

Synthesis and Antitremorine Activity of Amino Ketals

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Amino ketal derivatives of benzoin and α -hydroxycyclohexyl phenylketone were prepared for evaluation of central anticholinergic and anti-Parkinsonian activity. Selected members of the series exhibited antitremorine potency with low orders of peripheral anticholinergic activity. The most potent tremorine antagonist was tested against oxotremorine, an active metabolite of tremorine, and found to be inactive. It is concluded that the compounds probably act by preventing the *in vivo* conversion of tremorine to oxotremorine rather than by a central anticholinergic mechanism.

AGENTS PRESENTLY available for the symptomatic treatment of Parkinsonism have a restricted scope because of a low order of therapeutic efficacy and a high incidence of undesirable side effects. While many of these drugs exhibit local anesthetic and antihistaminic activity, the mutual pharmacologic action which the majority share is parasympatholytic, the peripheral manifestations of which are responsible for the emergence of a variety of unpleasant side effects. Several investigators have attempted to correlate anti-Parkinsonian efficacy with central anticholinergic activity and reduced peripheral anticholinergic potency (1). The search for compounds with selective central anticholinergic activity prompted the preparation of a number of amino ketals structurally analogous to orphenadrine, procyclidine, and diphenhydramine with a modified "esteratic" function.

While no reliable method for screening compounds for potential anti-Parkinson activity exists at the present time, a procedure that utilizes tremorine (2) as the tremorogenic agent appears to be a satisfactory technique. Tremorine (1,4-dipyrrolidino-2-butyne) elicits tremor and peripheral parasympathomimetic effects similar to those seen in Parkinsonism (3). In addition, the compound produces hypothermia and analgesia (4). Tremorine is converted *in vivo* to oxotremorine [1-pyrrolidino-4-(2-oxopyrrolidino)-butyne-2], an active metabolite which produces the characteristic effects (5). Whereas the pe-

ripheral autonomic effects appear to be due to stimulation of muscarinic receptors and autonomic ganglia (6), the tremorogenic action seems to be of central origin (7).

CHEMISTRY

The amino ketals of type III (Table I) were prepared in two steps by treatment of the epoxyether (I) (8) with dry freshly distilled ethylene chlorohydrin, followed by treatment of the resulting chloro ketal (II) with appropriate secondary amines. Application of the same method to the epoxyether (IV) (9) yielded type VI amino ketals (Table I). Although it seemed possible to obtain the amino ketals directly by the reaction of the appropriate amino alcohol with the epoxyethers, this method was not examined in detail because interest was centered on certain aspects of the reaction of epoxyethers with ethylene chlorohydrin (10). A one-step synthesis of IIIb subsequently was accomplished (11). The reactions of the epoxyethers (I, IV) with ethylene chlorohydrin were rapid, and yields of the corresponding chloro ketals (II, V) were high. The structures of the latter compounds were confirmed by NMR and infrared spectroscopic data (Table II) as well as by hydrolysis studies. Reaction of ethylene chlorohydrin with the presumably *D,L-trans* epoxyether (IV) (12) appears to proceed in one steric sense, as the presence of more than one diastereoisomer of the chloro ketal (V) could not be detected by column chromatography. The chloro ketal (V) exists in two polymorphic forms. Crystallization of the lower melting form under certain conditions yielded a higher melting material. The two forms had identical infrared and NMR spectra and yielded benzoin upon hydrolysis. Spontaneous decomposition of unprotected samples of the chloro ketal (V) yielded benzoin, benzil, and the dioxane dimer (VII) (13). The structure of the anhydro dimer (VII) was substantiated by infrared and NMR spectroscopic data (Table II).

Solvolysis of the chloro ketal (II) with dry methanol yielded the dimethyl ketal (VIII) (8). Treatment of the chloro ketal (II) with a secondary amine resulted partially in cyclization through elimination of HCl to yield the spirodioxane (IX). The latter was isolated from the mother liquors obtained during recrystallization of the amino ketal (IIIb). Infrared and NMR data (Table II) were in agreement with (IX).

