BASIC HYDROLYSIS OF 3-ACETOXY-7-BROMO-5-(o-CHLOROPHENYL)-1-ETHOXYCARBONYLMETHYL-1,2-DIHYDRO-3H-1,4-BENZADIAZEPIN-2-ONE

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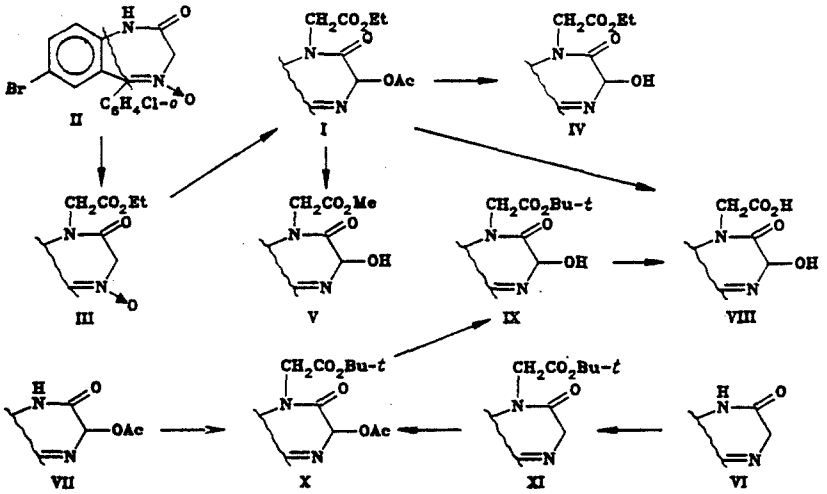
The selective basic hydrolysis of 3-acetoxy-7-bromo-5-(o-chlorophenyl)-1-ethoxycarbonylmethyl-1,2-dihydro-3H-1,4-benzdiazepin-2-one has been carried out, resulting in the sequential formation of 3-hydroxy-1-ethoxycarbonylmethyl-, 3-hydroxy-1-methoxycarbonylmethyl-, and 3-hydroxy-1-carboxymethyl derivatives. The structure of the 1-methoxycarbonylmethyl derivatives has been established by x-ray structural analysis.

The search for new psychotropic drugs has stimulated the introduction of a variety of different substituents into different positions in both the heterocyclic and aromatic rings of 1,4-benzdiazepines. During the course of these studies a series of interesting chemical reactions in this class of compounds was discovered.

The introduction of bulky substituents in the 1- and 3-positions of 5-aryl-1,2-dihydro-3H-1,4-benzdiazepin-2-ones reduces, as expected, their psychotropic activity [1]. This probably explains why the chemical behavior of 1-alkoxycarbonylmethyl-3-acyloxy-1,2-dihydro-3H-1,4-benzdiazepin-2-ones has not been studied.

We have investigated the basic hydrolysis of 3-acetoxy-7-bromo-5-(o-chlorophenyl)-1-ethoxycarbonylmethyl-1,2-dihydro-3H-1,4-benzdiazepin-2-one (I), which is obtained via alkylation of the corresponding N-oxide (II) [2] with ethyl bromoacetate followed by treatment of the resulting compound (III) with hot acetic anhydride.



Hydrolysis of the ester group in 3-acetoxy-1,4-benzdiazepin-2-ones is generally carried out with excess base in an aqueous organic solution [3]. Upon treatment of compound (I) with one equivalent of base at room temperature the acetoxy group is selectively removed and it is possible to isolate 1-ethoxycarbonylmethyl-1,4-benzdiazepin-2-one. The ease of this hydrolysis reaction under such mild conditions can be explained in terms of "anchimeric assistance" by the ethoxycarbonyl group, which can be oriented in space directly at the $C_{(3)}$ atom in the heterocycle and thus facilitate departure of the leaving group because of its electron donating effect.

