Agents Acting on the Central Nervous System. 19. (±)-1-(*o*- and *m*-Alkanoylphenoxy)-3-(N^4-arylpiperazinyl)propan-2-ols as Local Anesthetics, Hypotensives, and Tranquillizers†

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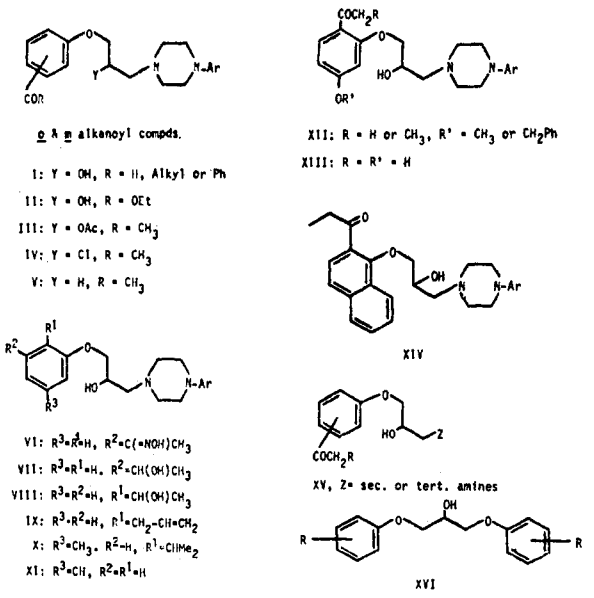
In a study of the synthesis and pharmacological screening of (±)-1-(alkanoylphenoxy)-3-(N^4-arylpiperazinyl)propan-2-ols and some related compounds it has been found that *o*-alkanoyl compounds possess marked hypotensive and local anesthetic activity, *m*-alkanoyl compounds showed tranquillizing activity, while *p*-alkanoyl compounds[1] have antidepressant activity; this dissociation in biological action is particularly marked in N^4-phenylpiperazinyl compounds. The marked local anesthetic activity of (±)-1-(*o*-acetylphenoxy)-3-[N^4-(3,4-dimethylphenyl)piperazinyl]propan-2-ol (23, centxylazine), in surface, infiltration, and spinal anesthesia, and its higher safety margin than known local anesthetics make it a promising candidate for clinical evaluation.

Synthesis and biological evaluation of (±)-1-(alkanoylphenoxy)-3-(N^4-arylpiperazinyl)propan-2-ols[1] and related compounds have been under investigation in this lab for a number of years. It has been found that position of the alkanone residue in the phenoxy moiety has a marked effect on the pattern of biological activities of these compounds even if it occupies an isoelectronic position. In an earlier communication[1] it was reported that the corresponding *p*-alkanoyl compounds in general possess antidepressant activity. It is now shown that *o*-alkanoyl compounds on the other hand possess hypotensive and local anesthetic activities while *m*-alkanoyl compounds possess tranquillizing activity. This communication is concerned with the synthesis and pharmacological screening of (±)-1-(2- and 3-alkanoylphenoxy)-3-(N^4-phenylpiperazinyl)propan-2-ols and related compounds of type I-XV.

Chemistry. Condensation of 1-aryloxy-2,3-epoxypropanes with the appropriate amines in EtOH led to the synthesis of compounds of type I, II, IX-XII, XIV, and XV (see Chart I). The required epoxy compounds were prepared by condensation of the appropriate phenols with epichlorohydrin under three reaction conditions described in the Experimental Section.

Chart I



m-Hydroxypropiophenone[2] was prepared either from *m*-benzyloxybenzaldehyde[3] *via* Grignard addition and oxidation of the resulting benzylic alcohol with MnO_2 or DMSO-DCC, followed by debenzylation or by treating *m*-acetoxybenzoyl chloride[2] with diethylcadmium followed by hydrolysis.

III was prepared by Ac_2O-pyridine or Ac_2O-NaOAc treatment of 1-aryloxy-2-hydroxy-3-aminopropanes and chloro compounds IV by treatment of I with $SOCl_2$ in C_6H_6. Condensation of phenols with 1-chloro-3-(N^4-arylpiperazinyl)propanes, obtained by the reaction of 1-chloro-3-bromopropane with arylpiperazines, gave V. $NaBH_4$ reduction of I furnished compounds of type VII and VIII presumably as a mixture of diastereoisomers which were not separated. NH_2OH treatment of I gave compounds of type VI. Hydrogenolytic debenzylation of XII gave XIII. A small quantity of the (±)-1,3-bisaryloxypropanols (XVI) was formed during the preparation of 1-aryloxy-2,3-epoxypropanes by condensation of phenols with epichlorhydrin and, when specifically required, was prepared in good yield by methods reported in our earlier communication.[1] All the epoxy compounds indicated in Table I showed the expected spectral characteristics reported in our earlier communication.[1]

Pharmacological Activity. Methods. The LD_{50} and gross behavioral effects were studied in mice by intraperitoneal administration of graded doses using five animals for each dose. At least five animals per dose level were also used in all the tests on rats or mice described below.

The effect on blood pressure and respiration and interaction with acetylcholine and epinephrine responses were studied in anesthetized (pentobarbitone, 35 mg/kg) cats. The contraction of nictitating membrane in response to preganglionic sympathetic stimulation was recorded.

