Table IV

Tests	Oral ED_{50} responses in mg/kg: Compd 30	Compd 40	Phenylbutazone
Antiedema[a]	40	40	17.9
Antipyresis	20.5	18	17.5
Analgetic (AcOH)	130	130	172
Vascular permeability (AcOH and Evans Blue)	160	170	160
Acute oral LD_{50} (mice)	1420	980	760

[a] ED_{50} values.

mole) of LAH in 200 ml of THF. The mixt was refluxed 12 hr and cooled, and the complex was carefully decompd by sequential dropwise addns of 2.9 ml of H_2O, 2.9 ml of 15% NaOH soln, and 8.7 ml of H_2O. After stirring for 3 hr the mixt was filtered, and the filter cake washed with Et_2O. The combined filtrates were dried ($MgSO_4$), filtered, and gassed with dry HCl. The crude HCl salt was crystd from EtOH to give 7.8 g (78%).

4-*p*-Chlorobenzoyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (45). A soln of 5.25 g (0.03 mole) of *p*-chlorobenzoyl chloride in 50 ml of Et_2O was added slowly to a stirred soln of 6.45 g (0.03 mole) of base prepd from **30**, and 2.4 g (0.03 mole) of pyridine in 300 ml of Et_2O. The mixt was stirred 6 hr at room temp and successively washed with H_2O, 5% HCl, H_2O, 5% $NaHCO_3$, and finally with H_2O. The dried Et_2O soln ($MgSO_4$) was concd *in vacuo*. One recrystn from EtOH gave 8.3 g (78%). Other compds prepd by this method were **37**, **38**, **41**, **44**, and **46**.

4-Chloroformyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (31). A satd soln of $COCl_2$ in EtOAc was made by bubbling a slow stream of the gas into 800 ml of EtOAc, chilled in ice, for 30 min. To this was added rapidly a soln of 47 g (0.22 mole) of base prepd from **30**, in a min of EtOAc. The mixt was refluxed for 3 hr and then gassed again with $COCl_2$ for 0.5 hr. The hot mixt was filtered, and the filtrate was washed with H_2O, and dried ($MgSO_4$). The dry filtrate was concd to an oil which crystd. One recrystn from EtOAc gave 21 g (43%).

4,5-Dihydro-1,3-dimethyl-4(2-propynylcarbamoyl)-1*H*-pyrazolo-[3,4-*b*][1,4]benzoxazepine (43). A soln of 2.2 g (0.04 mole) of propargylamine and 4.56 g (0.02 mole) of **31** in 100 ml of EtOAc was stirred 12 hr at room temp. The soln was washed with H_2O, dried ($MgSO_4$), and concd to a solid. Crude product was crystd from EtOAc to give 3.2 g (56%).

4-Azidoformyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (32). A soln of 4.56 g (0.02 mole) of **31** and 2.6 g (0.04 mole) of NaN_3 in 100 ml of 90% Me_2CO–H_2O was stirred for 12 hr. The soln was concd, and the residue was taken up in Et_2O and filtered, and the filtrate was dried ($MgSO_4$). The solid obtd upon concn was crystd from Skelly B to give 1.2 g (22%).

4-Carbamoyl and Thiocarbamoyl Derivatives of 4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine. A soln (0.037 mole) of RNCO or RNCS and 8 g (0.037 mole) of base prepd from **30** in 250 ml of Et_2O was stirred for 12 hr. The soln was concd, and the resulting solids were crystd to give yields ranging from 55 to 88%. Compds **39**, **42**, **47**, and **48** were prepd in this manner.

4,5-Dihydro-1,3-dimethyl-4-formyl-1*H*-pyrazolo[3,4-*b*][1,4]-benzoxazepine (33). Compd **30** (6.4 g, 0.03 mole) was refluxed for 2 hr in 75 ml of ethyl formate. The soln was concd and the oil chilled to effect crystn. Recrystn from Skelly B gave 4.3 g (60%).

5-Carbamoyl-4,5-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (34). An aq soln of KNCO (3.3 g, 0.04 mole) was added to 10 g (0.04 mole) of **31** in 70 ml of H_2O. After 1 hr the solid was collected and washed with H_2O. Crystn from EtOH gave 6.3 g (61%).

