl_3$, for VIII D_6-DMSO. The purity of the compounds was checked chromotographically on Silufol 254 plates (ChSSR).

3-Methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (II). A mixture of 40.5 g (375 mmoles) of o-phenylenediamine and 32.2 g (375 mmoles) of methacrylic acid was heated to 200°C and maintained at this temperature for 2 hours. The reaction mixture was then cooled, and, without allowing it to solidify, dissolved in 200 ml of MeOH. The solution was cooled, and the precipitated material filtered off to give compound II.

5-Acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (IV). A mixture of 8.1 g (50 mmoles) of I and 5.6 ml (60 mmoles) of Ac_2O in dry $CHCl_3$ was refluxed for 5 hours. The solution was cooled and washed sequentially with acidified water, Na_2CO_3 solution, and water. The solvent was evaporated and the residue recrystallized.

Analogously, compound I and $(EtCO)_2O$ gave V, and II and Ac_2O gave VI.

5-Formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (VIII). A mixture of 4.8 g (30 mmoles) of I and 1.63 ml (36 mmoles) of 85% HCOOH in 300 ml of dry benzene was refluxed for 15 hours. The hot solution was washed in turn with acidified water, Na_2CO_3 solution, and water. The solution was evaporated and the residue recrystallized.

Analogously IX was obtained from II. The acid wash-water was neutralized with Na_2CO_3 and gave 30% of the starting material II.

5-(3,4,5-Trimethoxybenzoyl)2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XIV). A solution of 11.4 g (70 mmoles) of I and 7.5 ml (87 mmoles) of pyridine in a dry $CHCl_3$ was stirred and cooled, and a solution of 16.4 g (71 mmoles) of the acid chloride of 3,4,5-trimethoxybenzoic acid in dry $CHCl_3$ was added. The reaction mixture was heated to 40°C and maintained at this temperature for 4 hours. The solution was then cooled and washed sequentially with acidified water, Na_2CO_3 solution, and water. The solvent was evaporated and the residue recyrstallized.

1-Benzoyl-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XVIII). A. A mixture of 4.08 g (20 mmoles) of IV and 4.6 ml (40 mmoles) of PhCOCl in dry $CHCl_3$ was refluxed for 10 hours, then cooled, and washed with a solution of Na_2CO_3, followed by water. The solvent was evaporated and the residue chromatographed on a L40/100 μ silica gel column (ChSSR) to give 0.7 g of material with mp 117-119°C, which on admixture with PhCOOH melted at 117°C, 0.1 g of unreacted IV, and 1.1 g (18%) of compound XVIII.

B. A suspension of 2.04 g (10 mmoles) of IV and 0.45 g of 55% NaH in dry benzene was refluxed for 1 hour, 1.15 ml (10 mmoles) of PhCOCl added and refluxing continued for a further 3 hours. The solution was cooled, washed with a solution of Na_2CO_3 and with water, the solvent removed by evaporation, and the residue recrystallized to give 0.6 g (20%) of XVIII.

C. A solution of 3.06 g (15 mmoles) of IV and 4.52 g (20 mmoles) of $(PhCO)_2O$ in 25 ml of pyridine was refluxed for 8 hours, cooled, and poured into 100 ml of water. After neutralization with HCl, the aqueous solution was extracted with $CHCl_3$. The extract was washed with a solution of Na_2CO_3 and with water, the solvent evaporated and the residue recrystallized to give 1.38 g (30%) of XVIII.

1,5-Diacetyl-4-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (XX). A. A Solution of 2.2 g (10 mmoles) of VII and 4.2 ml (45 mmoles) of Ac_2O in 25 ml of pyridine was refluxed for 8 hours, cooled, and poured into 100 ml of water. After neutralization with HCl, the aqueous solution was extracted with $CHCl_3$. The extract was washed with Na_2CO_3 solution, and with water, the solvent evaporated and the residue recrystallized to give 1.4 g (54%) of XX.

Using the same method, XV and XIX were obtained from IV and $(EtCO)_2O$ or $(PrCO)_2O$, and XVII from VIII and Ac_2O.