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TABLE 1. Coordinates of the Basis Atoms and Their Corresponding Thermal Parameters (× 10^3) in the Structure of (V)

Atom	x	y	z	U/U_{equiv} Å²
Br	197,1(3)	2,1(3)	144,0(3)	67*
Cl	347,5(9)	382,6(7)	−51,1(8)	90*
$O_{(1)}$	−319(1)	172(2)	−327(2)	56
$O_{(2)}$	11(2)	242(1)	−453(1)	56
$O_{(3)}$	229(1)	300(1)	−420(1)	64
$O_{(4)}$	−195(2)	253(1)	−218(2)	66
$N_{(1)}$	3(2)	147(2)	−302(2)	42
$N_{(4)}$	149(1)	323(1)	−244(1)	36
$C_{(2)}$	58(2)	214(2)	−366(2)	37
$C_{(3)}$	174(2)	253(2)	−332(2)	55
$C_{(5)}$	122(2)	289(2)	−150(2)	28
$C_{(6)}$	107(1)	180(1)	−123(1)	21
$C_{(7)}$	54(1)	114(1)	−199(1)	32
$C_{(8)}$	46(1)	14(1)	−172(1)	41
$C_{(9)}$	90(1)	−21(1)	−71(1)	34
$C_{(10)}$	142(1)	45(1)	4(1)	25
$C_{(11)}$	151(1)	145(1)	−22(1)	25
$C_{(12)}$	−122(1)	117(1)	−326(1)	19
$C_{(13)}$	−206(1)	188(2)	−282(2)	34
$C_{(14)}$	−422(2)	235(2)	−284(2)	68
$C_{(51)}$	103(1)	359(1)	−54(1)	30
$C_{(52)}$	−13(1)	380(1)	−16(1)	58
$C_{(53)}$	−30(1)	449(1)	69(1)	80
$C_{(54)}$	69(1)	496(1)	116(1)	65
$C_{(55)}$	185(1)	475(1)	79(1)	57
$C_{(56)}$	203(1)	407(1)	−6(1)	36

*U_{equiv} = U(11) + U(22) + U(33).