4,5-Dihydro-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine (36). A soln of 21.5 g (0.10 mole) of base prepd from **30** in 50 ml of dioxane was added to a stirred mixt of 4.8 g (0.10 mole) of NaH in 150 ml of dioxane. The mixt was heated to 70° for 2 hr and then cooled to 20° while a soln of 14.2 g (0.10 mole) of MeI in an equal vol of dioxane was added dropwise. The temp was then raised to 40° for 3 hr. After removal of solvent, the residue was taken up in 5% HCl and washed with Et_2O. The acid soln was basified, extd with Et_2O, dried, and filtered, and the filtrate was evapd to yield a solid. The solid crystd from Skelly B to give 15.6 g (67%). Compd **40** was also prepd by this method.

References

(1) W. E. Coyne and J. W. Cusic, *J. Med. Chem.*, **10**, 541 (1967).
(2) Karl Thomae, French Patent 1,510,324 (1968); *Chem. Abstr.*, **70**, 47516 (1969).
(3) Karl Thomae, British Patent 1,055,221 (1967); *Chem. Abstr.*, **66**, 65542 (1967).
(4) C. Musante, *Gazz. Chim. Ital.*, **75**, 109 (1945).
(5) A. O. Geiszler, U. S. Patent 3,121,092 (1962).
(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(7) B. A. Whittle, *Brit. J. Pharm. Chem.*, **22**, 296 (1964).

Studies on Cardiovascular Drugs. 5.[1] 1-Amino-3-phenoxy-2-propanol Derivatives as β-Adrenergic Blocking Agents

Michio Nakanishi,* Tomio Muro, Yasuaki Chihara, Hiroshi Imamura, and Tooru Nakao

Research Laboratories, Yoshitomi Pharmaceutical Industries, Ltd. Yoshitomi-cho, Chikujo-gun, Fukuoka-ken, Japan.

Received June 22, 1971

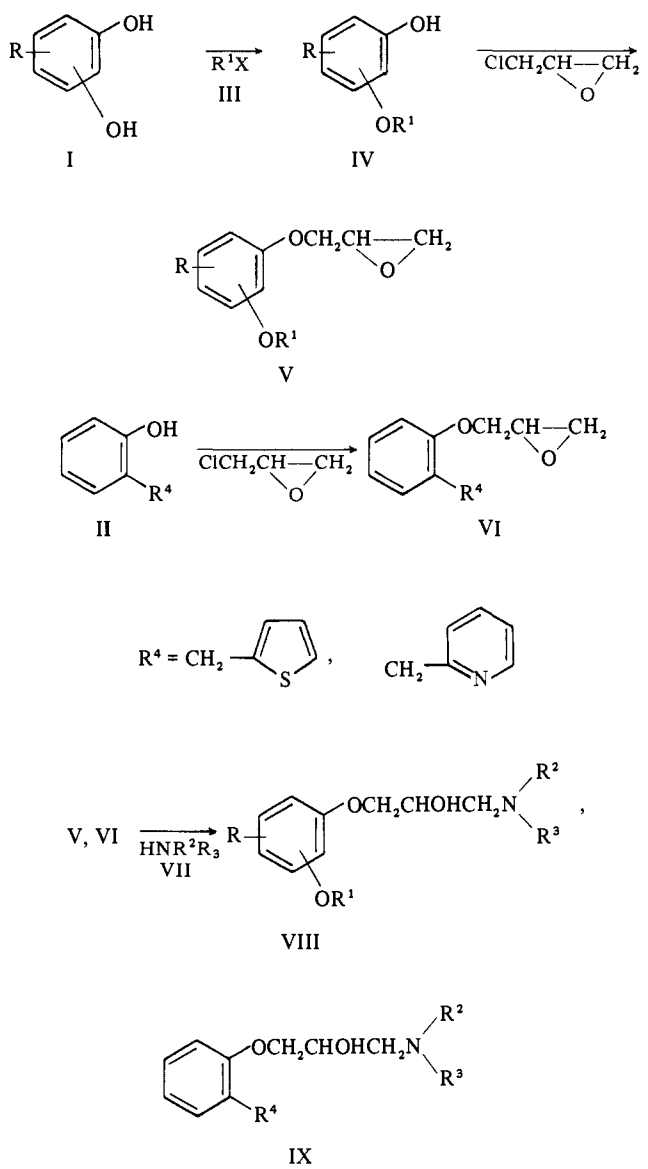
Several 1-amino-3-(substituted phenoxy)-2-propanols have been synthesized and examined for adrenergic β-receptor blocking activity. Of the compds synthesized and tested, 1-*tert*-butylamino-3-[*o*-(furfuryloxy)-phenoxy]-2-propanol (**24**), 1-[*o*-(allyloxymethoxy)phenoxy]-3-*tert*-butylamino-2-propanol (**21**), 1-*tert*-butylamino-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]-2-propanol (**26a**, **26b**), and 1-*tert*-butylamino-3-[*o*-(methoxymethoxy)phenoxy]-2-propanol (**2**) showed potent activity.

