# Agents Acting on the Central Nervous System. 14. 1-(*p*-Alkanoylphenoxy)-3-($N^4$-arylpiperazinyl)propan-2-ols. A New Class of Antidepressants†

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The synthesis and pharmacological screening of 1-[*p*-(alkanoyl, aralkanoyl, and aroyl)phenoxy and thiophenoxy]-3-($N^4$-arylpiperazinyl)propanes and -propan-2-ols, 1-[*p*-(alkylsulfinyl, alkylsulfonyl, alkenyl, cyclopropylcarbonyl, cinnamoyl, ethoxycarbonyl, acetonyl, and α-hydroxyalkyl)phenoxy]-3-($N^4$-arylpiperazinyl)propan-2-ols and 1-(*p*-acylanilino and 4-propionyl-1-naphthyloxy)-3-($N^4$-arylpiperazinyl)-propan-2-ols and some related compounds has been carried out. 1-(*p*-Propionylphenoxy)-3-($N^4$-phenylpiperazinyl)propan-2-ol has been found to possess marked antidepressant activity.

Aryloxypropanolamines are known to possess a number of biological activities which include local anaesthetic,[1] muscle relaxant,[2] hypotensive,[3] β-adrenolytic,[4] tranquilizing,[5] antiarrhythmic,[6] and diuretic[7] activities and thus provide an interesting system for possible dissociation and modulation of these activities. This prompted the synthesis of corresponding analogs carrying an alkanoyl residue in the phenoxy component. Quite early in this work it was found that 1-(acetyl- and propionylphenoxy)-3-($N^4$-phenylpiperazinyl)propan-2-ols possess marked and clinically useful pharmacological activities and the positions of the alkanoyl residue had a strong activity dissociating effect in this class of compds. The syntheses and pharmacological screening results of compds of type I-XVI are described in this paper.

**Chemistry.** Compds of type I-IV and XI-XV were prepared by condensation of the appropriate 1-aryloxy-2,3-epoxypropanes with amines. The epoxy compds were prepared by condensation of the required phenols with epichlorohydrin under 4 sets of conditions which are described in the Experimental Section. In every case a small quantity of the bis-1,3-aryloxypropan-2-ols XVI were formed besides other products. As these compds were also of interest as analogs of chromoglysic acid,[8] these were specifically synthesized either by condensation of 1-aryloxy-2,3-epoxypropanes with 1 mole of the phenol or by varying the proportion of alkali and phenols in the condensation with epichlorohydrin.

The required thiophenols were prepared from the appropriate phenols by condensation with dimethylthiocarbamyl chloride, followed by pyrolytic rearrangement and hydrolysis according to the method of Newman, *et al.*[9] Alkylsulfinyl and alkylsulfonylphenols were prepared by oxidation of the corresponding *p*-mesyloxyphenyl alkyl sulfides followed by hydrolysis of the mesylates.

Cyclopropyl *p*-hydroxyphenyl ketone required for preparation of compds of type III was prepared in reasonable yield by base-catalyzed cyclization of *p*-hydroxy-γ-chlorobutyrophenone. Compds of type V were prepared by base-catalyzed condensation of 1-(*p*-acetylphenoxy)-2,3-epoxypropane with the appropriate araldehyde and controlled catalytic reduction of cinnamoyl compds to dihydro compds followed by condensation with the appropriate amines.

Compds of type VI and VII were prepared by the reaction

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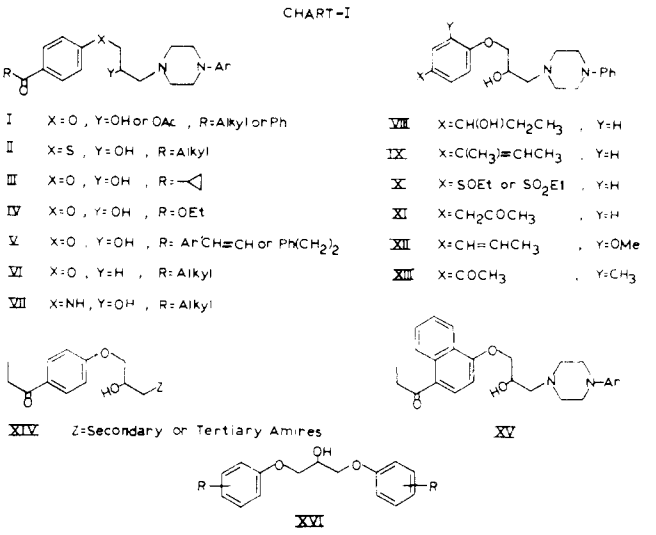


of 1-chloro-3-($N^4$-arylpiperazinyl)propanes and corresponding -propan-2-ols with the appropriate phenols and anilines, respectively.

I on reduction with $NaBH_4$ gave compds of type VIII, while Grignard reaction followed by dehydration gave compds of type IX.