The compounds which showed CNS activity in the gross behavior study were subjected to one or more of the following tests for evaluation of their CNS effects. The antagonism to amphetamine hyperactivity was tested in mice by the method of Christensen, *et al.*,[4] whereas the ability to counteract amphetamine induced toxicity in grouped mice was tested by the method of Burn and Hobbs.[5] Effect of the compounds on conditioned avoidance response (CAR) was tested in rats according to Cook and Weidley.[6] Muscle

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Table I

$ArOCH_2CH(O)CH_2$

No.[g]	ArO	Yield, %	Bp (mm) or mp, °C	Formula[f]
1	2-Propionylphenoxy	50[c]	80–120 (0.1–0.05)	$C_{12}H_{14}O_3$
2	2-Benzoylphenoxy	68[c]	Viscous oil[e]	$C_{16}H_{14}O_3$
3	2-Methoxycarbonylphenoxy	34[c]	168–172 (8)	$C_{11}H_{12}O_4$
4	Thymyloxy	75[a]	Oil,[e] n^{27}D 1.5045	$C_{13}H_{18}O_2$
5	2-Acetyl-5-methoxyphenoxy	70[a]	55–56[d]	$C_{12}H_{14}O_4$
6	2-Acetyl-5-benzyloxyphenoxy	44[b]	96–98[d]	$C_{18}H_{18}O_4$
7	2-Propionyl-5-benzyloxyphenoxy	70[a]	83–84[d]	$C_{19}H_{20}O_4$
8	2-Propionyl-1-naphthyloxy	35[b]	Viscous oil[e]	$C_{16}H_{16}O_3$
9	3-Propionylphenoxy	60[c]	Viscous oil,[e] n^{24}D 1.5355	$C_{12}H_{14}O_3$
10	3-Cyanophenoxy	67[a]	Viscous oil,[e] n^{27}D 1.5320	$C_{10}H_9NO_2$

[a-c]Refer to epoxidation methods described in Experimental Section. [d]Crystallized from C_6H_6–hexane. [e]Purified over alumina column using hexane, C_6H_6, and $CHCl_3$ as eluents and characterized by nmr. [f]All compounds were analyzed for C and H. [g]Showed no noteworthy antitumor and antimicrobial activity.

relaxant activity was tested in mice by the rotating rod method as described by Parkes.[7] Central muscle relaxant activity was evaluated by the effect of the compound on somatic reflexes in chloralosed (80 mg/kg iv) cats. The effect on linguomandibular reflex (LMR) was tested by the technique of King and Unna,[8] whereas the effect on flexer reflex was tested by the method of Witkin, *et al.*[9] Anticonvulsant activity was tested in mice by the supramaximal electroshock seizure test (MES) and metrazole-induced seizure threshold test according to Swinyard, *et al.*[10]

Primary local anesthetic activity was evaluated by the rabbit cornea reflex method for surface anesthesia according to the method of Kuna and Seeler.[11] Those compounds which showed significant activity in this test were then evaluated for infiltration and conductance anesthetic activity. Infiltration anesthetic activity was tested in guinea pigs according to the intradermal wheal method of Bulbring and Wajda.[12] Conductance anesthesia was studied according to Krantz, *et al.*,[13] using chloralosed cats for each compound, by recording the inhibition of the pressor response elicited by electrical stimulation of the central cut end of the sciatic nerve after injecting the compound in the sheath of the sciatic nerve proximal to the site of stimulation. Spinal anesthesia was tested in dogs by injecting the drug at the lumbo-sacral junction and observing the lack of sensation and paraplegia.[14] Local irritancy produced by local anesthetic compounds was tested in rabbits using three animals for each test according to the method of Hoppe, *et al.*,[15] and Shintami, *et al.*[16]

The anorexic activity was tested in overnight fasted rats weighing 200 ± 20 g, placed in individual cages without food or water. The compounds were administered by gastric tube. A liquid chocolate drink was then presented to them in graduated feeding tubes, and the amount of fluid consumed at 15, 30, 60, 120, and 180 min was recorded. ED_{50} values were determined from dose-response studies carried out at the 180-min time period.

Results and Discussion

Most of the compounds described in this paper were subjected to primary pharmacological screening by the methods described above, but the activity of only selected compounds, whose results have a bearing on structure-activity relationships (SAR), is given in the Tables II and III.

SAR. Quite early in this study it was observed that (±)-1-(*o*-acetylphenoxy)-3-(N^4-phenylpiperazinyl)propan-2-ol (**11**) caused a marked fall of blood pressure in anesthetized cats and also had marked local anesthetic activity, while the corresponding *m*-acetyl compound **15** caused hypothermia, inhibition of spontaneous motor activity, and counteracted amphetamine-induced hyperactivity and toxicity in mice. In subsequent study these two compounds thus served as prototypes for structural modification. The structure-activity relationships of *o*- and *m*-alkanoyl compounds are discussed below.

1-(*o*-Alkanoylphenoxy)-3-(N^4-arylpiperazinyl)propan-2-ols. Compound **11** lowered blood pressure, potentiated adrenaline responses, and caused an equal block of the pre- and postganglionic nerve stimulation. It appears to exert its hypotensive action by adrenergic neurone blockade. Replacement of the *N*-phenylpiperazine residue by N^4-methylpiperazine (**46**), 4-phenyl-4-hydroxypiperidine (**68**), and diisopropyl (**67**) residues still kept the overall hypotensive effect of these compounds; replacement by morpholine residue **66** greatly diminished the activity while by replacement with piperidine the activity completely disappeared. Substitution in the phenyl residue of *N*-phenylpiperazine affected more the order and not the pattern of activity. Almost all the analogs which differed from **11** in the substitution in the phenyl ring of *N*-phenylpiperazine (particularly **23**, **47–55**) showed hypotensive action though of varying degree. The effect of these compounds on adrenaline responses varied from marked potentiation (**24**) to adrenaline block (**41**, **45**, **47**) or even reversal (**33**, **48**). These variations led to the uncovering of marked hypotensive activity in 1-(*o*-acetylphenoxy)-3-[N^4-(3,4-dimethylphenyl)piperazinyl]-propan-2-ol (**23**, centxylazine). Further variations were, therefore, carried out in the aryloxy and propanol parts of the prototype **23**.

The 2-hydroxy group seems necessary for hypotensive activity as the 2-desoxy compound **45** and the 2-*O*-acetates **41**, **43**, and **44** showed greatly diminished hypotensive action, as compared to their hydroxy compounds.