TABLE 2. Bond Length and Bond and Torsional Angle Values in the Structure of V*

Bond length	l, Å	Bond angle	ω°	Torsional angle	τ°
Br—$C_{(10)}$	1,87	Br—$C_{(10)}$—$C_{(9)}$	121	$C_{(7)}$—$N_{(1)}$—$C_{(2)}$—$C_{(3)}$	1
Cl—$C_{(56)}$	1,72	Br—$C_{(10)}$—$C_{(11)}$	119	$C_{(2)}$—$C_{(3)}$—$N_{(4)}$—$C_{(5)}$	75
$N_{(1)}$—$C_{(2)}$	1,33	Cl—$C_{(56)}$—$C_{(51)}$	121	$N_{(4)}$—$C_{(5)}$—$C_{(6)}$—$C_{(7)}$	−37
$C_{(2)}$—$C_{(3)}$	1,44	Cl—$C_{(56)}$—$C_{(55)}$	119	$C_{(6)}$—$C_{(7)}$—$N_{(1)}$—$C_{(2)}$	44
$C_{(3)}$—$N_{(4)}$	1,44	$C_{(7)}$—$N_{(1)}$—$C_{(2)}$	122	$N_{(4)}$—$C_{(5)}$—$C_{(51)}$—$C_{(52)}$	105
$C_{(3)}$—$O_{(3)}$	1,38	$C_{(2)}$—$N_{(1)}$—$C_{(12)}$	120	$N_{(1)}$—$C_{(2)}$—$C_{(3)}$—$N_{(4)}$	−76
$N_{(4)}$—$C_{(5)}$	1,25	$C_{(7)}$—$N_{(1)}$—$C_{(12)}$	117	$C_{(3)}$—$N_{(4)}$—$C_{(5)}$—$C_{(6)}$	−3
$C_{(5)}$—$C_{(6)}$	1,53	$N_{(1)}$—$C_{(2)}$—$C_{(3)}$	119	$C_{(5)}$—$C_{(6)}$—$C_{(7)}$—$N_{(2)}$	−5
$C_{(6)}$—$C_{(7)}$	1,395	$N_{(1)}$—$C_{(2)}$—$O_{(2)}$	120	$C_{(12)}$—$N_{(1)}$—$C_{(2)}$—$O_{(2)}$	−9
$C_{(7)}$—$N_{(1)}$	1,43	$O_{(2)}$—$C_{(2)}$—$C_{(3)}$	120		
$N_{(1)}$—$C_{(12)}$	1,47	$C_{(2)}$—$C_{(3)}$—$N_{(4)}$	106		
$C_{(12)}$—$C_{(13)}$	1,44	$C_{(2)}$—$C_{(3)}$—$O_{(3)}$	110		
$C_{(13)}$—$O_{(1)}$	1,37	$O_{(3)}$—$C_{(3)}$—$N_{(4)}$	110		
$C_{(13)}$—$O_{(4)}$	1,18	$C_{(3)}$—$N_{(4)}$—$C_{(5)}$	118		
$C_{(14)}$—$O_{(1)}$	1,51	$C_{(6)}$—$C_{(7)}$—$N_{(1)}$	121		
$C_{(5)}$—$C_{(51)}$	1,51	$N_{(1)}$—$C_{(12)}$—$C_{(13)}$	111		
(C—C) ar	1,395	$C_{(12)}$—$C_{(13)}$—$O_{(1)}$	110		
$C_{(2)}$—$O_{(2)}$	1,23	$C_{(12)}$—$C_{(13)}$—$O_{(4)}$	132		
		$O_{(1)}$—$C_{(13)}$—$O_{(4)}$	118		
		$C_{(13)}$—$O_{(1)}$—$C_{(14)}$	117		
		$C_{(5)}$—$C_{(51)}$—$C_{(52)}$	120		
		$C_{(5)}$—$C_{(51)}$—$C_{(56)}$	120		
		(C—C—C) ar	120		
		$N_{(4)}$—$C_{(5)}$—$C_{(6)}$	125		
		$N_{(4)}$—$C_{(5)}$—$C_{(51)}$	119		
		$C_{(6)}$—$C_{(5)}$—$C_{(51)}$	116		
		$C_{(5)}$—$C_{(6)}$—$C_{(7)}$	122		

*The errors in the bond length measurements are less than 0.01 Å for C–Br(–Cl), 0.02 Å for C–C(–N, –O), and the errors in the angle measurements are less than 1°.

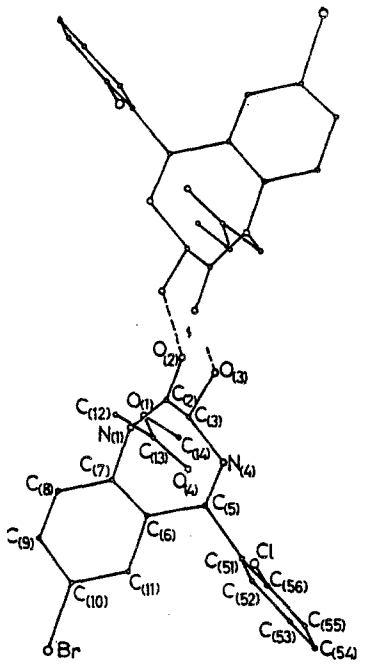

Fig. 1. Structural projection of compound (V) on the plane of the conjugated benzene ring.

Unexpectedly, however, it was found that upon treatment of compound (I) with two equivalents of base in aqueous methanol solution 3-hydroxy-1-methoxycarbonylmethyl-1,4-benzdiazepin-2-one (V) was isolated, namely, the product of transesterification of the ethyl ester (I), which was formed in weakly basic medium. The structure of (V) was verified by IR-spectroscopy, mass spectrometry, and by x-ray structural analysis (Table 1). It should be noted in this regard that during preparation of a single crystal of (V) from benzene auto-resolution occurred, resulting in the isolation of an optically active isomer.