**Pharmacological Activity.** Acute toxicity, gross observational effects, and interaction to reserpine and amphetamine effects were studied in mice by standard methods.[10] The effect on blood pressure and respiration, and interaction to norepinephrine and epinephrine responses were studied in anesthetised cats at 2.5 mg/kg. Effects on somatic reflexes were studied in chloralosed cats (80 mg/kg iv) according to the method of De Salva and Oester.[11]

The screening results are described in Table II. Compd 16 showed marked antireserpine activity, potentiated the activity of amphetamine at a low dose and blocked it at a high dose. Compd 16 served as a prototype for further molecular modification. It was found that optimum antidepressant activity was present in the propiophenones; a decrease in the length of the alkyl chain (**15**) or increase (**17**) markedly diminished the antidepressant activity. Reduction of CO to CHOH as in **28** completely changed the pattern of activity, the compd is no longer an antidepressant, and is actually a weak central depressant. The replacement of the alkanone residue by ester (**18**), benzoyl (**19**), cinnamoyl (**22**, **23** and **24**), β-phenylpropionyl (**25**), or α-methylpropenyl (**29**)

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Table I

| No. | Arx | Yield, % | Bp(mm) or mp,[f] °C | Formula[g] |
|---|---|---|---|---|
| | | ArXCH$_2$CH(O)CH$_2$ | | |
| 1 | 4-Butyrylphenoxy | 47[a] | 50-52 | $C_{13}H_{16}O_3$ |
| 2 | 2-Methyl-4-acetylphenoxy | 45[b] | 122-124($5 \times 10^{-4}$) | $C_{12}H_{14}O_3$ |
| 3 | 4-Propionyl-1-naphthyloxy | 62[c] | 95-96 | $C_{16}H_{16}O_3$ |
| 4 | 4-Ethylsulfonylphenoxy | 41[d] | [e] | $C_{11}H_{14}O_4S$ |
| 5 | 4-Cinnamoylphenoxy | 60 | 86 | $C_{18}H_{16}O_3$ |
| 6 | 4-(4-Methoxycinnamoyl)phenoxy | 70 | 98-100 | $C_{19}H_{18}O_4$ |
| 7 | 4-(4-Fluorocinnamoyl)phenoxy | 68 | 95-97 | $C_{18}H_{15}O_3F$ |
| 8 | 4-(β-Phenylethyl)propionylphenoxy | 53 | 70-71 | $C_{18}H_{18}O$ |
| 9 | 2-Methoxy-4-propenylphenoxy | 44[a] | 50-51 | $C_{13}H_{16}O_3$ |
| 10 | 2-Methoxy-4-allyphenoxy | 51[a] | 148-152($5 \times 10^{-3}$) | $C_{13}H_{16}O_3$ |
| 11 | 4-Acetonylphenoxy | 65[a] | [e] | $C_{12}H_{14}O_3$ |
| 12 | 4-Ethylsulfinylphenoxy | 38[d] | [e] | $C_{11}H_{14}O_3S$ |
| 13 | 4-Propionylthiophenoxy | 60[a] | [e],$n^{25}$D 1.5930 | $C_{12}H_{14}SO_2$ |
| 14 | 4-Cyclopropylcarbonyl | 60[c] | 82-83 | $C_{13}H_{14}O_3$ |

[a-d]Epoxidation methods A, B, C, and D, respectively, described in Experimental Section. [e]Purified over alumina column using $C_6H_6$-hexane, $C_6H_6$, and $C_6H_6$-$CHCl_3$ as eluants and identified by nmr. [f]Crystd from EtOH or aq EtOH. [g]All compds were analyzed for C, H.

residues completely abolished the antidepressant activity. In **26** and **27**, where CO is replaced by SO or $SO_2$, the antidepressant effect is no longer evident, and the compds, in fact show depressant activity and, in addition, have significant hypotensive activity. Many other analogs also show significant hypotensive activity, these include **20**, **22**, **25**, **26**, **31**, **33**, **49**, **53**, and **57**. Changing the position of the CO in the propanone residue from 1 to 2 (**20**) also leads to a complete loss of the antidepressant activity. The antidepressant activity of **16** thus seems quite specific.

**Antidepressant Activity of 16.** Its $LD_{50}$ is 270 mg/kg (ip) in mice. The compd in smaller doses (5-10 mg/kg, ip) by itself does not show any gross effects but it counteracted reserpine-induced depression (sedation, crouching, ptosis) and potentiated amphetamine-induced activity (hyperactivity, pyrexia) in mice and rats. Medium doses (20-40 mg/kg, ip) potentiated amphetamine toxicity in aggregated mice. In higher doses (100 mg/kg, ip and over) the drug counteracted amphetamine-induced hyperactivity as well as amphetamine toxicity in aggregated mice. It was an effective antagonist of reserpine-induced emesis in pigeons. At 6 mg/kg it inhibited polysynaptic reflexes (linguomandibular contralateral sciatic facilitation) in cats while the monosynaptic patillar reflex was unaffected. It had an antinicotinic and antitremorine effect in mice; 16 also caused a potentiation of yohimbine-induced hyperactivity, a specific test[12] for thymoleptics.

At 1-5 mg/kg (iv), **16** had no significant effect on the blood pressure of anesthetized cats; in larger doses (5-10 mg/kg, iv) it produced mild hypotension. Smaller doses, however, potentiated the pressor responses of epinephrine (E) and norepinephrine (NE) whereas larger doses produced reversal of response to E and a reduction in response to NE. The responses of ACh, histamine, and 5-HT were blocked by ng quantities of **16**.