Substitution in the phenoxy radical had marked effect both on the pattern and order of activity of the prototype. Introduction of a hydroxy group (**33**), a benzyloxy group (**32**), or methoxy group (**34**) in the 5 position almost completely abolished the hypotensive activity; **33** had marked adrenergic receptor blocking activity with very weak hypotensive action. Introduction of an additional benzene ring

Table II

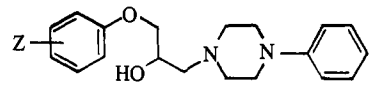
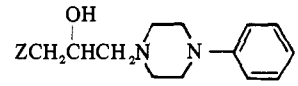
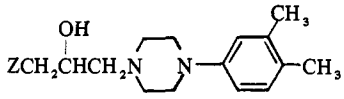
No.[a]	Z	Yield, %	Mp, °C[b]	Formula (analyses)	LD_{50}, mg/kg, mice ip	Gross effects[c]	Other noteworthy effects[d]
							
11	2-$COCH_3$	79	105	$C_{21}H_{26}N_2O_3$ (C, H, N)	100	Depressant	BP ↓ 78 (50), NMB 50
12	2-$COCH_2CH_3$	75	2HCl, 175–178	$C_{22}H_{30}N_2O_3Cl_2$ (C, H)	150	Depressant	Amphet hyp ED_{50} 15, mus relax ED_{50} 15, antihist[e] 0.01, BP ↓ 30 (65), NMB 36
13	2-$CH(OH)CH_3$	80	135–136	$C_{21}H_{28}N_2O_3$ (C, H)	200	Depressant	Mus relax ED_{50} 40, BP ↓ 40 (15)
14	2-CO_2CH_3	81	2HCl, 185–186	$C_{21}H_{28}N_2O_4Cl_2$ (C, H)	300	0	BP ↓ 30 (15), NMB 24
15	3-$COCH_3$	90	132	$C_{21}H_{26}N_2O_3$ (C, H, N)	225	Depressant	Hypothermia 7° F (10 mg), CAR ED_{50} 10, reduction of locomotor activity 20 ip 86%, MES ED_{100} 40, anorexic ED_{50} 20, amphet hyp ED_{50} 15, tox ED_{50} 21, linguomandibular and flexor reflex ED_{50} 5
16	3-$COCH_2CH_3$	73	124–125	$C_{22}H_{28}N_2O_3$ (C, H, N)	>800	Depressant	Amphet hyp ED_{50} 40, BP ↓ 44 (55), tachyphylaxis
17	3-$CH(OH)CH_3$	81	HCl, 131–134	$C_{21}H_{29}N_2O_3Cl$ (C, H, N)	200	0	
18	3-$C(CH_3)$=NOH	87	HCl, 215–216	$C_{21}H_{28}N_3O_3Cl$ (C, H, N)	150	Mild depressant	BP ↓ 16 (25), E ↓ 25
							
19	2-Isopropyl-5-methylphenoxy	86	2HCl, 210–214	$C_{23}H_{34}N_2O_2Cl_2$ (N)	400	Depressant	
20	2-Propionyl-1-naphthyloxy	86	2HCl, 190–192	$C_{26}H_{32}N_2O_3Cl_2$ (N)	600	0	BP ↓ 40 (5)
21	3-Cyanophenoxy	82	116–117	$C_{20}H_{23}N_3O_2$ (N)	>800	Depressant	
							
22	2-Formylphenoxy	95	2HCl, 190–192	$C_{22}H_{30}N_2O_3Cl_2$ (C, H, N)	600	0	Antihist 0.1, mus relax ED_{50} 60, marked respiratory depression, BP ↓ 20 (5)
23	2-Acetylphenoxy	66	83	$C_{23}H_{30}N_2O_3$ (C, H, N)	170	Depressant	Amphet hyp ED_{50} 20, BP ↓ 40 (>140), E ↑ 16
24	2-Propionylphenoxy	81	2HCl, 170–172	$C_{24}H_{34}N_2O_3Cl_2$ (C, H, N)	300	Depressant	BP ↓ 24 (15), E ↑ 87, NMB 56
25	3-Acetylphenoxy	53	74–76	$C_{23}H_{30}N_2O_3$ (C, H, N)	400	Depressant	Amphet hyp ED_{50} 10, amphet tox ED_{50} 30, muscle relax ED_{50} 10, respiratory depression, BP ↓ 70 (80)
26	4-Acetylphenoxy	60	120–121	$C_{23}H_{30}N_2O_3$ (C, H, N)	800	Depressant	Amphet hyp ED_{50} 20, tox ED_{50} 50, mus relax ED_{50} 150, BP ↓ 110 (20)
27	4-Propionylphenoxy	71	122–126	$C_{24}H_{32}N_2O_3$ (C, H, N)	1600	Depressant	Amphet hyp ED_{50} 70, BP ↓ 18 (35), E ↓ 50
28	2-Methoxycarbonylphenoxy	50	2HCl, 166–168	$C_{23}H_{32}N_2O_4Cl_2$ (C, H, N)	400	Depressant	Amphet hyp ED_{50} 80, BP ↓ 16 (15)
29	2-Benzoylphenoxy	66	112	$C_{28}H_{32}N_2O_3$ (C, H, N)	>800	0	0
30	2-Allylphenoxy	80	2HCl, 183–184	$C_{24}H_{34}N_2O_2Cl_2$ (N)	300	0	Amphet hyp ED_{50} 60
31	2-α-Hydroxyethylphenoxy	80	2HCl, 200–202	$C_{23}H_{34}N_2O_3Cl_2$ (N)	200	Depressant	Amphet hyp ED_{50} 40, antihist 0.5, BP ↓ 30 (20)
32	2-Acetyl-5-benzyloxyphenoxy	70	2HCl, 214–215	$C_{30}H_{38}N_2O_4Cl_2$ (N)	>800	0	0
33	2-Acetyl-5-hydroxyphenoxy	70	2HCl, 210	$C_{23}H_{32}N_2O_4Cl_2$ (N)	600	Depressant	BP ↓ 30 (2), E reversal