As the amount of base is increased, both ester groups in benzdiazepine (I) are hydrolyzed, resulting in the formation of hydroxyacid (VIII). It is known that exposure of 3-hydroxy-1,2-dihydro-3H-1,4-benzdiazepin-2-ones to basic solution leads to 1,4-benzdiazepin-2,3-diones [4]. In order to confirm the structure of (VIII) we carried out an independent synthesis of this compound under conditions excluding treatment or exposure by base. In anhydrous trifluoroacetic acid at room temperature 1-tert-butoxycarbonylmethyl-3-hydroxy-1,4-benzdiazepin-2-one (IX) is converted to its corresponding carboxylic acid (VIII). 3-Acetoxy-7-bromo-1-tert-butoxycarbonylmethyl-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one (X) was synthesized from benzdiazepines (VI) and (VII) via alkylation with tert-butyl bromoacetate. The acetoxy group was introduced via treatment of compound (XI) with lead tetraacetate.

The principal difference between the structure of compound (V) studied herein and that of similar compounds examined previously [6–8] is the existence of the crystal in an acentric space group $P2_12_12_1$, which guarantees that only one enantiomer will be present in a single crystal. The crystal structure consists of molecules with the seven-membered ring heterocycle in a pseudotub conformation; the molecules are bound together in infinite chains via weak hydrogen bonds. A projection of a fragment of the structure on the plane of the condensed benzene ring is illustrated in Fig. 1. The bond distances, bond angles, and several important torsional angles are summarized in Table 2. The conformation of the even-membered ring heterocycle, as well as the bond distances and bond angles in the structure, are all normal for these types of compounds [6–8]. As in most structures of this type, the $N_{(1)}$–$C_{(2)}$ and $N_{(1)}$–$C_{(7)}$ bonds are shortened to 1.33 and 1.43 Å, due to resonance interaction between the phenyl group and the amide fragment. Also noteworthy is the contraction of the $C_{(2)}$–$C_{(3)}$ bond to 1.44 Å, compared to 1.500–1.536 Å [7, 8] in related structures. As was the case in the heterocycle described in [9], in compound (V) the angle at $C_{(2)}$ is expanded to 119° (the normal bond angle does not exceed 116°). The $N_{(4)}$–$C_{(5)}$ distance of 1.25 Å corresponds to an N=C double bond, while the $C_{(2)}$–$O_{(2)}$ and $C_{(13)}$–$O_{(4)}$ bond lengths of 1.23 and 1.18 Å represent double bonds in COO groups. The $C_{(3)}$–$O_{(3)}$ distance is 1.38 Å. The hydroxyl group is engaged in intermolecular OH...O hydrogen bonding ($O_{(3)}$...$O_{(1)}$* = 3.11 Å), which connects adjacent molecules in a spiral along the screw axis in the direction of the *a* axis (Fig. 1).

As has been noted on many previous occasions [9, 10], the presence of bulky substituents in the 1-position in the heterocycle reduces its pharmacological activity. In addition, introduction of a bulky substituent also leads to conformational realignment or rearrangement of the seven-membered ring nearer to $N_{(1)}$ [11]. The value of the asymmetric parameter ΔC_s [12], calculated using Eq. (1), is 4.4°.

$$\Delta C_s = \sqrt{\frac{(T_1+T_6)^2+(T_2+T_5)^2+(T_3+T_4)^2+T_7^2}{4}}, \quad (1)$$

where T_i are the torsional angles around the bonds in the heterocycles $C_{(7)}$–N, ..., $C_{(6)}$–$C_{(7)}$.

It should also be noted that in compounds containing a methyl group in the 1-position the value of this parameter is generally higher than in benzdiazepine (V). Thus, for diazepam the value of the asymmetric parameter is equal to 11.3° [6], although in the N-substituted diazepine described in [13] the value of this parameter is only 3.6°. It is possible that the conformational change can be attributed to competing effects of the two substituents in the heterocycle. The conformation resembles a true "tub" conformation most closely when a hydrogen atom is present in the 1-position. Two factors may explain this observation: participation of the hydrogen atom in intermolecular hydrogen bond formation or lifting of the steric strain in the molecule due to replacement of relatively bulky CH_3 groups by hydrogen.