The profile of antidepressant activity of **16** is thus very similar to that of amitriptyline and imipramine.

## Experimental Section

Mps were determined in capillary tubes in a bath. The reaction products were checked routinely by nmr and ir spectroscopy and tlc. Ir spectra were detd on Perkin-Elmer Infracord and nmr spectra on Varian A-60D spectrometer and are expressed in $\tau$ units ($Me_4Si$). All the compds showed the expected spectral characteristics. Analyses are indicated only by symbols of the elements and were within ±0.4% of the calcd values.

The prepns described below illustrate the general methods of synthesis employed.

**1-Aryloxy-2,3-epoxypropanes** were prepared by 4 methods A, B, C, and D described below and the methods used in different cases are indicated in Table I. In the nmr spectra of ArOCH$_2$CH(O)CH$_2$, the C-1 and C-3 $CH_2$ showed nonequivalence in a typical ABC pattern. Generally, the two C-1 protons appeared as 2 quartets centered around 5.5-5.78 and 5.84-6.14, with $J_{gem}$ = 11-11.8 cps and $J_{vic}$ = 3-3.3 and 5-5.5 cps, respectively. The C-2 proton appeared as a multiplet centered around 6.5-6.67. The C-3 $CH_2$ also appeared as a pair of quartets around 7.07-7.16 and 7.25-7.35 and $J_{gem}$ = 5 cps and $J_{vic}$ = 4-4.5 and 2-3 cps, respectively.

**A. 1-(*p*-Butyrylphenoxy)-2,3-epoxypropane (1).** Epichlorohydrin (3.96 g, 33 mmoles) was added dropwise with stirring over 15 min at 15-20° to a soln of *p*-hydroxybutyrophenone (5 g, 30 mmoles) in aq KOH (30 ml, 6.7%). The reaction mixt was stirred at room temp for 40 hr, then extd with $C_6H_6$-EtOAc, the org layer was washed with 10% NaOH soln and $H_2O$, and dried ($Na_2SO_4$). The solvent was removed under reduced pressure and the residual oil was distd; ir (KBr) 1675 (C=O), 918 and 867 $cm^{-1}$ (epoxy).

**B. 1-(2-Methyl-4-acetylphenoxy)-2,3-epoxypropane (2).** A soln of 2-methyl-4-acetylphenol (7.5 g, 50 mmoles) in aq NaOH (25 ml, 8.4%) was added over a period of 1 hr to epichlorohydrin (6.95 g, 75 mmoles) while kept under reflux. Refluxing was contd for another 1.5 hr; the mixt was allowed to cool and worked up as usual.

**C. 1-(4-Propionyl-1-naphthyloxy)-2,3-epoxypropane (3).** A mixt of 4-propionyl-1-naphthol (0.2 g, 1 mmole), freshly baked $K_2CO_3$ (0.14 g, 1 mmole) and epichlorohydrin (3 ml) was refluxed for 15-20 hr. The reaction mixt was cooled, dild with $C_6H_6$, and filtered. The filtrate was concd to dryness under vacuum and the residue was chromatogd on a column of alumina ($C_6H_6$).

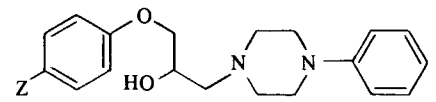
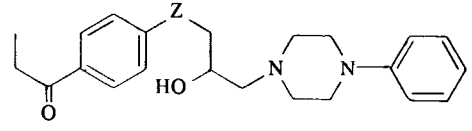
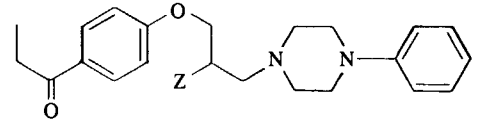
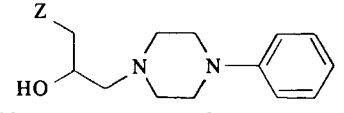
**D. 1-(*p*-Ethylsulfonylphenoxy)-2,3-epoxypropane (4).** A soln of *p*-ethylsulfonylphenol (1.3 g, 7 mmoles) in $H_2O$ (3 ml) and EtOH (15 ml) contg KOH (0.5 g, 8.7 mmoles) was added dropwise over a period of 0.5 hr to a refluxing soln of epichlorohydrin (1.3 g, 14 mmoles) in EtOH (10 ml). The mixt was stirred and refluxed for addnl 1 hr, concd, and dild with $H_2O$. It was then extd with $CHCl_3$, the org phase was washed with dil NaOH, satd NaCl, and dried ($Na_2SO_4$). Removal of solvent was followed by chromatog over alumina ($C_6H_6$).

**Bis-1,3-aryloxypropan-2-ols** were prepd by the following 2 general methods (Table III).

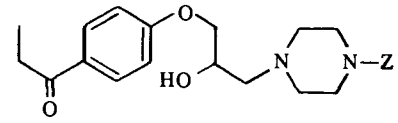
**Method 1.** A soln of the phenol (2 moles) in EtOH (2.5 l.) was mixed with a soln of KOH (1.2 moles) in $H_2O$ (250 ml) contg EtOH (250 ml) and was kept under reflux. To this was added dropwise during 40 min a soln of epichlorohydrin (1.0 mole) in EtOH (1.25 l). After stirring and refluxing for 4 hr, the soln was concd to dryness, dild with $H_2O$, and cooled, and the residue was taken up in $CHCl_3$, washed with 10% NaOH, satd NaCl, dried ($Na_2SO_4$), and concd. The residue crystd from aq EtOH, $CHCl_3$-hexane, or $C_6H_6$ to give the products in 70-80% yield.