Table II *(Continued)*

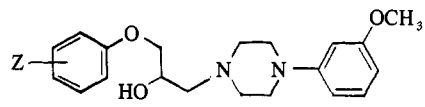
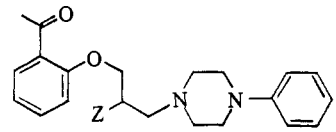
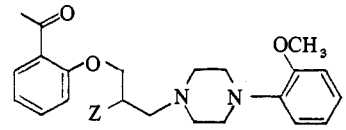
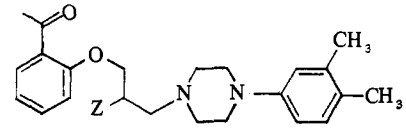
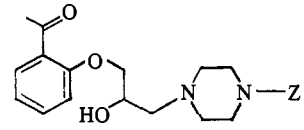
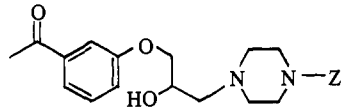
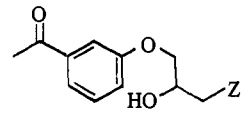
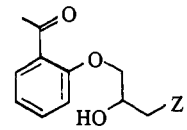
No.[a]	Z	Yield, %	Mp, °C[b]	Formula (analyses)	LD_{50}, mg/kg, mice ip	Gross effects[c]	Other noteworthy effects[d]
34	2-Acetyl-5-methoxy-phenoxy	50	2HCl, 191–193	$C_{24}H_{34}N_2O_4Cl_2$ (N)	300	Depressant	BP ↓ 50 (20), E ↓ 18
35	2-Propionyl-5-benzyloxy-phenoxy	84	2HCl, 167–170	$C_{31}H_{40}N_2O_4Cl_2$ (C, H, N)	>800	0	BP ↓ 68 (8), E ↓ 25
36	2-Isopropyl-5-methyl-phenoxy	79	2HCl, 213–216	$C_{25}H_{38}N_2O_2Cl_2$ (C, H, N)	600	Depressant	BP ↓ 16 (25) MES ED_{50} 120
37	2-Propionyl-1-naphthyloxy	86	2HCl, 187–190	$C_{28}H_{36}N_2O_3Cl_2$ (C, H, N)	>800	0	BP ↑ 20 (2)
							
38	3-Formyl	80	76–78	$C_{21}H_{26}N_2O_4$ (C, H, N)	800	Depressant	
39	3-Acetyl	75	78	$C_{22}H_{28}N_2O_4$ (C, H, N)	400	Depressant	CAR ED_{100} 10, amphet tox ED_{50} 25, blocks linguomandibular and flexor reflex ED_{50} 2.5–5, amphet hyp ED_{100} 80
40	3-Propionyl	79	96–98	$C_{23}H_{30}N_2O_4$ (C, H, N)	>800	Depressant	Amphet hyp ED_{50} 35, mus relax ED_{50} 160, BP ↓ 76 (95), E ↑ 30, NMB 33
							
41	OAc	95	2HCl, 187 dec	$C_{23}H_{30}N_2O_4Cl_2$ (N)	300	Depressant	Amphet hyp ED_{50} 60 mus relax ED_{50} 60, BP ↓ 46 (20), E ↓ 30
							
42	Cl	40	88–90	$C_{22}H_{27}N_2O_3Cl$ (C, H, N)			
43	OAc	90	110	$C_{24}H_{30}N_2O_5$ (N)	100	Depressant	Amphet hyp ED_{50} 25, mus relax ED_{50} 30, BP ↓ 48 (6)
							
44	OAc	77	2HCl, 180–182	$C_{25}H_{32}N_2O_4$ (N)	300	Depressant	Antihist 0.005, amphet hyp ED_{50} 30, mus relax ED_{50} 60, BP ↓ 34 (52), E ↓ 42, NMB 78
45	H	61	75–77	$C_{23}H_{30}N_2O_2$ (C, H, N)			BP ↓ 24 (10), E ↓ 50
							
46	Me	62	2HCl, 115–118	$C_{16}H_{26}N_2O_3Cl_2$ (C, H, N)	240	Mixed	BP ↓ 40 (>30) at 5 mg/kg
47	*o*-Methoxy-phenyl	73	102	$C_{22}H_{28}N_2O_4$ (C, H, N)	400	Depressant	BP ↓ 70 (>30) at 0.5 mg/kg tachyphylaxis, E ↓ 50
48	*o*-Chlorophenyl	76	99	$C_{21}H_{25}N_2O_3Cl$ (C, H, N)	150	Depressant	BP ↓ 36 (50), E reversal, NMB 100
49	*p*-Methoxy-phenyl	68	2HCl, 192 dec	$C_{22}H_{30}N_2O_4Cl_2$ (N)	175	0	NMB 100, BP ↓ 18 (17)
50	*p*-Methylphenyl	87	112	$C_{22}H_{28}N_2O_3$ (C, H, N)			BP ↓ 40 (20), E ↓ 60

Table II (Continued)

No.[a]	Z	Yield, %	Mp, °C[b]	Formula (analyses)	LD_{50}, mg/kg, mice ip	Gross effects[c]	Other noteworthy effects[d]
51	*m*-Methylphenyl	40	2HCl, 182-dec	$C_{22}H_{30}N_2O_3Cl_2$ (N)			BP ↑ 20 (10)
52	3,4-Dimethoxyphenyl	54	2HCl, 214-216 dec	$C_{23}H_{32}N_2O_5Cl_2$ (C, H)			BP ↓ 52 (27)
53	3,4-Dichlorophenyl	72	120-122	$C_{21}H_{24}N_2O_3Cl_2$ (C, H)			BP ↓ 20 (45)
54	*m*-Methoxyphenyl	58	2HCl, 178 dec	$C_{22}H_{30}N_2O_4Cl_2$ (N)	250	Depressant	BP ↓ 30 (25)
55	*m*-Trifluoromethylphenyl	53	90-92	$C_{22}H_{25}N_2O_3F_3$ (N)	1200	0	BP ↓ 14
							