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






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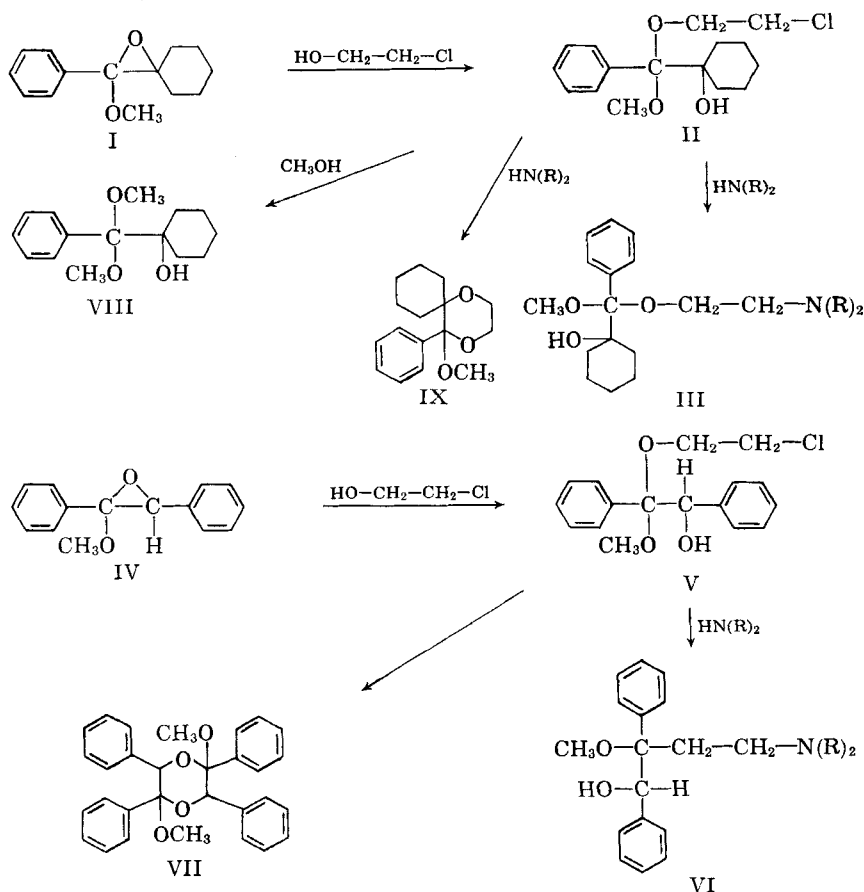
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TABLE I.—AMINO KETAL DERIVATIVES OF α -HYDROXYCYCLOHEXYL PHENYL KETONE AND α -HYDROXYBENZYL PHENYL KETONE

Compd.	-N(R) ₂	Reaction Conditions <i>t</i> (Hr.) <i>T</i> (°C.)		M. p., °C.	Yield, %	Formula	Anal., %					
							C		H		N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
IIIa		120	25	82.5–84.5 ^a 133–135 ^b	78 ..	C ₁₈ H ₂₃ NO ₃ C ₂₀ H ₃₁ NO ₇ ^h	70.32	70.11	9.51	9.49	4.56	4.66
							60.44	59.97	7.86	8.02	3.52	3.27
IIIb		3	89	119.5–120 ^c 171–172d ^d	68 ..	C ₂₀ H ₃₁ NO ₃ C ₂₀ H ₃₂ ClNO ₃ ⁱ	72.04	72.00	9.37	9.47	4.20	4.19
							64.94	64.66	8.72	8.53	3.78	3.89
IIIc		2	106	83–84d ^a 177–178 ^c	67 ..	C ₂₁ H ₃₃ NO ₃ C ₂₃ H ₃₅ NO ₇ ^h	72.58	72.53	9.57	9.73	4.03	3.96
							63.14	62.83	8.06	8.17	3.20	3.01
IIId		6	129	139–140d ^c 161–162d ^d	57 ..	C ₂₀ H ₃₁ NO ₄ C ₂₂ H ₃₃ NO ₈ ^h	68.74	68.52	8.94	8.86	4.01	3.99
							60.12	59.67	7.57	7.79	3.19	2.88
VIa		160	25	113–114 ^e	70	C ₁₉ H ₂₅ NO ₃	72.35	72.48	7.99	8.04	4.44	4.61
VIb		4	89	100–101.5 ^e 173–174d ^f	81 ..	C ₂₁ H ₂₇ NO ₃ C ₂₁ H ₂₈ ClNO ₃ ⁱ	73.87	73.83	7.97	8.15	4.10	4.03
							66.74	65.78	7.47	7.22	3.71	3.51
VIc		1	106	135–137d ^g	..	C ₂₄ H ₃₁ NO ₇ ^h	64.70	64.32	7.01	7.12	3.14	3.14