**Method 2.** The appropriate phenol (1.0 mole) and the required 1-aryloxy-2,3-epoxypropane (1.1 moles) were dissolved in EtOH (2.5

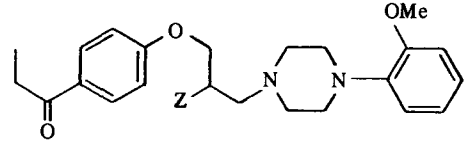
Table II

| No.[d] | Z | Yield, % | Mp,[a] °C | Formula | Analysis | $LD_{50}$, mg/kg mice ip | Gross effects[b] | Other noteworthy effects[c] |
|---|---|---|---|---|---|---|---|---|
| |  | | | | | | | |
| 15 | $COCH_3$ | 84 | 166–168 | $C_{21}H_{26}N_2O_3$ | C, H, N, | 100 | | Weak antidepressant |
| 16 | $COCH_2CH_3$ | 82 | 162–164 | $C_{22}H_{28}N_2O_3$ | C, H, N | 270 | | Antidepressant, central muscle relaxant, adrenaline reversal and hypotension at 5 mg/kg. |
| 17 | $COCH_2CH_2CH_3$ | 84 | 122 | $C_{23}H_{30}N_2O_3$ | C, H, N | 100 | | Weak antidepressant |
| 18 | $CO_2CH_2CH_3$ | 83 | 122–124 | $C_{22}H_{28}N_2O_4$ | C, H, N | 600 | | |
| 19 | COPh | 80 | 2HCl, 199–201 dec | $C_{26}H_{30}N_2O_3Cl_2$ | C, H, N | 150 | | |
| 20 | $CH_2COCH_3$ | 72 | 114–115 | $C_{22}H_{28}N_2O_3$ | C, H, N | >800 | Depressant | BP ↓ 40 (75), E ↓ 25 |
| 21 | Cyclopropylcarbonyl | 90 | 166–168 | $C_{23}H_{28}N_2O_3$ | C, H, N | >800 | | |
| 22 | COCH=CHPh | 70 | 148–149 | $C_{28}H_{30}N_2O_3$ | N | 1600 | Depressant | Counteracts amphetamine induced toxicity. BP ↓ 50 mm (85) |
| 23 | $COCH=CHC_6H_4(p\text{-MeO})$ | 72 | 168–170 | $C_{29}H_{32}N_2O_4$ | C, H, N | >800 | Depressant | |
| 24 | $COCH=CHC_6H_4(p\text{-F})$ | 69 | 160–163 | $C_{28}H_{29}N_2O_3F$ | C, H, N | >800 | Depressant | |
| 25 | $COCH_2CH_2Ph$ | 82 | 103–104 | $C_{28}H_{32}N_2O_3$ | C, H | 75 | Depressant | BP ↓ 46 (>90), E ↓ 66 |
| 26 | $SOCH_2CH_3$ | 54 | 2HCl, 179–181 | $C_{21}H_{30}N_2SO_3Cl_2$ | C, H, N | 600 | Depressant | BP ↓ 50 (75), E ↓ 40 |
| 27 | $SO_2CH_2CH_3$ | 53 | 2HCl, 184–186 | $C_{21}H_{30}N_2SO_4Cl_2$ | C, H, N | 300 | Depressant | BP ↓ 36 (30), E ↓ 44 |
| 28 | $CH(OH)CH_2CH_3$ | 80 | 134–36 | $C_{22}H_{30}N_2O_3$ | C, H | 800 | Depressant | BP ↓ 50 (10) |
| 29 | $C(CH_3)=CH-CH_3$ | 68 | 2HCl, 190–192 Base, 135 | $C_{23}H_{32}N_2O_2Cl_2$ | C, H, N | 800 | Depressant | |
| 30 | $CH_2CH_2CH_3$ | 50 | 82–84 | $C_{22}H_{30}N_2O_2$ | C, H, N | | | |
| |  | | | | | | | |
| 31 | S | 89 | 154–156 | $C_{22}H_{28}N_2O_2S$ | C, H, N | >800 | | BP ↓ 26 (70) |
| 32 | NH | 25 | 178–180 | $C_{22}H_{29}N_3O_2$ | C, H | | | |
| |  | | | | | | | |
| 33 | H | 49 | 124–125 | $C_{22}H_{28}N_2O_2$ | C, H | >800 | Depressant | BP ↓ 82 (>60) |
| 34 | OAc | 95 | 114 | $C_{24}H_{30}N_2O_4$ | C, H, N | 600 | Depressant | Weak tranquillizer BP ↓ 42 (10) |
| |  | | | | | | | |
| 35 | 4-Acetyl-2-methylphenoxy | 80 | 106–108 | $C_{22}H_{28}N_2O_3$ | C, H | 600 | Depressant | |
| 36 | 4-Propionyl-1-naphthyloxy | 72 | 2HCl, 220–222 | $C_{26}H_{30}N_2O_3 \cdot 2HCl$ | N | 800 | Depressant | |