56	Me	55	2HCl, 100-104	$C_{16}H_{26}N_2O_3Cl_2$ (N)	540		
57	*o*-Methoxyphenyl	80	112	$C_{22}H_{28}N_2O_4$ (N)	200	Depressant	Hypothermia 7.5° (25 mg), amphet tox ED_{50} 35, CAR ED_{50} 10, BP ↓ 40 (45), E ↓ 60 tachyphylaxis
58	*p*-Methylphenyl	78	86	$C_{22}H_{28}N_2O_3$ (C, H, N)	150	Depressant	Hypothermia 8° (30 mg), antihist 0.5, amphet hyp ED_{50} 30, mus relax ED_{50} 30, anorexic ED_{50} 40, BP ↓ 50 (7), ED ↓ 40, NMB 25
59	3,4-Dimethoxyphenyl	64	2HCl, 196 dec	$C_{23}H_{32}N_2O_5Cl_2$ (C, H, N)	200	0	E ↓ 31
60	*m*-Trifluoromethylphenyl	86	2HCl, 196-197	$C_{22}H_{27}N_2O_3Cl_2F_3$ (N)	600	Depressant	Amphet hyp ED_{50} 30, mus relax ED_{50} 30, BP ↓ 80 (9)
							
61	Morpholinyl	92	91	$C_{15}H_{21}NO_4$ (C, H, N)	800	Depressant	0
62	Piperidyl	86	86	$C_{16}H_{23}NO_3$ (C, H, N)	160		
63	4-Hydroxy-4-phenylpiperidyl	70	98	$C_{22}H_{27}NO_4$ (C, H, N)	190		
64	Diisopropylamino	77	HCl, 138	$C_{17}H_{28}NO_3Cl$ (C, H, N)	290		BP ↓ 14 (4), E ↑ 16
65	β-Phenylethylamino	42	HCl, 121-125	$C_{19}H_{24}NO_3Cl$ (C, H, N)	800	Stimulant	BP ↑ 70 (13), BP ↓ after rigitine treatment
							
66	Morpholinyl	77	HCl, 139	$C_{15}H_{22}NO_4Cl$ (C, H, N)			BP ↓ 18 (3)
67	Diisopropylamino	76	HCl, 140	$C_{17}H_{28}NO_3Cl$ (N)	800	0	BP ↓ 30 (30)
68	4-Hydroxy-4-phenylpiperidyl	70	HCl, 165-167	$C_{22}H_{28}NO_4Cl$ (C, H, N)	100		Amphet tox ED_{50} 10, BP ↓ 46 (>150), respiratory depression

[a]Compounds 11, 12, 14-16, 19-30, 32, 34-40, and 46-68 were prepared as described for 23. Compounds 13 and 31 were prepared as described for 17 and 41 as described for 43. Preparations of 18, 33, 42, 44, and 45 described in the Experimental Section. [b]Compounds 42 and 45 were crystallized from C_6H_6-hexane and $CHCl_3$-hexane, respectively, and the rest of the compounds from EtOH or C_6H_6-hexane and their hydrochlorides from MeOH-Et_2O. [c]Depressant implies reduced spontaneous motor activity, ptosis, ataxia, loss of righting reflex; stimulant implies altertness, Straub phenomenon, excitement, hyperreflexia, preconvulsiveness, and convulsions. [d]BP ↓ = fall in blood pressure measured in mm at 2.5 mg/kg iv except where specified; numbers in parentheses represent time of recovery in minutes; E = responses to epinephrine, ↓ = block in per cent and ↑ = potentiation in per cent; NMB = per cent nictitating membrane block which implies block of ganglia and sympathetic nerve endings; 0 = no noteworthy effect; CAR = conditioned avoidance response; amphet hyp and tox denotes inhibition of amphetamine-induced hyperactivity and toxicity, respectively, and the figure describes the dose in mg/kg body weight; mus relax denotes muscle relaxant and gives rotating rod test results; MES, inhibition of maximal electroshock seizures. [e]μg/ml of dose required for complete block of histamine response in isolated guinea pig ileum preparation.

(37) also abolished the hypotensive activity. Increasing or decreasing the length of the alkanone moiety (24, 22), replacing it by an ester group as in 28, reduction of alkanone to alkanol (31), or its replacement by a benzoyl or allyl group (29, 30) greatly reduced or abolished the hypotensive activity. Surprisingly, the corresponding *m*-acetyl (25) and *p*-acetyl (26) compounds still showed considerable hypotensive activity, while in the *N*-phenylpiperazine analog 11 shifting of *o*-acetyl residue to the meta position (15) completely abolished the hypotensive action.

Table III. Local Anesthetic Activity[a,b]

Compd	% solution	Duration in min of complete anesthesia: Surface	Infiltration
11	0.05	>30	30
12	0.5	15	0
15[c]	0.5	30	20
23	0.1	30	>30
25	0.5	30	15
45	0.05	15	30
50	0.05	>60	20
68	0.1	>30	0

[a]Results are an average of three determinations. [b]The other compounds which were tested for local anesthetic activity but showed no noteworthy effect include 13, 22, 24, 26, 28, 31, 34, 36, 41, 44, 46, 51-53, and 66. [c]The *p*-acetyl and *p*-propionyl compounds corresponding to compound 15 were inactive.

Local Anesthetic Activity (Tables III and IV). As in the case of hypotensive activities, the *o*-alkanoyl compounds (**11**, **23**) have more marked local anesthetic activity than the corresponding *m*- or *p*-alkanoyl compounds **15**, **25**, and **26**. The *o*-alkanoyl substituent seems necessary for local anesthetic activity as its reduction to CHOH (**13**, **31**) or to alkane (**36**) leads to complete loss of this activity. The 2-hydroxy group on the propoxy chain does not seem essential for local anesthetic activity as the corresponding 2-desoxy compound **45** also has marked local anesthetic activity; 2-*O*-acetates **41** and **44** showed no local anesthetic activity. The phenyl group at a distance of 2.8 Å from the nitrogen atom attached to propoxy chain seems necessary along with an additional binding site also located at the same distance from the same nitrogen, as evidenced by the activity in arylpiperazinyl compounds **11**, **23**, and **50** and 4-hydroxy-4-phenyl compound **68** and lack of activity in the morpholinyl **66** and *N*-methylpiperazinyl compound (**46**). Substitution in the phenyl ring of the piperazine moiety does not seem necessary for this activity as the *N*-phenylpiperazinyl compound **11** has marked local anesthetic activity. However, *p*-methylphenyl **50** and the 3,4-dimethylphenyl compound **23** showed marked activity while the corresponding *m*-methylphenyl compound **51** had no activity; **51** also had no hypotensive activity. Introduction of other substituents such as Cl or OMe in the phenylpiperazine part (**52**, **43**) completely abolished the activity. Among all the compounds tested, centxylazine (**23**) seemed to have the most favorable therapeutic ratio, and, therefore, its local anesthetic activity was studied in greater detail.