Recrystallization solvents: ^a petroleum ether, ^b dioxane–tetrahydrofuran (1:1), ^c 95% ethanol, ^d dioxane, ^e hexane, ^f *n*-propanol, ^g benzene–dioxane (3:1). ^h Oxalate. ⁱ Hydrochloride.



The structures of the amino ketals (types III and VI) were confirmed by NMR and infrared spectroscopic data (Table II) and by hydrolysis studies. While it has been shown that certain ketals are stabilized by the presence of a nitrogen function (14),

it seemed unlikely that amino ketals of the present type would be very resistant to acid hydrolysis. Preliminary studies indicated that the compounds were fairly stable as hydrochloride or oxalate salts in aqueous solutions. Subsequent studies showed

TABLE II.—PROTON NMR AND INFRARED SPECTROSCOPIC DATA

Compd.	Phenyl multiplet	Benzyl	Hydroxyl ^b	Alkoxyethylene multiplet	δ P.P.M. (Relative Peak Area)	Methoxyl	Aminomethylene multiplet	Methylene	Chloroethoxy multiplet	OH	C—O—C	Phenyl
II ^c	7.3(5)	...	2.13(1)	...	3.38(3)	3.38(3)	...	0.6-2.0(10)	3.5-4.4(4)	2.8	8.97 9.3; 9.35	13.2; 14.1
III ^a	3.15	9.52; 9.50	13.2; 14.05
IIIb ^d	7.3(5)	...	3.65(1)	3.5-4.4(2)	3.38(3)	3.38(3)	2.61, 2.86(6)	0.5-2.0(14)	...	3.15	9.51	13.2; 14.2
IIIc	3.10	8.95	13.25; 14.25
IIId	3.10	8.95	13.2; 13.95
V ^e	6.95(10)	4.91(1)	2.56(1)	...	3.20(3)	3.20(3)	3.4-4.2(4)	2.80	9.50	14.2
VI ^a	2.80	8.95; 9.3	12.7; 13.9
VIb ^d	7.1(10)	5.03(1)	6.8(1)	3.2-4.5(2)	3.19(3)	3.19(3)	2.7(6)	1.8(4)	...	3.30	8.93	12.7; 14.5
VII ^c	7.2(20)	4.90(2)	^e	...	3.08(6)	3.08(6)	3.28	8.95	12.7; 14.5
IX ^c	7.2(5)	...	^e	3.1-4.1(4)	2.97(3)	2.97(3)	...	0.5-2.5(10)	9.25	13.2; 14.1
										...	9.1	14.4
										...	9.44; 9.95	13.2; 14.2

^a All compounds had prominent bands at 3.4 and 6.9 μ . ^b Value dependent upon concentration; peak disappeared on treatment with D₂O. ^c Carbon tetrachloride. ^d Deuteriochloroform. ^e Treat ment with D₂O did not alter the spectrum.