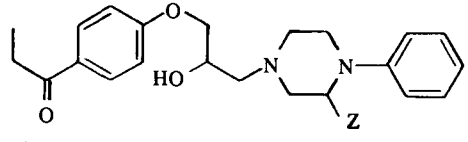
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 37 | 2-Methoxy-4-propenylphenoxy | 50 | 89-91 | $C_{23}H_{30}N_2O_3$ | C, H, N | 600 | Depressant | Counteracts amphetamine-induced hyperactivity. BP ↓ 48 (25) |



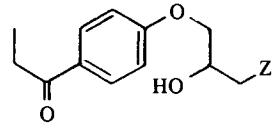
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 38 | Me | 63 | 2HCl, 216 dec | $C_{17}H_{28}N_2O_3Cl_2$ | C, H, N | | | |
| 39 | *o*-$MeOC_6H_4$ | 81 | 132 | $C_{28}H_{30}N_2O_4$ | C, H, N | >500 | Depressant | Weak antihistaminic, counteracts amphetamine-induced toxicity, BP ↓ 24 (>60) |
| 40 | *o*-$ClC_6H_4$ | 62 | 102 | $C_{22}H_{27}N_2O_3Cl$ | C, H, N | >800 | | |
| 41 | *m*-$MeOC_6H_4$ | 86 | 135 | $C_{23}H_{30}N_2O_4$ | C, H, N | >800 | Depressant | |
| 42 | *m*-$F_3CC_6H_4$ | 78 | 2HCl, 184-186 | $C_{23}H_{29}N_2O_3F_3Cl_2$ | N | 600 | Depressant | Counteracts amphetamine-induced hyperactivity, BP ↓ 70 (8) |
| 43 | *p*-$MeOC_6H_4$ | 94 | 159 | $C_{23}H_{30}N_2O_4$ | C, H, N | | | |
| 44 | $PhCH_2$ | 94 | 129-131 | $C_{23}H_{30}N_2O_3$ | C, H | 150 | | BP ↓ 26 |
| 45 | 3,4-$(MeO)_2C_6H_3$ | 60 | 2HCl, 223 dec | $C_{24}H_{34}N_2O_5Cl_2$ | C, H, N | 216 | | Weak antihistaminic, E ↓ 64 |
| 46 | α-Naphthyl | 80 | 126-128 | $C_{26}H_{30}N_2O_3$ | N | >800 | | |
| 47 | 1-[3-(*p*-Propionylphenoxy)-2-hydroxy]propyl | 64 | 140-142 | $C_{28}H_{38}N_2O_6$ | C, H, N | >800 | Stimulant | |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 48 | OAc | 95 | 2HCl, 123-126 dec | $C_{25}H_{34}N_2O_5Cl_2$ | N | | | |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 49 | $CH_3$ | 71 | 121-123 | $C_{23}H_{30}N_2O_3$ | N | 800 | Depressant | BP ↓ 50 (40) |



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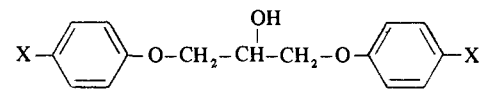
|---|---|---|---|---|---|---|---|---|
| 50 | Morpholinyl | 89 | 105 | $C_{16}H_{23}NO_4$ | C, H, N | 100 | Depressant | Weak antihistaminic |
| 51 | Piperidyl | 78 | 78 | $C_{17}H_{25}NO_3$ | C, H, N | | | |
| 52 | 4-Hydroxy-4-phenylpiperidyl | 83 | 185 | $C_{23}H_{29}NO_4$ | C, H, N | 100 | | Weak anticonvulsant and antihistaminic, BP ↓ 54 (3) |
| 53 | 4-Phenylpiperidyl | 65 | 94-96 | $C_{23}H_{29}NO_3$ | C, H, N | 300 | Depressant | Antihistaminic, BP ↓ 40 (40), E ↓ 63 |
| 54 | 4-Phenyl-3-piperidienyl | 88 | 152-154 | $C_{23}H_{27}NO_3$ | C, H, N | 150 | Depressant | BP ↓ 16 (25), E ↓ 25 |
| 55 | β-Phenylethylamino | 52 | 85 | $C_{20}H_{25}NO_3$ | N | 90 | Depressant | |
| 56 | β-Hydroxy-β-phenylethylamino | 35 | 147 | $C_{20}H_{25}NO_4$ | C, H, N | 800 | Depressant | Anorexic, $ED_{50}$ 25 mg/kg |