B. A solution of 2.2 g (10 mmoles) of VII and 4.2 ml (45 mmoles) of Ac_2O in 30 ml of toluene was refluxed for 8 hours, washed with NaOH solution and with water, and the solvent removed by evaporation. The residue was recrystallized to give 1.2 g (46%) of XX.

Compound XVI was obtained from X by the same method.

EXPERIMENTAL (BIOLOGICAL)

The following biological properties were studied: acute toxicity (LD_{50}), analgesic activity, and antiinflammatory action.

Acute toxicities were obtained by intraperitoneal injections of the compounds into white mice. The LD_{50} varied over a wide range — 10 to 1000 mg/kg (Table 3). The majority of the compounds, in both sublethal and lethal doses caused tremors and convulsions in the animals, and compounds XII and XX, in similar doses, caused a depressor reaction.

The analgesic activity of the compounds was studied in tests on white mice using the hot-plate method [10]. Compounds IV-VI, XII, and XIII were found to possess weak analgesic activity, but were less active than amidopyrine. Only one of the test compounds — VI — increased the duration of sodium barbiturate sleep, and only by a small amount.

The antiinflammatory activity was determined using models of agar inflammation produced by a subplantar injection into the back paw of the rat of 0.15 ml of 0.15% DIFKO agar [4]. The increase in the volume of the inflamed paw was treated oncometrically. The compounds, in a constant volume of 1% starch paste, were injected intraperitoneally one hour before the injection of the inflammatory agent. The results of the tests are summarized in Table 3, and show that compounds IV, IX, XVII, and XX exhibited significant antiinflammatory action. Compounds V, VI, and XIV showed weaker activity. The remaining compounds showed no antiinflammatory action.

Thus, the compounds tested displayed antiinflammatory activity, not previously observed in 1,5-benzodiazepin-2-one derivatives. We would like to draw attention to the role of the acyl and formyl groups at positions 1 and 5 of the heterocyclic ring in the manifestation of antiinflammatory activity. The results of this work indicate that this is a promising series of compounds to examine for antiinflammatory agents.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME ORGANO-PHOSPHORUS DERIVATIVES OF RUBIDOMYCIN WITH DI[2-CHLOROETHYL]AMINE GROUPS

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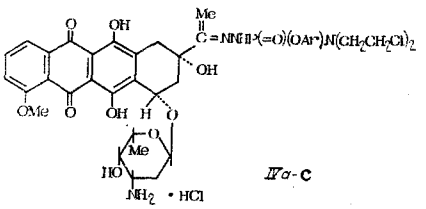
The antitumor antibiotic rubidomycin (I) is known to be effective in the treatment of acute leukosis [5]. A series of papers has recently appeared which describes attempts to chemically modify rubidomycin in order to reduce its cardiotoxicity and widen its spectrum of action [5, 9]. A group of phsophorylated chloroethylamines, known for their antiblastic activity, are the hydrochloride salts of the aryl esters of hydrazido-di(2-chloroethyl)amido-phosphoric acids (II) [1, 4].

It was of interest to study the reaction between I and II in order to obtain the phosphorylated derivatives of the hydrazones (IVa-c) containing cytotoxic groups, and to study their toxicity and antitumor action. To carry out this reaction, the hydrochloride salt II was first converted to the corresponding base (III); the reaction between I and III was conducted at room temperature in methanol—chloroform solution.



IVa: Ar = Ph; IVb: Ar = C_6H_4Br-p; IVc Ar = C_6H_4Me-p.

The hydrazones IVa-c were red crystalline substances, soluble in water and alcohols, and insoluble in benzene, ether, and petroleum ether (Table 1).

The pharmacological properties of IVa-c were compared with those of I and II. A change in toxicity was expected because the difference in the toxic parameters of I (LD_{50} 28.6 g/kg) and II (LD_{50} 500 mg/kg) is much more than an order of magnitude [3, 4]. It was also assumed that there was a possibility of an increase in selectivity of the antitumor action of IVa-c in comparison with I, a preparation with a wide spectrum of antitumor activity [3], and II which has a definite selectivity of antitumor action [4].

The test compounds displayed less toxicity, antitumor and antileukemic activity than rubidomycin and at the same time significantly inhibited leucosis La.

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