1-(*m*-Alkanoylphenoxy)-3-(*N*[4]-arylpiperazinyl)propan-2-ols. The most significant tranquillizing activity was found in *m*-acetophenones which caused hypothermia, inhibited spontaneous motor activity, had central muscle relaxant action, and blocked polysynaptic reflexes in cats. An increase in length of the alkyl chain or the alkanone residue as in **16** diminished the order of activity; compound **16** caused only mild depression and, in addition, caused significant hypotension. Replacement of the CO function by C=N as in oxime (**18**) or by C≡N (**21**) modified the activity whereas its replacement by CHOH as in **17** abolished the tranquillizing activity.

The *N*-phenylpiperazine residue seems necessary for tranquillizing activity as the corresponding analogs having instead *N*-methylpiperazine (**56**), piperidine (**62**), morpholine (**61**), or 4-hydroxy-4-phenyliperidine (**63**) groups showed no activity. Substitution in the phenyl ring of *N*-phenylpiperazine did not materially alter the pattern of activity; most of these compounds had CNS depressant activity of the same order as that of the prototype, *e.g.*, **57** and **39**. Some of the derivatives in addition showed hypotensive and antiadrenaline activity (**16**, **25**, **57**). The corresponding β-phenylethylamine compound **65**, however, had sympathomimetic activity; it caused a hypertensive response and showed stimulant action on gross behavior.

The above discussion would show that in spite of the reasonably large number of substituent variations carried out having different stereoelectronic effects, no definite structure-activity pattern has emerged. The results described, however, show that compound **23** had significant hypotensive and local anesthetic activity, while **15**, **39**, and **57** showed significant tranquillizing actvity. The hypotensive and local anesthetic activities of **23** were studied in considerable detail.

Hypotensive Activity of 23 (Centxylazine). Its LD_{50} was 170 mg/kg (ip) in mice. It is equally effective by intravenous and intraduodenal routes. The magnitude and duration of hypotensive action is dose dependent; 1 mg/kg produced 25% lowering of blood pressure in anesthetized cats for 60 min. Similar effects were obtained in conscious cats immoblized with *d*-tubocurarine and in decerebrated cats. The hypotension was accompanied by mild tachycardia. The carotid occlusion pressor response was partially blocked, epinephrine response was potentiated, but tyramine response was unaffected. The response of the nictitating membrane to electrical stimulation of preganglionic nerve was uneffected. The compound failed to produce hypotension following intracerebroventricular or intravertebral arterial injection and excitability of the medullary vasomotor loci to electrical stimulation was unaltered following topical administration. Similarly, intrathecal administration had no effect on spinal compression vasomotor response. The compound thus does not appear to have any effect on the central vasomotor loci.

Hypotension was observed in spinal transected as well as hexamethonium or dibenamine-treated animals. This suggested a more peripheral effect which was not due to β-receptor stimulation, since it could not be prevented by β-adrenergic blocking agents like *N*-isopropyl-*p*-methanesulfonamidophenylethanolamine[17] (MJ 1999). Administration of 100-200 μg of the compound in the femoral artery of the cat significantly increased the blood flow to the hind limb, thereby suggesting a vasodilator effect which probably is mainly responsible for the hypotensive activity as well.

Table IV. Local Anesthetic Activity of Centxylazine (23) and Comparison with Lidocaine[a]

		Surface anesthetic activity				Infiltration anesthetic activity				Nerve blocking potency		Spinal anesthetic activity	
Compd	pH	MEC, %	Duration in min	MIC, %	TR	MEC, %	Duration in min	MIC, %	TR	MEC, %	Duration in min	MEC, %	Duration in min
Centxylazine	6.0	0.1	30	1.0	10	0.05	20	0.5	10	0.1	90	0.1	60
Lidocaine	6.4	1.0	15	2.0	2	0.5	15	2.0	4	1.0	90	2	150

[a]MIC = minimum irritating concentration, results described in each case are an average of three determinations; MEC = minimum effective concentration, results described are an average of determinations performed on ten rabbits for surface, six guinea pigs for infiltration, four cats for conductance, and three dogs for spinal anesthesia; TR = therapeutic ratio.

The compound had no effect on cardiac rhythmicity and contractility as seen in *in vitro* and *in vivo* experiments on the guinea pig, dog, and cat. It had a nonspecific spasmolytic effect on smooth muscle of isolated rabbit ileum in 1-4.0 μg/ml concentration.

Local Anesthetic Activity of 23 (Centxylazine). In view of the marked surface and infiltration anesthetic activity shown by **23**, its conductance and spinal anesthetic activity was studied using lidocaine as a standard and the results are described in Table IV. As the results show **23** has a better thereapeutic ratio than lidocaine, and dose for dose is about ten times more active in conductance anesthesia. This compound is at present under preclinical studies.

Experimental Section‡

1-Aryloxy-2,3-epoxypropane. These were prepared by using any one of the reaction conditions described below as methods A, B, and C (Table I).

A. **1-(2-Acetyl-5-methoxyphenoxy)-2,3-epoxypropane (5).** A mixture of 2-acetyl-5-methoxyphenol (3 g, 18 mmol), freshly baked K_2CO_3 (3 g, 22 mmol), and epichlorohydrin (15 ml, 190 mmol) was refluxed for 20 hr. The reaction mixture was filtered, the precipitate washed with C_6H_6, and the filtrate concentrated *in vacuo* to remove epichlorohydrin and C_6H_6. A solution of the residue in C_6H_6 was chromatographed on a column of alumina to give 3.0 g of epoxide.