Table II (Continued)

| No. | Z | Yield, % | Mp,[a] °C | Formula | Analysis | $LD_{50}$, mg/kg mice ip | Gross effects[b] | Other noteworthy effects[c] |
|---|---|---|---|---|---|---|---|---|
| 57 | β-(3,4-Dimethoxyphenyl)ethylamino | 47 | HCl, 144 | $C_{22}H_{30}NO_5Cl$ | C, H, N | 292 | | BP ↓ 54 (>60), E ↓ 41 |
| 58 | β-Diethylaminoethylamino | 50 | 72-74 | $C_{18}H_{30}N_2O_3$ | C, H, N | 300 | Stimulant | BP ↓ 30 (10) |
| 59 | Diisopropylamino | 80 | HCl, 141 | $C_{18}H_{30}NO_3Cl$ | C, H, N | 228 | Stimulant | |
| 60 | α-Methyl-β-phenylethylamino | 53 | HCl, 160-162 | $C_{21}H_{27}NO_3 \cdot HCl$ | N | 150 | | |
| 61 | α-Methyl-β-phenylethylaminomethyl | 51 | HCl, 160-163 | $C_{22}H_{30}NO_3Cl$ | N | >150 | | |
| 62 | 4-Methyl-2-iminopyridyl | | 184-186 | $C_{18}H_{22}N_2O_3$ | C, H, N | 300 | Depressant | |
| 63 | 3-Methyl-2-iminopyridyl | 71 | 173-175 | $C_{18}H_{22}N_2O_3$ | C, H, N | | | |
| 64 | 2-Imino-4-methylpyridyl | 66 | 188-189 | $C_{19}H_{22}N_2O_3$ | C, H, N | 300 | | |

[a]Compds 15-17 were crystd from pyridine-EtOAc and rest of the compds from EtOH and their hydrochlorides from MeOH-$Et_2O$. [b]Stimulant implies alertness, straub phenomenon, excitement, hyperreflexia, preconvulsiveness, and convulsions; depressant implies reduced spontaneous motor activity, ataxia, loss of righting reflex. [c]Antidepressant implies (i) CVS, with low doses of drug the norepinephrine (NE) and epinephrine (E) responses are increased, medium dose of drug the NE and E responses are decreased, and with high dose the E response is reversed and NE response decreased, (ii) CNS, at low doses reserpine antagonism and amphetamine potentiation (mouse) and in high doses amphetamine activity decreased; BP ↓ = fall in blood pressure, measured in nm; E = responses to epinephrine, numbers in parentheses represent time of recovery in minutes; ↓ = block in per cent; - = no noteworthy effect. [d]Compds 15-24, 26, 27, 30, 31, 35-47, 49-54, and 59-64 were prepd as described for 16. Compds 55-58 were prepd as described for 56 and 34, and 48 as described for 34. Prepn of 25, 28, 29, 32, and 33 is described in the Experimental Section.

Table III

| No | X[a] | Yield, % | Mp,[b] °C | Formula[c] |
|---|---|---|---|---|
| |  | | | |
| 65 | p-Ac | 77 | 97-99 | $C_{19}H_{20}O_5$ |
| 66 | p-COEt | 75 | 89-91 | $C_{21}H_{24}O_5$ |
| 67 | p-COPr | 70 | 72-74 | $C_{23}H_{28}O_5$ |
| 68 | p-$CO_2Et$ | 78 | 88-89 | $C_{21}H_{24}O_7$ |
| 69 | p-CO-◁ | 71 | 129-31 | $C_{23}H_{24}O_5$ |
| 70 | p-SOEt | 62 | 66 | $C_{19}H_{24}S_2O_5$ |
| 71 | p-$SO_2Et$ | 70 | 125-26 | $C_{19}H_{24}S_2O_7$ |

[a]Compd 65 was prepd by method i and 66-71 by method ii (Experimental Section). [b]Crystd (aq EtOH, $C_6H_6$-hexane or $CHCl_3$-hexane). [c]All compds were analyzed for C, H.

l.), and the soln was refluxed for 15 hr in the presence of aq NaOH (1.5 ml, 50%). The progress of the reaction was monitored by tlc and the product worked up in the usual manner.

**1-(p-Propionylphenoxy)-3-($N^4$-phenylpiperazinyl)propan-2-ol (16).** A soln of 1-(p-propionylphenoxy)-2,3-epoxypropane[13] (5.15 g, 25 mmoles) in EtOH (30 ml) was added to N-phenylpiperazine (4.86 g, 25 mmoles) in EtOH. The mixt was refluxed for 3 hr; colorless crystals started sepg during the first hr. The product was filtered and crystd (pyridine-EtOAc or $Me_2CO$).

**1-(p-Propionylphenoxy)-3-[(2-hydroxyphenethyl)amino]propan-2-ol (56).** A mixt of 1-(p-propionylphenoxy)-2,3-epoxypropane[13] (5.15 g, 25 mmoles) and phenylethanolamine (4.1 g, 30 mmoles) in aq EtOH (40 ml) was heated for 5 hr at 80°. On cooling the product sepd as a colorless cryst mass, which was filtered and crystd (EtOH).

**1-(p-Cinnamoylphenoxy)-2,3-epoxypropane (22).** A soln of 1-(p-acetylphenoxy)-2,3-epoxypropane[13] (1.52 g, 8 mmoles) in EtOH (8-10 ml) was cooled in an ice-bath, PhCHO (0.7 ml) and aq NaOH (4.0 g in 6 ml of $H_2O$) were added, and the mixt was stirred for 30 min in an ice-bath and then for 3 hr at 10-15°, and cooled overnight; the sepd product was collected by filtration, washed with aq EtOH, and crystd (EtOH); ir (KBr) 1656 (C=C-C=O). 920, 867 $cm^{-1}$ (epoxy).