TABLE III.—STABILITY OF 1-[α -METHOXY- α -(β -PYRROLIDINOETHOXY)-BENZYL]-CYCLOHEXANOL HYDROCHLORIDE (IIIb)^{a,b}

	0 Days (Immediate)	% Remaining After 1 Day	2 Days	5 Days
1 N Hydrochloric acid	0	0
0.1 N Hydrochloric acid	6	0
Phosphate buffer, pH 4.4	99.6	78	58	23
Phosphate buffer, pH 7	99.7	99.3	...	98.7
Water, pH 6.8	100	100	...	99.7

^a See Reference 11. ^b Aqueous solutions were stored in the dark at room temperature. Extent of decomposition was determined by the per cent change between initial low and final high ultraviolet absorption at 247 m μ .

only 1% hydrolysis of IIIb in 5 days at pH 7, but rapid hydrolysis at lower pH values (11) (Table III). Unlike the chloro ketal (II), the amino ketal (IIIb) was resistant to methanol solvolysis.

PHARMACOLOGY

Compounds IIIa (oxalate) and IIIb (hydrochloride) were studied in dogs anesthetized with 30 mg./Kg. (i.v.) of pentobarbital. Intravenous injection of IIIa and IIIb (20-30 mg./Kg. and 1-10 mg./Kg., respectively) produced a slight to marked transient fall in blood pressure. Pretreatment of anesthetized dogs with 10 mg./Kg. of IIIb or 20 mg./Kg. of IIIa did not alter the blood pressure responses to carotid occlusion or to effective doses of epinephrine, acetylcholine, or histamine. In contrast, 1 mg./Kg. of atropine sulfate reversed the blood pressure response to acetylcholine (50 mcg./Kg.). Both IIIa and IIIb were effective in inhibiting the blood pressure and electrocardiographic responses to electrical stimulation of the peripheral end of the cut vagus. This action persisted for several minutes. Acute toxicities were measured in male albino mice, in which toxic doses produced convulsions. Estimated LD₅₀ values were for IIIa, 250 mg./Kg. and for IIIb, 100 mg./Kg. The antitremorine potency of IIIb (ED₅₀ 5 mg./Kg.) was determined in mice according to the technique described by deJonge *et al.* (15). The ED₅₀ for atropine measured by this method is 2.5 mg./Kg. The activity of IIIb as an antagonist to oxotremorine was examined in male albino mice. Twenty minutes after an injection of IIIb i.p., the animals were given oxotremorine (125 and 250 mcg./Kg. i.p. or s.c.) and examined for tremor and other typical effects. Doses of IIIb as high as 100 mg./Kg. were ineffective in preventing the tremor induced by oxotremorine.

The following pharmacological studies were carried out at the Parke-Davis Research Laboratories (11). Tested by Haffner's method for analgesia in mice (4), the antitremorine ED₅₀ for VIb (hydrochloride) was 17.5 mg./Kg. i.p. and for IIIb was 2.5 mg./Kg. By this test method the ED₅₀ for atropine is 2.15 mg./Kg. Further antitremorine tests showed that IIIb was active perorally in mice. Compound VIb was 1/250 and IIIb was 1/500 as active as atropine in producing mydriasis in mice. Compound IIIb had practically no antihistaminic effect on the isolated guinea pig ileum and showed no antagonism of pentylenetetrazol convulsions in mice up to a dose of 100 mg./Kg. Compound IIIb (5 mg./Kg. i.m.) had no activity against tremors in monkeys produced by phenothiazine type drugs.

DISCUSSION

The initial hypotensive effect of IIIb and its ability to block the effects of vagal stimulation in dogs suggest that the compound possesses ganglion blocking activity. The relatively potent tremorine antagonism exhibited by IIIb together with its inability to block the actions of oxotremorine, the active metabolite of tremorine, suggest that IIIb prevents the *in vivo* conversion of tremorine to oxotremorine.

