SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 1-AMINO-2-PHENYLETHYL DERIVATIVES OF 1,5-BENZODIOXEPINE AND 1,6-BENZODIOXOCINE

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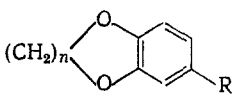
6-(Aminoalkyl)-1,4-benzodioxanes which contain a phenyl group in the side chain exhibit local anesthetic activity [2]. Therefore, in order to investigate new drugs we have synthesized and studied 1,5-benzodioxepine and 1,6-benzodioxocine compounds which are similar to them in structure.

7-(1-Amino-2-phenylethyl)-2H-3,4-dihydro-1,5-benzodioxepine (Id) is synthesized by the Leuckart reaction on heating 7-phenylacetyl-2H-3,4-dihydro-1,5-benzodioxepine (Ib) with formamide and formic acid followed by acid hydrolysis of the N-formyl derivative that is produced. 8-Phenylacetyl-2,3,4,5-tetrahydro-1,6-benzodioxocine (IIb) forms tar under these reaction conditions, but it was possible to obtain 8-(1-amino-2-phenylethyl)-2,3,4,5-tetrahydro-1,6-benzodioxocine (IId) by reduction of the respective ketoxime (IIc) with metallic sodium in butanol. Ketones Ib and IIb are synthesized by acylation of the corresponding benzodioxa heterocycles Ia and IIa with phenylacetyl chloride in the presence of anhydrous aluminum chloride



R = H (Ia, IIa), $COCH_2Ph$ (Ib, IIb), $C(=NOH)CH_2Ph$ (IIc) $CH(NH_2)CH_2Ph$ (Id), IId); $n = 3$ (Ia, b, d), 4 (IIa-d).

In the IR spectrum of ketone IIb the stretching vibrations from the carbonyl group appear at lower frequency and the absorption bands in the UV spectrum are displayed to longer wavelength in comparison with those in ketone Ib (Table 1). In the latter, as a result of the lesser conformational mobility of the seven-membered ring compared to the eight-membered ring, it is more difficult for the unshared electron pairs of heterocyclic oxygen atoms (electron-donor) to undergo conjugation with the aromatic ring and also with the carbonyl group (electron-acceptor) via it by rotation of the alkoxy substituents about the C_{Ar}–O bond [5].

The structures of the new compounds Ib, d, and IIb, d were confirmed by the PMR spectroscopy data (Table 2), while those of compounds Ia and IIa have been reported in [9].

It transpired that amine Id was essentially no different from its 1,4-benzodioxane and benzene analogs [2] with respect to its pharmacological characteristics. Amine Id was similar to trimecaine and lidocaine in acute toxicity and activity during infiltration anesthesia but irritated tissues to a greater extent and had a higher activity and duration of effect during conductor anesthesia. Compared to novocaine, amine Id was more toxic, produced a greater irritation of tissues, but exhibited a stronger and more prolonged local anesthetic action. Introduction of a further methylene group into the heterocyclic ring of amine Id leads to amine IId, which has lower acute toxicity, a higher local anesthetic activity, and produces a more marked local irritant effective (Table 3). Amine IId has similar activity to lidocaine during surface anesthesia while amine Id is almost inactive under these conditions.

EXPERIMENTAL CHEMICAL

UV spectra were recorded on a Specord UV-Vis instrument (GDR) in ethanol; IR spectra were recorded on a UR-20 instrument (GDR) in petrolatum oil; PMR spectra were recorded

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TABLE 1. Characteristics of Compounds Ib, d and IIb, d

Compound	Yield, %	mp, °C (solvent)	UV spectrum		IR spectrum	Empirical formula
			λ_{max}, nm	lg ε	$\nu_{C=O}$, cm^{-1}	
Ib	68	38—9 (ethanol)	225 272	4,19 3,95	1680	$C_{17}H_{16}O_3$
Id	53	231—2 (ethanol–acetone)*	226 280	4,23 3,52	—	$C_{17}H_{19}NO_2 \cdot HCl$
IIb	80		226 277	4,10 3,99	1665	$C_{18}H_{18}O_3$
IIc	81	101—2 (ethanol)	263	4,23	3225**	$C_{18}H_{19}NO_3$
IId	65	227—8 (ethanol–acetone)	277	3,38	—	$C_{18}H_{21}NO_2 \cdot HCl$