**1-[p-(β-Phenylpropionyl)phenoxy]-2,3-epoxypropane (25).** A soln of 22 (1.5 g) in EtOH was hydrogenated over 10% Pd/C (0.2 g). After absorption of 1 mole of $H_2$, the catalyst was filtered off, and the filtrate was concd to dryness. Its $C_6H_6$ soln was purified by chromatog on silica; ir (KBr) 1672 (C=O), 912, 869 $cm^{-1}$ (epoxy).

**1-[p-(α-Hydroxypropyl)phenoxy]-3-($N^4$-phenylpiperazinyl)propan-2-ol (28).** Compd 16 (1.84 g, 5 mmoles) was suspended in MeOH and treated with powd $NaBH_4$ (0.25 g) in 3 portions. The mixt was stirred for 24 hr at 25-30° followed by refluxing for 2 hr on a steam bath. The product was worked up in the usual manner.

**1-[p-(α-Methylpropenyl)phenoxy]-3-($N^4$phenylpiperazinyl)propan-2-ol (29).** A hot soln of 16 (3.6 g, 10 mmoles) in anisole was added in 5 min to a stirred suspension of MeMgI (prepd from 2.0 g of Mg and 11.2 g of MeI) in $Et_2O$ (50 ml) and anisole (25 ml). The reaction mixt was heated slowly to distil off $Et_2O$, then kept 5 min at 160° and then cooled with stirring. The complex was decompd by adding a cold soln of $NH_4Cl$ (15 g in $H_2O$), the org layer sepd and worked up in the usual manner. The product was converted to its hydrochloride in $Et_2O$.

**1-(p-Propionylanilino)-3-($N^4$-phenylpiperazinyl)propane (32).** A soln of p-propionylaniline (0.75 g, 5 mmoles) and 1-chloro-3-($N^4$-phenylpiperazinyl)propan-2-ol[14] (1.3 g, 5 mmoles) in o-$Cl_2C_6H_4$ was refluxed for 3 hr and cooled, and the ppt was filtered off and crystd (EtOH).

**1-(p-Propionylphenoxy)-3-($N^4$-phenylpiperazinyl)propane (33).** A soln of 1-chloro-3-($N^4$-phenylpiperazinyl)propane[15] (2.38 g, 10 mmoles) in MeOH (15 ml) was added in 50 min to a soln of p-hydroxypropiophenone (1.5 g, 10 mmoles) in MeOH (15 ml) contg NaOH (0.4 g), and the mixt was stirred for 3 hr at 65°, cooled, and dild with $H_2O$, and the ppt was filtered and crystd (aq EtOH).

**1-(p-Propionylphenoxy)-2-acetoxy-3-($N^4$-phenylpiperazinyl)propane (34).** A pyridine soln of 16 (1.23 g, 3.3 mmoles) was treated at room temp with $Ac_2O$ (0.7 ml, 7.3 mmoles) for 20 hr. The reacn mixt was concd to dryness under vacuum and the residual oil was crystd (EtOH).

**O-p-Propionylphenyl Dimethylthiocarbamate (72).** NaH (3.4 g, 60 mmoles; 50% in oil) was added in small portions to a stirred soln of p-hydroxypropiophenone (9.0 g, 60 mmoles) in dry DMF (45 ml). After $H_2$ evoln ceased the soln was cooled to 10° in an ice bath and dimethylthiocarbamoyl chloride (10 g, 80 mmoles) was added all at

once. The temp rose rapidly to 40°. The mixt was then heated during 1 hr to 80°, cooled, and poured onto aq KOH (200 ml, 1%) cooled in ice. The resulting solid was filtered and crystd from EtOH; mp 101-102°; ir (KBr) 1675 (C=O), 1130 and 1140 $cm^{-1}$ (C=S); nmr ($CDCl_3$) 8.78 (t, 3, $CH_3$, $J$ = 7 cps), 7.00 (q, 2, $CH_2$, $J$ = 7 cps), 6.64 (s, 3, $NCH_3$), 6.54 (s, 3, $NCH_3$). *Anal.* ($C_{12}H_{15}NO_2S$) C, H, N.

*S-p*-**Propionylphenyl Dimethylthiocarbamate (73).** Compd 72 was heated at 240-245° for 40 min, the conversion was checked on tlc and the product crystd (EtOH); mp 85-87°; ir (KBr), 1686 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 6.94 (s, 6, $N=(CH_3)_2$). *Anal.* ($C_{12}H_{15}NO_2S$) C, H, N.

*p*-**Propionylthiophenol (74).** A soln of 73 (0.95 g) in MeOH (10 ml) contg aq NaOH (1.5 ml, 10%) was refluxed for 4 hr under $N_2$. The soln was concd to dryness, the residue was suspended in $H_2O$, and extd with $Et_2O$. The aq layer was acidified with dil HCl and extd with $Et_2O$, which on concn gave 0.6 g (90%) of the thiophenol; mp 47-49°; nmr ($CDCl_3$) 8.76 (t, 3, $CH_3$, $J$ = 7 cps), 7.04 (q, 2, $CH_2$, $J$ = 7 cps), 2.48 (d each splitting into t, 2, ArH ortho to SH), 2.08 (d each splitting into t, ArH, ortho to C=O) for ArH $J$ = 7, 1.5-2.0 and 0.5 cps. *Anal.* ($C_9H_{10}OS$) C, H.