The methoxycarbonylmethyl radical is planar, with a maximum deviation of O(4) from the plane of 0.04 Å, and is rotated at an angle of 67° relative to the conjugated ring. The phenyl rings form an angle of 84° between them. A distinguishing feature of this structure is the presence in the 3-position of a chiral center. Formation of crystalline racemates is typical of other 1,4-benzdiazepin-2-one and 1,5-benzdiazepin-2-one derivatives. The structures of this type of chiral compounds have not been examined previously.

EXPERIMENTAL

IR spectra were recorded on an IKS-29 spectrophotometer using chloroform solutions. Mass spectra were measured on a Varian MAT-112 spectrometer at an ionizing electron energy of 70 eV. The purity of compounds was monitored by TLC using Silufol plates and the following eluent solvent systems: benzene–acetone–acetic acid (100:50:1) (A); benzene–acetone–hexane–acetic acid (100:50:100:1) (B), and acetone–chloroform–hexane (1:1:1) (C).

The results of C, H, N, elemental analysis of compounds III, V, VIII–X, and XII agreed with their calculated values.

X-Ray Structural Analysis. A colorless single crystal of (V) was chosen; it had a lamellar crystal habit or appearance, and its linear dimensions were less than 0.7 mm. Its unit cell parameters and rhombohedral syngony were determined using a photographic method and were refined on an RED-4 automated diffractometer: a = 11.058(7), b = 13.532(6), c = 12.018(5) Å. The space group is $P2_12_12_1$, Z = 4 for an empirical composition $C_{18}H_{14}N_2O_4ClBr$, ρ (x-ray) = 1.616 g/cm^3.

The experimental intensities were measured using the RED-4 automated diffractometer with MoK_α irradiation ω-scanning method at a constant rate 8°/min, $\sin\theta/\lambda \le 0.6$ Å^{-1}. In all 615 nonzero reflections were measured $I(hkl) > 3\sigma(I)$. The small volume of experimental data is due to the small dimensions of the crystal and the sample's low scattering ability. In transforming the I(hk*l*) data to F(hk*l*) data the Lorentz polarization factor was taken into account, while absorption and extinction were not accounted for.

The structure was solved by the heavy atom method and refined by full-matrix least squares; the six-membered rings were refined as rigid groups having ideal geometry (C–C 1.395 Å, C–C–C angle 120°). The chlorine and bromine atoms were refined using anisotropic thermal approximations, the other atoms using isotropic thermal parameters. It was not possible to visualize the hydrogen atoms in the structure. The final R-factor was equal to 0.076 (R_w = 0.87, $w = (\sigma(F)^2 + 0.01|F|^2)^{-1}$). Call calculations were performed using the SHELXSM program on an SM-4 computer [5]. The final coordinates for the basis atoms in the structure are presented in Table 1.

7-Bromo-4-(o-chlorophenyl)-1-ethoxycarbonylmethyl-1,2-dihydro-3H-1,4-benzdiazepin-2-one-4-oxide (III, $C_{19}H_{16}BrClN_2O_4$). To a solution of 1 g (2.7 mmoles) II in 20 ml methanol was added 0.295 g (5.4 mmoles) sodium hydride; the reaction mixture was refluxed for 10 min, then 0.6 ml (5.4 mmoles) ethyl bromoacetate was added. The solution was refluxed for 2 h, cooled to 2°C, and 100 ml water and 50 ml chloroform were added. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated; the residue was washed with methanol to give 1 g (81%) compound III, mp 232–233°C. IR spectrum: 3050, 1735, 1670, 1610, 1390, 1270, 1190, 1085 cm^{-1}.