Since the original description of the tremorogenic and other Parkinson-like effects of tremorine, it has been used widely as a screening agent for potential anti-Parkinson type compounds. The selective blockade of the peripheral autonomic effects by quaternary anticholinergic agents suggests that the central and peripheral actions are distinct. The results of a number of studies have been interpreted as indicative of selectively central anticholinergic activity or anti-Parkinson efficacy by tremorine antagonists (16). Because the peripheral and probably the central effects of tremorine can be ascribed to the intense muscarinic activity of oxotremorine formed *in vivo*, it is possible that tremorine antagonism is associated with parasympatholytic activity. However, as indicated in the present study, it is also possible that the antagonists merely prevent the biotransformation of tremorine and possess little or no central anticholinergic or anti-Parkinson properties. Hence, the use of oxotremorine rather than tremorine as a screening agent is advisable.

EXPERIMENTAL¹

1 - [α -Methoxy- α -(β -chloroethoxy)-benzyl]-cyclohexanol (II).—To 2.18 Gm. (0.01 mole) of 2-phenyl-2-methoxy-1-oxaspiro(2.5)octane (I) (8) dissolved in 10 ml. of petroleum ether was added 0.81 Gm. (0.01 mole) of freshly distilled ethylene chlorohydrin, and the mixture was magnetically stirred for 20 minutes. After chilling, the crystalline material was filtered and washed with petroleum ether. The crude product (2.5 Gm., 83%, m.p. 108–110°) was recrystallized from ethyl acetate, m.p. 114–115°.

Anal.—Calcd. for $C_{18}H_{23}ClO_3$: C, 64.31; H, 7.76; Cl, 11.87. Found: C, 64.19; H, 7.51; Cl, 11.72.

Hydrolysis of 1-[α -Methoxy- α -(β -chloroethoxy)-benzyl]-cyclohexanol (II).—A solution of 3.0 Gm. (0.01 mole) of the chloro ketal (II) in 60 ml. of methanol was refluxed for 5 hours with no attempt to exclude moisture. The solvent was removed by air-current evaporation leaving an oil which crystallized upon chilling. After recrystallization from petroleum ether, the crude yield of α -hydroxycyclohexyl phenyl ketone was 1.8 Gm. (88%), m.p. 46–48° [lit. (8) m.p. 48–49°]. A mixed melting point with authentic α -hydroxycyclohexyl phenyl ketone, prepared by hydrolysis of α -bromocyclohexyl phenyl ketone, was not depressed. The infrared spectrum was identical to that of the authentic hydroxy ketone.

1,2-Diphenyl-2-methoxy-2-(β -chloroethoxy)-ethanol (V).—To 5.4 Gm. (0.024 mole) of

1,2-diphenyl-1-methoxyethylene oxide (IV) (9) in 50 ml. of dry petroleum ether was added 1.93 Gm. (0.024 mole) of freshly distilled ethylene chlorohydrin. The mixture was stirred magnetically for 15 minutes. After chilling, the crystalline material was filtered and washed with petroleum ether. The crude product (7.0 Gm., 95%, m.p. 112–115°) was recrystallized from benzene-petroleum ether (1:1), m.p. 119–120°.

Anal.—Calcd. for $C_{17}H_{19}ClO_3$: C, 66.55; H, 6.24; Cl, 11.56; OCH_3 , 10.12; mol. wt., 307. Found: C, 66.64; H, 6.20; Cl, 11.28; OCH_3 , 12.70; mol. wt., 296, 302.

Column chromatography of the recrystallization mother liquors (neutral alumina) afforded additional crystalline material (V), melting at 119–122° (undepressed upon admixture with the previous sample), and a small amount of amorphous material.

Refluxing the chloro ketal (V) (m.p. 118–120°) for 4.5 hours in tetrahydrofuran containing an equimolar amount of piperidine yielded the chloro ketal, m.p. 129–131°, after recrystallization from benzene-hexane (1:1). Infrared and NMR spectra of the two forms were identical.

Hydrolysis of the Low and High Melting Forms of 1,2-Diphenyl-2-methoxy-2-(β -chloroethoxy)-ethanol (V).—The low melting chloro ketal (V) (0.92 Gm., 0.003 mole, m.p. 118–120°) was dissolved in 20 ml. of 95% ethanol, to which was added 3 ml. of concentrated hydrochloric acid. After standing at room temperature for 3.5 days, the solvent was evaporated on a steam cone. The residue was recrystallized from 95% ethanol. The yield of benzoïn was 450 mg. (70%), m.p. 132–134°, undepressed upon admixture with an authentic sample.