*p*-**Mesyloxyphenyl Ethyl Sulfide (75).** MsCl (12.5 ml, 160 mmoles) was added to a soln of *p*-hydroxyphenyl ethyl sulfide[16] (12.3 g, 80 mmoles) in 160 ml of dry pyridine below 5°, the mixt was kept for 16 hr at 0-5° and poured onto ice-concd HCl (200 ml) with stirring. The ppt which sepd was filtered and crystd (aq MeOH); yield 16 g; mp 63-65°; nmr ($CDCl_3$) 8.71 (t, 3, $CCH_3$, $J$ = 7 cps), 7.09 (q, 2, $CH_2$, $J$ = 7 cps), 6.89 (s, 3, $OSO_2CH_3$), 2.55-2.82 (m, 4, ArH).

*p*-**Ethylsulfonylphenyl Methanesulfonate (76).** A mixt of 75 (6.9 g, 30 mmoles), $H_2O_2$ (30 ml of 30%, 270 mmoles), and glacial AcOH (40 ml) was heated for 30 min under reflux. The mixt was poured onto ice, the ppt which sepd was filtered and washed with $H_2O$; yield 6.2 g; mp 90-92°; nmr ($CDCl_3$) 8.72 (t, 3, $CH_3$, $J$ = 7 cps), 6.83 (q, 2, $SO_2CH_2$, $J$ = 7 cps), 6.7 (s, 3, $OSO_2CH_3$). *Anal.* ($C_9H_{12}S_2O_5$) C, H.

*p*-**Ethylsulfinylphenyl Methanesulfonate (77).** Fuming $HNO_3$ (1.01 g, 16 mmoles) in $Ac_2O$ (8 ml) was added slowly under stirring to a soln of 75 (6.9 g, 30 mmoles) in $Ac_2O$ (8 ml) below −10°. The mixt was kept at 0-5° for another 20 hr, poured onto ice-$H_2O$ and neutralized with $NaHCO_3$. It was then extd with $CHCl_3$, washed with satd NaCl, and dried ($Na_2SO_4$). Removal of solvent gave oil which was purified by passing its $C_6H_6$ soln through an alumina column to yield 6.0 g of colorless oil, crystd ($C_6H_6$-hexane); mp 68-70°. *Anal.* ($C_9H_{12}S_2O_4$) C, H.

**Cyclopropyl** *p*-**Hydroxyphenyl Ketone (78).** *p*-Hydroxy-γ-chlorobutyrophenone[17] (9.9 g, 50 mmoles) was added, in portions during 20 min, to a refluxing soln of aq NaOH (8 ml, 50%). After addn of half of the compd, aq NaOH (35 ml, 25%) was added followed by addn of the remaining chloro ketone. The mixt was heated to 140° and an addnl 8 g of NaOH was added. A yellow ppt sepd out which remained undissolved by heating and stirring. After 1 hr, 10 ml of $H_2O$ was added to dissolve the solid and stirred with heating at 140° for another 1 hr. The reaction mixt was cooled, dild with $H_2O$, and neutralized with AcOH. The ppt was filtered, air-dried, and extd with $CHCl_3$. The ext concd and crystd ($CHCl_3$-hexane); yield 5.6 g (70%); mp 95-99°; nmr ($CDCl_3$) 8.6-9.1 (complex multiplet, 4, cyclopropyl $CH_2$ 7.1-7.5 (complex multiplet, 1, $COCH\langle\rangle$), 3.8 (d, 2, ArH, ortho to OH, $J$ = 9 cps), 2.79 (d, 1, ArH, ortho to CO, $J$ = 9 cps), 2.3-3.2 (broad hump, 1, $D_2O$ exchangeable, OH); mass fragmentation, $M^+$ 162 and other prominent fragments at *m/e* 136 ($M^+ - C_2H_2$), 121 ($M^+ - C_3H_5$), 93 ($M^+ - C_4H_5O$), 65 and 39 (cyclopropenyl).

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# Local Anesthetic Activity of 2-Piperazinecarboxanilides


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The synthesis and local anesthetic activity of a series of 2-piperazinecarboxanilides, -toluidides, -xylidides, and -mesidides are described. This series may be described as relatively active local anesthetics exhibiting acceptable irritation liabilities and toxicities. Structure-activity studies revealed the following relationships: increased duration of activity and toxicity with increased alkyl function of the piperazine rings; decreased $pK_1$ and increased distribution coefficient with increased alkyl function of the piperazine rings. Increased duration of activity with decreased $pK_1$ and with increased distribution coefficient, which should follow, was not statistically significant. It appears that the dialkylpiperazine function plays a greater role in altering physicochemical and biological properties than does the anilide function.


N-Substituted piperazinoacyl anilides have been prepared as analogs of procainamide[1] and lidocaine,[2-6] but no C-substituted piperazines have been synthesized as potential local anesthetics. Furthermore, no 2-piperazinecarbox- or -acylanilides have appeared in the literature. In view of the local anesthetic activity reported for 2-piperidine analogs,[7] the synthesis of a series of 2-piperazinecarboxanilide analogs of lidocaine (comprising anilides, toluidides, xylidides,