3-Acetoxy-7-bromo-5-(o-chlorophenyl)-1-ethoxycarbonylmethyl-1,2-dihydro-3H-1,4-benzdiazepin-2-one (Ia, $C_{20}H_{18}BrClN_2O_5$). Compound III (1 g, 2.2 mmoles) was refluxed in 10 ml acetic anhydride for 20 min. The reaction mixture was poured into 100 ml water, and the resulting precipitate was filtered, dried under vacuum, and dissolved in 10 ml ether. The resulting crystals were separated again and washed with ether. Yield 1 g (92%), mp 164–165°C. IR spectrum: 3040, 3015, 1740, 1685, 1600, 1460, 1400, 1225, 1175, 1100 cm^{-1}.

7-Bromo-3-hydroxy-5-(o-chlorophenyl)-1-ethoxycarbonylmethyl-1,2-dihydro-3H-1,4-benzdiazepin-2-one (IV, $C_{19}H_{16}BrClN_2O_4$). To a solution containing 930 mg (1.9 mmoles) I in 20 ml methanol was added a solution of 75 mg (1.9 mmoles) NaOH in 6 ml water. The reaction mixture was stirred 3 min, and 40 ml chloroform was added. The chloroform layer was separated, washed with water, dried over $MgSO_4$, and evaporated under vacuum. The residue was treated with 5 ml ether and the resulting solution was filtered. The filtrate yielded upon crystallization 660 mg (78%) of compound IV, mp 182–184°C, R_f 0.61 (C). IR spectrum: 3560, 3340, 3020, 1730, 1655, 1595, 1460, 1385, 1300, 1200, 1070, 990 cm^{-1}. Mass spectrum, m/z 451.

7-Bromo-3-hydroxy-1-methoxycarbonylmethyl-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one (V, $C_{18}H_{14}BrClN_2O_4$). To a solution of 1 g (2.0 mmoles) compound I in 20 ml methanol was added 160 mg (4.0 mmoles) NaOH in 10 ml water. The mixture was stirred 3 min, then 50 ml chloroform was added. The chloroform solution was washed with water, dried over $MgSO_4$, and evaporated under vacuum; the residue was crystallized from benzene. Yield 670 mg (76%) of compound V, mp 186-188°C $[\alpha]_{578}^{20} = -3.6°$ (c = 0.9, trifluoroethanol); $[\alpha]_D^{20} = +20°$ (c = 1, methanol), R_f 0.67 (C). IR spectrum: 3650, 3030, 1740, 1675, 1600, 1470, 1385, 1310, 1190, 1125 cm^{-1}. Mass spectrum, m/z 437.

7-Bromo-3-hydroxy-1-carboxymethyl-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one-(VIII, $C_{17}H_{12}BrClN_2O_4$). A. To a solution of 1 g (2 mmoles) compound I in 20 ml methanol was added 2.5 ml of 4 N NaOH solution. The reaction mixture was stirred for 3 min, 30 ml water was added, and the mixture was acidified to pH 3, then extracted with 30 ml chloroform. The chloroform solution was dried over $MgSO_4$, evaporated under vacuum, and the residue crystallized from ethanol-ether. Yield 0.5 g (58%) of compound VIII, mp 218-220°C (decomp.).

7-Bromo-1-tert-butyloxycarbonylmethyl-3-hydroxy-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one (IX, $C_{21}H_{20}BrClN_2O_4$). To a solution of 0.83 g (1.6 mmoles) compound X in 30 ml methanol was added 64 mg (1.6 mmoles) NaOH in 5 ml water. After 5 min 50 ml chloroform was added to the reaction mixture. The chloroform layer was washed with water, dried over $MgSO_4$, and evaporated under vacuum. Yield 0.7 g (92%) of compound IX, mp 215-217°C (decomp.). R_f 0.68 (A), 0.18 (B).