A series of 1-amino-3-naphthoxy-2-propanols was synthesized by Crowther, *et al.*,[2] and proved to possess potent adrenergic β-receptor blocking properties. Among these compounds, 1-isopropylamino-3-(1-naphthoxy)-2-propanol (propranolol) was selected and has been used in the treatment of various cardiac arrhythmias and angina pectoris. Many synthetic and pharmacological investigations[3] on 1-amino-3-bicyclic aromaticoxy-2-propanols have been pursued by a number of workers.

The syntheses and adrenergic β-receptor blocking activities of 1-amino-3-(substituted phenoxy)-2-propanols were reported by Crowther, *et al.*[4] They showed that compds bearing substituents on the benzene nucleus, such as alkyl, alkoxy, aryloxy, arylthio, OH, Cl, and NO_2, were highly active. These findings prompted us to synthesize some further 1-amino-3-phenoxy-2-propanol derivatives bearing substituents on the benzene nucleus and to evaluate their pharmacological properties in comparison with propranolol.

Chemistry. The dihydroxybenzenes I were allowed to react with the halides III to give the substituted phenols IV, and these (II[5] and IV) with epichlorohydrin to afford the corresponding epoxides V and VI. Finally, the epoxides (V, VI) were treated with amine VII to give the desired compds

Scheme I



VIII and IX in the usual manner. Formulas and physical properties of the derivatives are shown in Tables I and II.

Assay of the Adrenergic β-Receptor Blocking Activity. Activity was evaluated by the antagonistic activity of test compounds to the relaxing effect of isoproterenol. A guinea pig weighing 250–350 g was sacrificed and its tracheal tube was removed. A tracheal strip prepn was made according to Takagi, *et al.*,[6] and suspended in 20 ml of organ bath filled with aerated Tyrode solution at 37°. An initial basal tension of 0.5 g was applied to the tracheal prepn. A constant response of the prepn to ACh was induced by repeated administration of ACh at 10^{-5} g/ml into the bath. Following this procedure, a cumulative concn response curve of isoproterenol was determined before and after administration of test compds. Isoproterenol was added into the tube beginning with 10^{-8} g/ml. The activities of test compounds were evaluated by PA_2, which was reported by Van Rossum.[7] The results were shown as mean value of the PA_2 of several experiments.

Structure–Activity Relationships. The amino group of 1-amino-3-aryloxy-2-propanols had to be secondary for potent adrenergic β-receptor blocking activity, as also reported by Ghouri, *et al.*,[8] and by Boissier, *et al.*[9] Introduction of a bulky substituent, such as cyclohexyl, into the amino group led to less active compounds, as reported by Schwender, *et al.*[3d] The potency order for amino substituents in this series was *tert*-Bu > *i*-Pr > *sec*-Bu. Introduction of a CN group into alkyl substituents on the amino group reduced the activity.

As for the substituents on benzene nucleus, an *o*-(alkoxy-substituted)alkoxy group enhanced the activity, whereas para isomers (**3** and **22**) showed low activity. The lowering of the activity was observed when either the bulkiness of an alkyl group or the chain length of an alkylene group of alkoxy-substituted alkoxy group on the benzene nucleus became larger or longer, respectively. In this type of substituent an allyloxymethoxy group unexpectedly enhanced the activity. It was noteworthy that tetrahydrofurfuryloxy group, which was considered to be a cyclized form of 2-propyloxyethoxy group, potentiated the activity, while the tetrahydropyranyl-2-methoxy group did not.