B. **1-(2-Acetyl-5-benzyloxyphenoxy)-2,3-epoxypropane (6).** A solution of 2-acetyl-5-benzyloxyphenol (2.42 g, 10 mmol) in H_2O (5 ml) and EtOH (40 ml) containing KOH (0.7 g, 12.5 mmol) was added dropwise over a period of 1 hr to a refluxing solution of epichlorohydrin (1.6 ml, 20 mmol) in EtOH (25 ml). The mixture was stirred and refluxed for an additional 1 hr, concentrated, and diluted with H_2O. It was then extracted with $CHCl_3$, washed with 10% KOH, H_2O, and saturated NaCl, and dried (Na_2SO_4). The solvent was removed by distillation and the residue was crystallized to give 1.2 g of bis product, mp 131–133° ($CHCl_3$–C_6H_6), and 1.3 g of epoxide. *Anal.* ($C_{33}H_{32}O_7$) C, H.

C. **1-(*m*-Propionylphenoxy)-2,3-epoxypropane (9).** Epichlorohydrin (2.1 g, 23 mmol) was added dropwise with stirring over 15 min at 15–20° to a solution of *m*-hydroxypropiophenone (3.0 g, 20 mmol) in aqueous EtOH (21 ml, 6.7%). The reaction mixture was kept under stirring at room temperature for 40 hr. The oil was taken up in $CHCl_3$, washed with 10% NaOH solution and H_2O, and dried (Na_2SO_4). The solvent was removed by distillation and the crude compound in C_6H_6 was chromatographed on a column of alumina (C_6H_6) to give 2.4 g of epoxide as an oil.

1-(2-Acetylphenoxy)-3-[N^4-(3,4-dimethylphenyl)piperazinyl]-propan-2-ol (23). A mixture of 1-(2-acetylphenoxy)-2,3-epoxypropane (6.4 g, 33 mmol) and *N*-(3,4-dimethylphenyl)piperazine (6.4 g, 33 mmol) in EtOH (40 ml) was refluxed for 5 hr at 90-95° On cooling the product separated as a colorless crystalline mass which was filtered and crystallized from EtOH, mp 188–191° (2HCl).

1-(3α-Hydroxyethylphenoxy)-2-hydroxy-3-(N^4-phenylpiperazinyl)propane (17). Compound **15** (1.0 g, 3 mmol) was suspended in MeOH (20 ml) and treated with powdered $NaBH_4$ (0.2 g, 5 mmol) in three portions. The mixture was stirred for 5 hr at room temperature and then MeOH was removed by distillation. The residual oil was suspended in H_2O, heated 1.5 hr on steam bath and extracted with AcOEt, washed with H_2O and saturated NaCl, dried (Na_2SO_4), and concentrated. The oil in MeOH was converted into the hydrochloride.

1-(*m*-Acetylphenoxy)-2-hydroxy-3-(N^4-phenylpiperazinyl)-propane Oxime (18). A mixture of **15** (0.5 g, 1.5 mmol), NH_2OH, HCl (0.5 g, 7.3 mmol), EtOH (5 ml), and pyridine (0.5 ml) was refluxed for 30–45 min at 90–95°. The solution was concentrated to dryness and the residue crystallized from aqueous EtOH to give required oxime as the hydrochloride.

1-(2-Acetyl-5-hydroxyphenoxy)-2-hydroxy-3-[N^4-(3,4-dimethylphenyl)piperazinyl]propane (33). A solution of the dihydrochloride of 32 (2.8 g, 5 mmol) in EtOH was hydrogenated over 10% Pd/C (0.3 g) at room temperature and pressure and the reaction mixture worked up in the usual manner.

1-(*o*-Acetylphenoxy)-2-chloro-3-[N^4-(*o*-methoxyphenyl)piperazinyl]propane (42). A solution of $SOCl_2$ (0.65 g, 5.5 mmol) in C_6H_6 was added with stirring to a suspension of 47 (1.9 g, 5 mmol) in C_6H_6. The reaction mixture was stirred a few minutes at room temperature and then refluxed with stirring for 1 hr. The solid was separated by filtration, suspended in H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with H_2O and saturated NaCl, dried (Na_2SO_4), and concentrated to dryness. The residue in C_6H_6–hexane was chromatographed on a column of silica to give the chloro compound which was crystallized (C_6H_6–hexane).

1-(*o*-Acetylphenoxy)-2-acetoxy-3-[N^4-(*o*-methoxyphenyl)-piperazinyl]propane (43). A pyridine solution of 47 (2.68 g, 7 mmol) was stirred at room temperature with Ac_2O (1.4 ml) for 20 hr. The reaction mixture was concentrated to dryness under vacuum and the residual oil was crystallized (EtOH).

1-(*o*-Acetylphenoxy)-2-acetoxy-3-[N^4-(3,4-dimethylphenyl)-piperazinyl]propane (44). A mixture of 23 (1.0 g, 2.6 mmol), Ac_2O (8 ml), and fused NaOAc (2 g) was refluxed for 15 min; the solution was poured onto ice–H_2O, neutralized with $NaHCO_3$, and worked up in the usual manner. The residue was converted to its hydrochloride and crystallized from MeOH–Et_2O.

1-(2-Acetylphenoxy)-3-[N^4-(3,4-dimethylphenyl)piperazinyl]-propane (45). A solution of 7-chloro-3-[N^4-(3,4-dimethylphenyl)-piperazinyl]propane (1.4 g, 5 mmol) in dry dioxane (3 ml) was added dropwise with stirring to a suspension of the sodium salt of *o*-hydroxyacetophenone (0.68 g, 5 mmol) in dry dioxane (5 ml). The stirring was continued for 0.5 hr at room temperature followed by 5 hr at 100–105°. The reaction mixture was cooled, the inorganic salts were removed by filtration, the filtrate was concentrated to dryness, and the residue was crystallized (C_6H_6–hexane) to give the required product.