3-Acetoxycarbonyl-7-bromo-1-tert-butyloxycarbonylmethyl-5-(o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one (X, $C_{22}H_{22}BrClN_2O_5$). A. To a solution of 0.65 g (1.6 mmoles) compound VII in 5 ml DMF was added 45 mg (1.9 mmoles) NaH, and the mixture was stirred 30 min; 0.47 ml (3.2 mmoles) tert-butyl bromoacetate was then added and the mixture was stirred an additional 3 h. To the reaction mixture was then added 20 ml ethyl acetate and 30 ml water. The organic layer was washed with water, dried over $MgSO_4$, and evaporated under vacuum; the residue was treated with 10 ml hexane. Yield 0.57 g (69%) of compound X, mp 226-227°C, R_f 0.29 (B).

B. A solution of 0.95 g (2 mmoles) compound XI in 7 ml acetic acid was heated to 60°C and 0.45 g (3 mmoles) NaI was added; the mixture was stirred 15 min and 1.3 g (3 mmoles) lead tetraacetate was added. The reaction mixture was stirred 1 h at 60°C, cooled to 20°C, and 5 ml chloroform was added; after 15 min stirring the mixture was filtered and the precipitate was washed with 5 ml chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, evaporated under vacuum, and the residue was crystallized from ethanol. Yield 0.6 g (56%) of compound X, mp 226–227°C, R_f 0.29 (B).

5-Bromo-1-tert-butyloxycarbonylmethyl-5- (o-chlorophenyl)-1,2-dihydro-3H-1,4-benzdiazepin-2-one (XI, $C_{21}H_{20}BrClN_2O_3$). To a solution of 1 g (2.9 mmoles) compound VI in 10 ml DMF was added 82 mg (3.4 mmoles) NaH, and the mixture was stirred 30 min, then 0.75 ml (5.8 mmoles) tert-butyl bromoacetate was added. The reaction mixture was stirred an additional 2 h, then poured onto 50 g ice and extracted with 50 ml ethyl acetate. The organic solution was dried over $MgSO_4$, evaporated under vacuum, and the residue treated with 10 ml hexane. Yield 1.2 g (90%) of compound XI, mp 144–145°C, R_f 0.60 (A).

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SYNTHESIS OF MACROHETEROCYCLIC ANALOGS OF DIBENZOCROWN ETHERS.

5.* 16- AND 17-MEMBERED OXAAZACROWN ETHERS

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Macrocyclic diamides are synthesized by condensation of 1,5-bis(2-aminophenyl)-1,5-dioxapentane and 1,6-bis(2-aminophenyl)-1,6-dioxahexane with the dichlorides of glutaric, diglycolic, thiodiglycolic, and N-tosyliminodiacetic acids under high dilution conditions. Reduction with diborane gives the 16- and 17-membered dibenzodiazacrown ethers. The structure of the compounds synthesized is confirmed by IR, NMR (^1H and ^{13}C), and mass spectral data.

16- and 17-Membered crown ethers are very rare among known macroheterocyclic compounds [2]. 16- and 17-Membered macrocyclic compounds containing a variety of donor atoms (O, N, S, or a combination of these) are practically unknown. The synthesis of 16-membered crown lactams containing two nitrogens and four oxygens in various arrangements has been described [3].

16- and 17-Membered crown lactones containing two sulfurs and two oxygens were described in [4, 5]. Macrocyclic crown lactams with three different donors (S, O, and N) in the ring are known [5].

The number of azacrown ethers is even smaller. Only in [6, 7] is the synthesis of 16- and17-memberedoxaazacrown ethers with varying content of oxygens and nitrogens in the ring (2N–3O, 3N–3O, 4N–O) reported.

In an attempt to fill this gap and to continue the systematic search for highly selective macrocyclic compounds suitable for extraction of heavy and transition metals, we synthesized a series of 16- and 17-membered oxathiazacrown ethers in the 6,7;15,16-dibenzo-1,5-dioxa-8,14-diazacyclohexadecane and 7,8;16,17-dibenzo-1,6-dioxa-9,15-diazacycloheptadecane systems. These contained O, N, or S donor atoms in the 11 (n = 3) or 12 (n = 4) positions of the macroheterocycle (compounds IVa–h).

*For Communication 4, see [1].

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