*bp 190-192°C (1 mm Hg).
**ν=N·OH·

TABLE 2. PMR Spectroscopy Data (δ, ppm) for Compounds Ib, d and IIb, d

Compound	NH_2	$(CH_2)_{n-2}$	CH_2Ar	CHAr	CH_2O	ArH
Ib	—	2,13 q*	4,06 s	—	4,14t* 4,23t*	6,71—7,53 m
Id**	1,40 s	2,05 q*	2,53—2,98 m	3,93 t*	4,03t*	6,65—7,28 m
IIb	—	1,56—1,97 m	4,01 s	—	4,11t* 4,41t*	6,69—7,59 m
IId**	1,11 s	1,50—2,26 m	2,55—3,05 m	3,81—4,38 m		6,55—7,33 m

*J = 5.0-5.5 Hz.
**Free base.

on a Tesla BS 487C instrument (Czechoslovakia) (80 MHz) in CCl_4 with tetramethylsilane as the internal standard.

The characteristics and yields of the new compounds are given in Tables 1 and 2. The experimental elemental analysis data corresponded to that calculated.

Ketones (Ib, IIb). Anhydrous $AlCl_3$ (7.5 g, 56 mmole) was added at 5-10°C to a mixture of 70 ml of anhydrous CH_2Cl_2, 8.5 g (55 mole) of phenylacetyl chloride, and 50 mmole of compound Ia or IIa. The mixture was agitated for 3 h at 20°C, poured onto ice, acidified with HCl, and the organic layer was separated, washed with water, and the solvent distilled off.

7-(1-Amino-2-phenylethyl)-2H-3,4-dihydro-1,5-benzodioxepine Hydrochloride (Id). A mixture of 10.7 g (40 mmole) of ketone Ib, 7.4 g (165 mmole) of formamide, and 4 ml (88 mmole) of 85% HCOOH was heated for 12 h at 180°C, cooled, and washed with water. The insoluble residue was boiled for 6 h with 70 ml concentrated HCl, diluted with water, made alkaline with KOH, extracted with benzene, the extract was dried, and the solvent distilled off. The hydrochloride was obtained by passing anhydrous gaseous HCl through a solution of the base in anhydrous ether.

Oxime (IIc). A solution of 14.1 g (50 mmole) of ketone IIb and 20.9 g (300 mmole) of $H_2NOH \cdot HCl$ in 70 ml of pyridine was heated for 8 h at 100°C, cooled, poured into water, extracted with ether, and the solvent was distilled off from the extract.

8-(1-Amino-2-phenylethyl)-2,3,4,5-tetrahydro-1,6-benzodioxocine Hydrochloride (IId). Small portions of metallic sodium (8.0 g, 350 mmole) were added to a solution of 11.9 g (40 mmole) of oxime IIc in 110 ml of n-butanol at the boiling point of the solvent, which was then cooled, acidified with HCl, and concentrated under vacuum. The residue was made alkaline with NaOH, extracted with benzene, and the solvent was distilled off from the dried extract. Hydrochloride IId was obtained in a similar manner to hydrochloride Id.

TABLE 3. Acute Toxicity, Local Anesthetic Activity, and Local Irritant Effect of Amine Id and IId Hydrochlorides

Compound	LD_{50}, mg/kg	Infiltration anesthesia		Conductor anesthesia			Local irritant effect		
		relative activity	ED_{50}, mg/kg	minimum effective concentration, mmole	half-life period, min	duration of motor paralysis from 0.25% solution,	degree of irritation from 1% solution	average tissue-irritant concentration, %	threshold tissue-irritant concentration, %
Id	290 (240—351)	2,0	20,0	3,0	31,0	44,7	1,3	2,0	0,3
IId	850 (691—1045)	5,5	7,0	1,9	31,1	63,0	2,4	0,7	0,1
Novocaine	570 (539—602)	1,0	25,0	7,1	9,3	5,0	0,0	6,6	1,8
Trimecaine	390 (372—410)	1,7	22,5	5,0	10,8	12,5	1,2	3,6	0,1
Lidocaine	270 (204—356)	1,9	16,2	7,4	16,4	10,8	0,3	6,9	0,7

Note. Limits of variation given in brackets; data is statistically reliable ($p \leq 0.05$).

EXPERIMENTAL PHARMACOLOGICAL

Amines Id and IId were studied as their hydrochlorides. The acute toxicity in white mice by subcutaneous administration of aqueous solutions was determined by the method of Litchfield and Wilcockson modified by Roth [1]. Infiltration anesthesia was studied on guinea pigs as in [4], surface anesthesia was determined on rabbit eye cornea as in [3], and conductor anesthesia was studied on white mice by recording motor paralysis [7]. Local irritant action was studied on white rats according to the method in [6] modified in [8]. Mongrel white mice of weight 18-25 g and white rats of weight 150-230 g of both sexes were used.

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