A solution of the high melting chloro ketal (V) (0.92 Gm., 0.003 mole, m.p. 129–131°) and 2 ml. of concentrated hydrochloric acid in 20 ml. of dioxane-water (3:1) was refluxed for 2 hours. Evaporation on a steam cone produced a solid residue which, after recrystallization from 95% ethanol, yielded 480 mg. (75%) of benzoïn, m.p. 133–135°, undepressed upon admixture with an authentic sample.

Spontaneous Decomposition of 1,2-Diphenyl-2-methoxy-2-(β -chloroethoxy)-ethanol (V).—A 7.0-Gm. sample of the chloro ketal (V), m.p. 118–120°, was stored in a green glass screw-capped bottle without special precautions against contamination by moisture. After 4 months at room temperature, the sample exhibited a sweet aromatic odor and had partially liquified. The liquid and solid portions were separated by centrifugation and the solid portion washed with ether. The ether wash was combined with the liquid portion, and the resulting solution was filtered and evaporated to a yellow oil which partially crystallized. From this partly crystalline material was obtained 0.5 Gm. of benzil, m.p. 95–96°, after recrystallization from 95% ethanol, undepressed upon admixture with an authentic sample.

The ether-washed solid portion (1.5 Gm.) of the decomposition mixture was recrystallized from pyridine, yielding 0.6 Gm. of crude high melting material, m.p. 255–270°. Recrystallization several times from benzene gave 0.2 Gm. of material, m.p. 293–295°. Evaporation of the pyridine mother liquors afforded 0.7 Gm. of low melting material. Recrystallization from 95% ethanol gave 0.3 Gm. of benzoïn, m.p. 133–135°, undepressed upon admixture with an authentic sample.

A sample of the original ether-washed solid was

¹ Analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Melting points were determined on a Thomas-Hoover apparatus. Infrared spectra were obtained on a Perkin-Elmer model 21 spectrophotometer. NMR spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as internal reference and carbon tetrachloride as solvent, except where noted otherwise. The instrument was made available through funds from the National Science Foundation grant NSF-G21268. Values of chemical shifts, δ , are reported in parts per million downfield from the TMS peak taken as zero.

subjected to thin-layer chromatography (silica gel G, benzene). Two spots were obtained indicating two discrete components with R_f values of 0.28 and 0.88. Samples of benzoin and the high melting component obtained above (m.p. 293–295°) were chromatographed as a mixture. The prepared mixture gave two spots with R_f values of 0.26 and 0.88 in agreement with the values obtained for the solid component of the decomposition mixture.

The infrared spectrum of the component melting at 293–295° displayed prominent bands at 8.75 and 9.75 μ (C=O). No bands corresponding to hydroxyl carbonyl, or alkene moieties were present. The NMR spectrum indicated that the decomposition product, melting at 293–295°, was 2,3,5,6-tetraphenyl-2,5-dimethoxy-1,4-dioxane (VII) (Table II), the reported melting point of which is 285° and 296° (13).

Solvolysis (Transketalation) of 1-[α -Methoxy- α -(β -chloroethoxy)-benzyl]-cyclohexanol (II).—A solution of the chloro ketal (II) (2.99 Gm., 0.01 mole) in 60 ml. of dry methanol was refluxed for 5 hours. The solvent was evaporated under reduced pressure, yielding an oil which partially crystallized. The crystals were washed with cold methanol and amounted to 1.1 Gm. (44%) of the dimethyl ketal (VIII), m.p. 101–102° [lit. (8), 100–101°], undepressed upon admixture with authentic dimethyl ketal prepared from the epoxyether (I). From the oil was obtained 500 mg. (25%) of α -hydroxycyclohexyl phenyl ketone, m.p. 44–47°, undepressed upon admixture with an authentic sample.

