KETONES OF THE 1,4-BENZODIOXANE SERIES

VIII. Synthesis and Reduction to Amino Alcohols of 6-(α-Phenyl-α-Aminoacetyl)- and 6-(α-Phenyl-β-Aminopropionyl)-1,4-Benzodioxanes*

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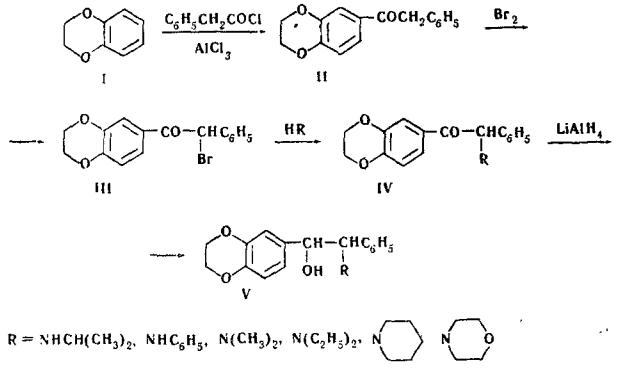
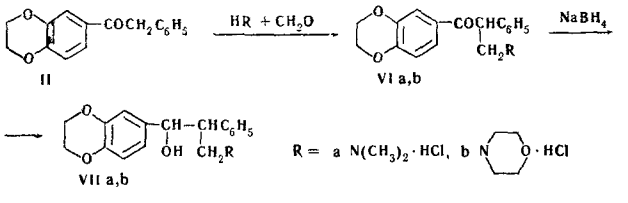
New amino ketones and amino alcohols of the 1,4-benzodioxane series, of pharmacological interest, are synthesized.

We previously [2] described 6-(α-aminoacetyl)- and 6-(β-aminopropionyl)-1,4-benzodioxane, which affect blood pressure. To ascertain how introduction of a phenyl radical at the α position in the side chains of these compounds affects their pharmacological properties, we synthesized 6-(α-phenyl-α-aminoacetyl)- (IV) and 6-(α-phenyl-β-aminopropinoyl)-1,4-benzodioxane (VI). Acylation of 1,4-benzodioxane I with phenylacetyl chloride gave 6-(α-phenylacetyl)-1,4-benzodioxane (II), which with bromine gave the α-bromo derivative III. Reaction of the latter with primary or secondary amines led to the synthesis of amino ketones IV, identified as their hydrochlorides and methylhalides.** Reduction of amino ketones IV with $LiAlH_4$ gave the amino alcohols V.



Amino ketones VI were synthesized by the action of hydrochlorides of secondary amines and paraform on ketone II. Reduction of amino ketones VI with $NaBH_4$ gave the corresponding aminoalcohols VII.



It is of interest to note that bromo ketone III readily reacted with all the amines submitted to reaction, giving amino ketones IV, while ketone II readily underwent the Mannich reaction only with the hydrochlorides of dimethylamine and morpholine, and was recovered when diethylamine hydrochloride was used, even when the reaction time was increased 5-fold.

A pharmacological study* of amino ketones IV and VI showed, that their reactivities did not differ substantially from those of their analogs [2] lacking a phenyl group at the α position. Amino alcohols V and VII have the same activity as the corresponding amino ketones (IV and VI).

EXPERIMENTAL

6-(α-Phenylacetyl)-1,4-benzodioxane (II). 240 g (1.8 mole) $AlCl_3$ was added to 408 g (3 mole) 1,4-benzodioxane (I) at 0–10°, and then 235 g (1.5 mole) phenylacetyl chloride added over a period of 2 hr. The mixture was stirred for 3 hr at 90–100°, cooled, the products poured onto ice, acidified with HCl, and extracted with dichloroethane. Distillation of the extract gave 170 g I and 342 g (89%) ketone II, bp 223–225° (0.15 mm); mp 97–98° (ex EtOH); λ_{max} 232, 280, 307 nm, (lg ε 3.90, 3.73, 3.78.** Found: C 75.86, 75.63; H 5.65, 5.71%, calculated for $C_{16}H_{14}O_3$: C 75.58; H 5.55%.

6-(α-Bromo-α-phenylacetyl)-1,4-benzodioxane (III). 25.4 g (0.1 mole) ketone II was dissolved in a mixture of 50 ml dioxane and 70 ml ether, 16 g (0.1 mole) bromine added, the mixture left for 3 hr, and the main part of the solvent then distilled off. III was precipitated by adding petrol ether, and was recrystallized from EtOH. Yield 27 g (81%), mp 96–97°; λ_{max} 234, 284, 310 nm (lg ε 4.15, 4.01, 3.88). Found: C 57.88, 57.81; H 4.11, 4.02%, calculated for $C_{16}H_{13}BrO_3$: C 57.58; H 3.93%.