1-Chloro-3-[N^4-(3,4-dimethylphenyl)piperazinyl]propane (69). 1-Chloro-3-bromopropane (8.2 g, 55 mmol) was added dropwise to a stirred suspension of *N*-(3,4-dimethylphenyl)piperazine (9.5 g, 50 mmol) in Me_2CO (10 ml) containing aqueous NaOH (7.5 ml, 25%), the mixture was stirred for 10 hr at 30–35°, the organic layer was separated and dried (Na_2SO_4), the solvent was removed, and the residue was distilled *in vacuo*. The product thus obtained was taken up in Et_2O; the precipitate which separated was filtered and found to be the hydrochloride of the required compound. The filtrate was concentrated and redistilled to give the required free base as an oil. *Anal.* ($C_{15}H_{23}N_2Cl$) C, H, N.

1-(*m*-Benzyloxyphenyl)propanol (70). *m*-Benzyloxybenzaldehyde (5.25 g, 25 mmol) in Et_2O (50 ml) was added to EtMgBr (prepared from 17.44 g of EtBr and 4 g of Mg) in Et_2O (150 ml) in 1 hr and then refluxed for 0.5 hr under stirring. The complex was decomposed by adding aqueous NH_4Cl (40 g in 200 ml of H_2O); the Et_2O layer was separated, washed with H_2O, dried (Na_2SO_4), and concentrated to dryness to yield 5.0 g (83%), $n^{22}D$ 1.5640. *Anal.* ($C_{16}H_{18}O_2$) C, H.

***m*-Benzyloxypropiophenone (71).** A solution of 70 (3.6 g, 15 mmol) in dry C_6H_6 (150 ml) was refluxed for 3 hr with activated MnO_2 (20 g). After checking on tlc, the catalyst was removed by filtration and the filtrate was concentrated to dryness to give the required product, 2.4 g (67%), as an oil, $n^{25}D$ 1.568. *Anal.* $C_{16}H_{16}O_2$) C, H.

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‡Melting points were determined in capillary tubes in a bath. Ir spectra were determined on a Perkin-Elmer Infracord and nmr spectra on Varian A-60D spectrometer. All the compounds showed the expected spectral characteristics. The reaction products were checked routinely by nmr and ir spectroscopy and tlc. Analyses are indicated only by symbols of the elements and were within ±0.4% of the calculated values. The preparations described illustrate the general methods of synthesis employed. The compounds described are racemic diastereomeric mixtures.

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Potential Psychotomimetics. 2-Amino-1,2,3,4-tetrahydronaphthalene Analogs†

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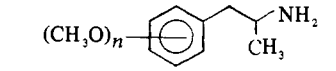
The synthesis of 2-amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (5,8-ADT) and evaluation of ADT and 2-amino-1,2,3,4-tetrahydronaphthalene (2-AT) as partial congeners of LSD and restricted conformers of psychotomimetic phenylisopropylamines were undertaken. Theoretical aspects of psychotomimetics are discussed. Both compounds depressed spontaneous motor activity in mice and had a pressor effect in the anesthetized dog. In the Sidman avoidance test in rats, 2-AT was probably hallucinogenic, while 5,8-ADT had only an amphetamine-like, stimulatory effect. In the isolated rat fundus strip, 2-AT caused contraction and was antagonized at low doses by BOL. Agonistic effects were not seen for 5,8-ADT.

In the study of psychotomimetic indolealkylamines, phenylisopropylamines, and lysergic acid analogs, many theories have been advanced to explain the mechanism of psychotomimetic action. In the early literature,[2-5] lysergic acid derivatives were considered phenylethylamines primarily for purposes of exploring the structural features required for oxytocic activity. Later, in studying the structure-activity relationships of psychotomimetic activity, the analogy to the 3-indoleethylamines received widespread attention.[6,7]

The methoxylated phenylisopropylamines **1** are potent psychotomimetics. Since the isopropylamine side chain is flexible, a large number of conformations are possible. Many of these are unfavorable for receptor interaction. Restricting the number of conformations may result in enhanced potency for the drug if one of the remaining conformations is favorable for interaction with the receptor. Using molecular models, it can be shown that **1** and 2-amino-1,2,3,4-tetrahydronaphthalenes (**2**) are nearly superimposable on the structures of LSD (**3**), where the aromatic ring of **1** and **2** corresponds to the A ring of **3** and the amino functions correspond to the N-6. Analogs of **2** with the proper activation would be expected to exhibit enhanced potency over the corresponding **1** analog.

Violland, *et al.*,[8] have also considered this approach and prepared **2** analogs. They surveyed the derivatives of **2** which have been synthesized and evaluated for a number of other pharmacological activities.

The importance of the 2-aminotetralin moiety to the



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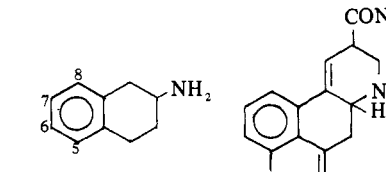

2a, no substituents
b, 6-CH_3O
c, 7-CH_3O
d, 7-HO
e, 5,8-di-CH_3O

3

activities of lysergic acid derivatives was suggested by Marini-Bettolo and coworkers,[9] as a result of the study of **2** analogs as oxytocic drugs, and by Kang and Green,[10] as based on stereochemical and electronic considerations of psychotomimetic effects. Recently, Green and coworkers‡ have predicted psychotomimetic activity in **2b–d** using quantum mechanics. In their experimental studies **2d** showed cross tolerance with mescaline, as does LSD. **2b** and **2c**, which were predicted to be mescaline-like, resembled amphetamine in their central effects. The central effects of **2a** have been examined by a number of groups who characterized the effects as amphetamine-like.

In selecting molecules for synthesis and evaluation, we have considered points of electron density as suggested by

†For a preliminary report, see ref 1.

‡J. P. Green, K. Dressler, and N. Khazan, unpublished results.