5-Phenyl-5-methoxy-1,4-dioxaspiro(5.5)undecane (IX).—From the recrystallization mother liquors of the amino ketal (IIIb) was obtained a crystalline solid, melting at 95–95.5° after recrystallization from 95% ethanol. The infrared spectrum exhibited no bands corresponding to hydroxyl, carbonyl, or olefinic groups (Table II).

Anal.—Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; mol. wt., 262. Found: C, 73.33; H, 8.34; mol. wt., 262.

Preparation of Amino Ketals; 1-[α -Methoxy- α -(β -piperidinoethoxy)-benzyl]-cyclohexanol (IIIc).—The following is illustrative of the procedures used for the preparation of amino ketals (types III and VI). A solution of 5.99 Gm. (0.02 mole) of the chloro ketal (II) in 70 ml. of piperidine was refluxed for 2 hours. The reaction mixture was chilled and filtered to remove precipitated piperidine hydrochloride. The solvent was removed by evaporation and the residue recrystallized from petroleum ether, yielding 4.7 Gm. (67%), m.p. 80–82°. An analytical sample was obtained by further recrystallization from the same solvent, m.p. 83–84°. Additional piperidine hydrochloride was obtained from the mother liquors by precipitation with acetone, making the total yield 2.15 Gm. (90%).

For preparation of the dimethylamino ketals (IIIa, VIa), the chloro ketal (II or V) was dissolved in dimethylamine at 0°. The solution was kept in a sealed citrate bottle at room temperature for several days. The solution was chilled, decanted from the precipitate of dimethylamine hydrochloride, and allowed to evaporate to a dry residue which was recrystallized from a suitable solvent (Table I).

Salts were prepared by bubbling dry HCl gas into a dry ether solution of the amino ketal or by adding a solution of oxalic acid dihydrate in a minimum of dry ethanol to an equimolar amount of the amino

ketal in dry ether. The precipitated salts were washed with dry ether and recrystallized (Table I).

1,2-Diphenyl-2-(β -piperidinoethoxy)-ethanol Oxalate (VIc).—The chloro ketal (V) (1.53 Gm., 0.005 mole, m.p. 118–120°) was dissolved in 15 ml. of piperidine and refluxed for 1 hour. The reaction mixture was chilled and filtered to remove piperidine hydrochloride (0.54 Gm., 90%). Air-current evaporation of the solvent yielded a viscous noncrystallizable oil. The oil was dissolved in dry ether, and a solution of 630 mg. (0.005 mole) of oxalic acid dihydrate in dry ethanol was added. The oil, which separated immediately, gradually crystallized. The material was recrystallized from benzene-dioxane (3:1) and melted at 133–135°. Further recrystallization afforded an analytical sample melting at 135–137° dec. (Table I).

Attempted Solvolysis (Transketalation) of 1-[α -Methoxy- α -(β -pyrrolidinoethoxy)-benzyl]-cyclohexanol (IIIb).—The amino ketal (IIIb) (1.67 Gm., 0.005 mole) was dissolved in 15 ml. of dry methanol. The solution was refluxed for 6 hours, allowed to stand overnight at room temperature, and evaporated to a thick slurry, from which was obtained 1.6 Gm. of unreacted amino ketal (93% recovery), m.p. 118–120°, undepressed upon admixture with an authentic sample.

Hydrolysis of the Hydrochloride Salt of 1-[α -Methoxy- α -(β -pyrrolidinoethoxy)-benzyl]-cyclohexanol (IIIb).—A solution of 0.56 Gm. (0.0015 mole) of the amino ketal hydrochloride (IIIb) in 15 ml. of water was allowed to stand at room temperature for several weeks. The water was allowed to evaporate spontaneously. The residual oil slowly crystallized; after washing with cold 95% ethanol, the product melted at 45–48°, undepressed upon admixture with authentic α -hydroxycyclohexyl phenyl ketone. The infrared spectrum was identical to that of the authentic hydroxy ketone. The crude yield was 0.2 Gm. (65%).

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