6-(α-Phenyl-α-aminoacetyl)-1,4-benzodioxane (IV). (Table 1). 0.05 mole bromoketone III was dissolved in 200 ml benzene, 0.1 mole of the appropriate secondary amine added, or 0.2 mole isopropylamine, and the mixture left for 50 hr. The precipitate of starting amine hydrobromide was filtered off, the filtrate washed with dilute HCl, the acid layer made alkaline with K_2CO_3, and then extracted with benzene. The aminoketones IV were isolated by distilling the extract. The phenylamino derivative (IV, R = NHC_6H_5) was synthesized by adding 5.6 g (0.06 mole) aniline to 6.7 g (0.02 mole) compound III in 100 ml EtOH heated to 60°, and then cooling to 10°. The hydrochlorides were obtained by passing dry HCl gas into benzene–ether solutions of the bases IV; the alkyl halides by adding 0.02 mole MeBr or MeI to a benzene solution of 0.01 mole amino ketone IV; the quaternary bro-

* For Part VII see [1].

** Reaction of the bromoketone III with tertiary amines (pyridine and tetramethylhexamethylenediamine) gives quarternary bromides [IV, R = NC_5H_5, $(CH_3)_2N(CH_2)_6N(CH_3)_2$], analogous to the alkyl halides of amino ketones IV.

*Carried out in the Dept. of Pharmacology of Vil'nyus State University, under the supervision of Associate Prof. G. Polukordas.

**All UV spectra were observed with an SF-4 spectrophotometer and in EtOH solution.

Table 1

6-(α-Phenyl-α-Aminoacetyl)-1,4-Benzodioxane (IV)

R		Mp, °C (solvent for crystallizing)	UV spectrum		Formula	Found, %		Calculated, %		Yield, %
			λ_{max}, nm	lg ε		Cl	N	Cl	N	
$NHCH(CH_3)_2$	Hydrochloride	158—159 (Acetone)	283, 318	4.07, 3.93	$C_{19}H_{21}NO_3 \cdot HCl$	10.15, 10.23	4.21, 4.14	10.19	4.02	69
NHC_6H_5	Base	158.5—159.5 (EtOH)	238, 280, 303	4.32, 4.05, 3.90	$C_{22}H_{19}NO_3$	—	4.18, 4.33	—	4.06	91
	Hydrochloride	161.5—162 (EtOH)	—	—	$C_{22}H_{19}NO_3 \cdot HCl$	9.50, 9.52	3.93, 3.75	9.28	3.67	—
	Base	Bp 218—220 (0.5 mm)	—	—	$C_{18}H_{19}NO_3$	—	4.74, 4.79	—	4.71	66
$N(CH_3)_2$	Hydrochloride	235—237 (Acetone)	234, 282, 315	4.15, 3.98, 3.86	$C_{18}H_{19}NO_3 \cdot HCl$	10.48, 10.35	3.96, 4.10	10.62	4.19	—
	Methobromide	155—156 (EtOH–ether)	237, 293, 323	4.12, 4.01, 3.92	$C_{18}H_{19}NO_3 \cdot CH_3Br$	—	3.49, 3.55	—	3.66	—
$N(C_2H_5)_2$	Base	Bp 215—217 (0.3 mm) n_D^{20} 1.5890	233, 281, 309	4.19, 3.97, 3.84	$C_{20}H_{23}NO_3$	—	4.28, 4.08	—	4.31	80
	Hydrochloride	225—226 (methylethyl ketone)	—	—	$C_{20}H_{23}NO_3 \cdot HCl$	9.81, 9.94	3.93, 3.99	9.79	3.87	—
	Base	98—99,5 (Heptane)	233, 281, 310	4.30, 4.12, 3.97	$C_{21}H_{23}NO_3$	—	4.28, 4.31	—	4.15	87
	Hydrochloride	238—239 (PrOH)	—	—	$C_{21}H_{23}NO_3 \cdot HCl$	9.68, 9.74	3.80, 3.66	9.48	3.75	—
	Methiodide	137—139 ($CHCl_3$–ether)	292, 324	4.01, 3.91	$C_{21}H_{23}NO_3 \cdot CH_3I$	—	2.73, 2.66	—	2.92	—
	Base	124—125 (Heptane)	234, 281 310	4.26, 4.08, 3.93	$C_{20}H_{21}NO_4$	—	4.35, 4.37	—	4.12	90
	Hydrochloride	223—225 (PrOH)	—	—	$C_{20}H_{21}NO_4 \cdot HCl$	9.25, 9.36	3.91, 3.94	9.43	3.72	—
	Methiodide	140—142 ($CHCl_3$–ether)	292, 323	4.01, 3.93	$C_{20}H_{21}NO_4 \cdot CH_3I$	—	2.72, 2.85	—	2.91	—
	Bromide	162.5—163.5 (Acetone)	238, 289, 318	4.40, 4.25, 1.11	$C_{21}H_{18}NO_3 \cdot Br$	—	3.55, 3.61	—	3.39	75
$(CH_3)_2N(CH_2)_6N(CH_3)_2$	Dibromide	162—163.5 (Dioxane)	238, 291, 325	4.42, 4.31, 4.23	$C_{42}H_{50}N_2O_6 \cdot 2Br$	—	3.32, 3.25	—	3.34	85

* Bp 238—240° C (0.3 mm).
** Bp 244—246° C (0.3 mm).