The compounds bearing *o*-furfuryloxy, *o*-[(2-thienyl)-methoxy], *o*-[(3-pyridyl)methoxy], and *o*-[(2-pyridyl)-methyl] groups showed potent activity, but those with an *o*-[(2-thienyl)methyl] group showed moderate activity. The potency order observed with ortho substitution on a benzene nucleus in the 1-*tert*-butylamino-3-(substituted phenoxy)-2-propanol series was furfuryloxy (**24**) > allyloxymethoxy (**21**) > tetrahydrofurfuryloxy (**26a**) > methoxymethoxy (**2**), 2-methylthioethoxy (**20**) > ethoxymethoxy (**6**), 2-thienylmethoxy (**28**) > 3-pyridylmethoxy (**32**), 2-pyridylmethyl (**37**) > 2-methoxyethoxy (**13**) > tetrahydropyranyl-2-methoxy (**35**) > 2-pyridyloxy (**33**), benzyloxymethoxy (**10**) > 2-phenyloxyethoxy (**18**), 2-thienylmethyl (**38**).

As described above, the compounds showing PA_2 values above 8.75 were **2**, **21**, **24**, and **26a**. Further pharmacological and chemical studies on **26a** and **26b** are in progress in view of their low toxicity and chemical stability.

Experimental Section

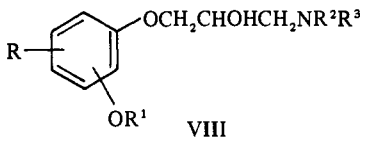
All melting points were determined in an open capillary tube in a bath and are uncorrected. Representative procedures for the syntheses of the compds listed in Tables I and II are given below.

***o*-Furfuryloxyphenol.** Into a mixt of 47.5 g (0.43 mole) of pyrocatechol, 60 g (0.435 mole) of K_2CO_3, and 300 ml of Me_2CO was dropped 50 g (0.43 mole) of furfuryl chloride[10] with stirring at room temp. After addn, the mixt was gently refluxed for 7 hr and filtered to remove insol material. The filtrate was evapd to dryness *in vacuo*. The residual oil was dissolved in C_6H_6 and insol resinous material was removed (Celite). The soln was extd with aq 5% NaOH, and the ext was acidified (HCl). The sepd oil was extd with C_6H_6, washed with aq 5% $NaHCO_3$ and H_2O, dried ($MgSO_4$), and concd to dryness. The residue was distd to give 40 g (48.8%) of the product, bp 105–112° (0.01 mm), $n^{20}D$ 1.5672.

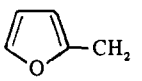
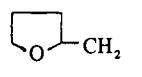
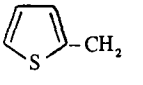
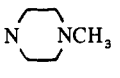
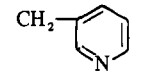
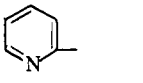
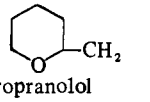
***o*-(2-Pyridyloxy)phenol.** A mixt of 11.0 g (0.1 mole) of pyrocatechol, 14.5 g (0.1 mole) of K_2CO_3, 0.1 g of KI, a small amt of Cu powder, and 16.0 g (0.1 mole) of 2-bromopyridine in 60 ml of DMF was stirred at 110–120° for 10 hr, then filtered, and the filtrate was evapd to dryness *in vacuo*. The oily residue was dissolved in C_6H_6 and extd with aq 5% NaOH. The ext was acidified with 5% HCl and then basified with $NaHCO_3$. The solid was collected and recrystd from MeOH–H_2O to give 10.0 g (53.5%) of the product, mp 108–111°. *Anal.* ($C_{11}H_9NO_2$) C, H, N.

1,2-Epoxy-3-[*o*-(methoxymethoxy)phenoxy]propane. To a soln of 3.3 g (0.059 mole) of KOH in 50 ml of H_2O were added 8.5 g (0.055 mole) of *o*-(methoxymethoxy)phenol[11] and 5.3 g (0.057 mole) of epichlorohydrin. The mixt was stirred at room temp for 7 hr, then extd with C_6H_6. The ext was washed with H_2O and dried ($MgSO_4$). C_6H_6 was removed *in vacuo* and the residue was distd to give 7.0 g (64%) of the product, which crystd on standing, bp 135–140° (0.12 mm), mp 30–33°.