Table 2

Hydrochlorides of 6-(β-Phenyl-β-amino-α-hydroxyethyl)-1,4-Benzodioxane (V)

R	Mp, °C (solvent for crystallizing)	UV spectrum		Formula	Found, %		Yield, %		Calculated, %
		λ_{max}, nm	lg ε		Cl	N	Cl	N	
$NHCH(CH_3)_2$	220—221 (EtOH–ether)	282	3.44	$C_{19}H_{23}NO_3 \cdot HCl$	10.12 10.15	4.26 4.11	10 13	4.00	78
NHC_6H_5	162—164 (EtOH–ether)	243 283	3.83 3.65	$C_{23}H_{21}NO_3 \cdot HCl$	9.16 9.18	3.35 3.47	9.23	3.65	84
$N(CH_3)_2$	225—226 (EtOH–ether)	282	3.17	$C_{18}H_{21}NO_3 \cdot HCl$	10.65 10.79	4.35 4.28	10.55	4.17	89
$N(C_2H_5)_2$	208—209 (BuOH)	284	3.45	$C_{20}H_{25}NO_3 \cdot HCl$	9.80 9.94	4.00 3.99	9.74	3.85	87
	228—229 ($CHCl_3$)	282	3.61	$C_{21}H_{25}NO_3 \cdot HCl$	9.55 9.38	3.55 3.65	9.43	3.73	89
	222—223 (EtOH)	282	3.38	$C_{20}H_{23}NO_4 \cdot HCl$	9.42 9.60	3.48 3.47	9.38	3.71	85

mides by adding 0.02 mole pyridine or correspondingly 0.005 mole tetramethylhexamethylenediamine to a benzene solution of 0.01 mole bromo ketone III.

Hydrochlorides of 6-(β-phenyl-β-amino-α-hydroxyethyl)-1,4-benzodioxanes (V) (Table 2). A benzene solution of 0.02 mole amino ketone IV was added to an ethereal suspension of 0.02 mole $LiAlH_4$, the mixture refluxed for 2 hr, AcOEt added, the mixture poured onto ice, and a solution of potassium sodium tartrate added. The organic layer was separated off, and the aqueous layer was extracted with benzene. Passing HCl gas into the washed water, and drying the combined extracts gave the hydrochlorides of the amino alcohols V.

Hydrochlorides of 6-(α-phenyl-β-aminopropionyl)-1,4-benzodioxane (VI). 0.02 mole of the Ketone II and 0.025 mole of the appropriate secondary amine hydrochloride were dissolved together in 20 ml EtOH, and 0.03 mole paraform. 2–3 drops HCl was added, and the whole heated on a water bath for 10 hr. The precipitate of VI hydrochloride which came down on cooling the reaction products, was purified by recrystallizing.

Compound **VIa** [$R = N(CH_3)_2 \cdot HCl$]. Yield 80%, mp 184.5–185.5° (ex EtOH); λ_{max} 281, 311 nm lg ε 4.04, 3.87). Found: Cl 10.05, 10.16; N 4.16; 4.31%, calculated for $C_{19}H_{21}NO_3 \cdot HCl$: Cl 10.19; N 4.03%. Compound **VIb** ($R = N(\square)O \cdot HCl$). Yield 35%, mp 173–175° (ex PrOH); λ_{max} 280, 309 nm (lg ε 3.95, 3.78). Found: Cl 9.11, 9.18; N 3.84; 3.65%, calculated for $C_{21}H_{23}NO_4 \cdot HCl$: Cl 9.09; N 3.59%.

Hydrochlorides of 6-(β-phenyl-γ-amino-α-hydroxypropyl)-1,4-benzodioxanes (VII). 0.015 mole Amino ketone VI hydrochloride was dissolved in 50 ml EtOH, 0.03 mole $NaBH_4$ added, the mixture refluxed for 3 hr, then acidified with HCl, the EtOH distilled off, and the residue made alkaline with KOH. The mixture was extracted with benzene. Passing HCl gas into the extract, after washing with water and drying, gave the hydrochlorides of amino alcohols VII. Compound **VIIa** [$R = N(CH_3)_2 \cdot HCl$]. Yield 68%, mp 206–207° (ex dichloroethane); λ_{max} 282 nm (lg ε 3.41). Found: Cl 10.10, 10.17; N 4.11, 4.22%, calculated for $C_{19}H_{23}NO_3 \cdot HCl$: Cl 10.13; N 4.00%. Compound **VIIb** ($R = N(\square)O \cdot HCl$). Yield 64%, mp 227.5–228.5° (ex EtOH). λ_{max} 283 nm (lg ε 3.45). Found: Cl 9.15, 9.22; N 3.76, 3.69%, calculated for $C_{21}H_{25}NO_4 \cdot HCl$: Cl 9.04; N 3.57%.

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