Table I



VIII

No.	R	R¹	R²	R³	Mp, °C	Crystn solvent	Formula[a]	PA_2 value[g]
1	H	2 CH_3OCH_2	H	*i*-Pr	145–146	MeOH–Et_2O	$C_{14}H_{23}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.32 (n = 9)
2	H	2 CH_3OCH_2	H	*tert*-Bu	162–163	MeOH–Et_2O	$C_{15}H_{25}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.75 (n = 8)
3	H	4 CH_3OCH_2	H	*i*-Pr	95–98	MeOH–Et_2O	$C_{14}H_{23}NO_4 \cdot C_4H_4O_4$[b]	6.38 (n = 4)
4	H	2 *i*-$C_3H_7OCH_2$	H	C_6H_{11}	115–117	Me_2CO–Et_2O	$C_{19}H_{31}NO_4 \cdot 0.5C_4H_4O_4$[b]	7.24 (n = 4)
5	H	2 CH_3OCH_2	H	$CH(CH_3)C_2H_5$	125–127	EtOH–Et_2O	$C_{15}H_{25}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.16 (n = 10)
6	H	2 $C_2H_5OCH_2$	H	*tert*-Bu	168–171	MeOH–Et_2O	$C_{16}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.70 (n = 4)
7	H	2 CH_3OCH_2	H	H	133–136	MeOH–Et_2O	$C_{11}H_{17}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$[b]	7.98 (n = 6)
8[c]	4- and 5-CH_3	2 CH_3OCH_2	H	*tert*-Bu	136–139	MeOH–Et_2O	$C_{16}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.58 (n = 4)
9[c]	4- and 5-CH_3	2 CH_3OCH_2	H	*i*-Pr	125–127	MeOH–Et_2O	$C_{15}H_{25}NO_4 \cdot 0.5C_4H_4O_4$[b]	7.73 (n = 4)
10	H	2 $C_6H_5CH_2OCH_2$	H	*tert*-Bu	154–156	EtOH–Et_2O	$C_{21}H_{29}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.14 (n = 8)
11	H	2 $CH_2{=}CHCH_2OCH_2$		Piperidyl	120–122	MeOH–Et_2O	$C_{18}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	7.51 (n = 9)
12	H	2 $CH_3O(CH_2)_2$	H	*i*-Pr	50–54	MeOH–Et_2O	$C_{15}H_{25}NO_4 \cdot C_4H_4O_4$[d]	8.27 (n = 5)
13	H	2 $CH_3O(CH_2)_2$	H	*tert*-Bu	140–142	MeOH–Et_2O	$C_{16}H_{27}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$[b]	8.49 (n = 6)
14	H	2 $CH_3O(CH_2)_2$	H	$CH(CH_3)C_2H_5$	85–88	Me_2CO–Et_2O	$C_{16}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.06 (n = 8)
15	H	2 $C_2H_5O(CH_2)_2$	H	*i*-Pr	104–107	MeOH–Et_2O	$C_{16}H_{27}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$[b]	7.43 (n = 4)
16[e]	H	2 $CH_3OCH_2CH(CH_3)$	H	*i*-Pr	108–112	MeOH–Et_2O	$C_{16}H_{27}NO_4 \cdot C_4H_4O_4$[b]	7.78 (n = 4)
17	H	2 $CH_3OCH_2C{\equiv}CCH_2$	H	*i*-Pr	89–92	Me_2CO–Et_2O	$C_{17}H_{25}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$[b]	8.12 (n = 4)
18	H	2 $C_6H_5O(CH_2)_2$	H	*tert*-Bu	152–153	EtOH–Et_2O	$C_{21}H_{29}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.02 (n = 8)
19	H	2 $CH_3O(CH_2)_2$	H	$CH(CH_3)CH_2CN$	102–104	MeOH–Et_2O	$C_{16}H_{24}N_2O_4 \cdot C_4H_4O_4 \cdot 0.5H_2O$[b]	6.42 (n = 4)
20	H	2 $CH_3S(CH_2)_2$	H	*tert*-Bu	138–140	EtCOMe	$C_{16}H_{27}NO_3S \cdot 0.5C_4H_4O_4$[b]	8.74 (n = 6)
21	H	2 $CH_2{=}CHCH_2OCH_2$	H	*tert*-Bu	161–163	MeOH–Et_2O	$C_{17}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.96 (n = 6)
22	H	4 $CH_3O(CH_2)_2$	H	*i*-Pr	92–95	EtCOMe	$C_{15}H_{26}NO_4 \cdot HCl$	6.43 (n = 4)
23	H	2 	H	*i*-Pr	165–166	MeOH–Et_2O	$C_{17}H_{23}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.38 (n = 4)
24	H		H	*tert*-Bu	148–150	MeOH–Et_2O	$C_{18}H_{25}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$[b]	9.05 (n = 12)
25[e]	H	2 	H	*i*-Pr	120–137	EtCOMe–Et_2O	$C_{17}H_{27}NO_4 \cdot 0.5C_4H_4O_4$[b]	8.49 (n = 4)
26a	H		H	*tert*-Bu	151–154	MeOH–Et_2O	$C_{18}H_{29}NO_4 \cdot HCl$	8.81 (n = 8)
26b[f]	H		H	*tert*-Bu	118	MeOH–Et_2O	$C_{18}H_{29}NO_4 \cdot HCl$	8.48 (n = 4)
27[e]	H		H	C_6H_{11}	151–154	MeOH–Et_2O	$C_{20}H_{31}NO_4 \cdot 0.5C_4H_4O_4$[b]	7.66 (n = 4)
28	H	2 	H	*tert*-Bu	142–146	EtOH–Et_2O	$C_{18}H_{25}NO_3S \cdot 0.5C_4H_4O_4 \cdot H_2O$[b]	8.70 (n = 9)
29	H		H	*i*-Pr	179–182	MeOH	$C_{17}H_{23}NO_3S \cdot 0.5C_4H_4O_4$[b]	8.40 (n = 3)
30	H			Piperidyl	148–149	MeOH–Et_2O	$C_{19}H_{25}NO_3S \cdot C_4H_4O_4$[b]	7.79 (n = 4)
31	H				159–161	MeOH	$C_{19}H_{26}N_2O_3S \cdot 2C_4H_4O_4 \cdot 0.5H_2O$[b]	6.98 (n = 4)
32	H	2 	H	*tert*-Bu	142–146	MeOH–Et_2O	$C_{19}H_{26}N_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$[b]	8.57 (n = 7)
33	H	2 	H	*tert*-Bu	198–200	MeOH–Et_2O	$C_{18}H_{24}N_2O_3 \cdot 0.5C_4H_4O_4$[b]	8.15 (n = 4)
34	H			Piperidyl	150–153	EtOH–Et_2O	$C_{19}H_{24}N_2O_3 \cdot C_4H_4O_4$[b]	7.79 (n = 4)
35[e]	H	2 	H	*tert*-Bu	141–145	MeOH–Et_2O	$C_{19}H_{31}NO_4 \cdot C_4H_4O_4$[b]	8.22 (n = 4)
36[e]	H		H	*i*-Pr	125–128	MeOH–Et_2O	$C_{18}H_{29}NO_4 \cdot 0.5C_4H_4O_4$[b]	7.62 (n = 3)
Propranolol					162–164	*n*-PrOH	$C_{16}H_{21}NO_2 \cdot HCl$	8.31 (n = 12)

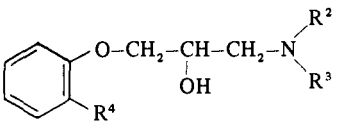
[a] All compds were analyzed for C, H, N. [b] Fumaric acid. [c] Mixt of 4-methyl-2-(methoxymethoxy)phenoxy derivative and 5-methyl-2-(methoxymethoxy)phenoxy derivative. [d] Maleic acid. [e] Mixt of rac diastereoisomers. [f] **26b** is the rac diastereoisomer of **26a**. [g] Antiisoproterenol guinea pig's trachea. n = number of experiments.

1-*tert*-Butylamino-3-[*o*-(methoxymethoxyphenoxy)]-2-propanol Fumarate (2). To a soln of 5.0 g (0.024 mole) of 1,2-epoxy-3-[*o*-(methoxymethoxy)phenoxy]propane in 50 ml of MeOH were added 2.0 g (0.027 mole) of *tert*-$BuNH_2$ and 0.5 g of H_2O. The mixt was allowed to stand at room temp for 48 hr and then evapd *in vacuo*. The residue was dissolved in aq 5% oxalic acid. The aq layer was made alk with KOH, and the sepd oil was extd with C_6H_6. The ext was dried (K_2CO_3). C_6H_6 was removed *in vacuo*, and the residue was distd to give 5.6 g (83%) of the product which crystd on standing, bp 140–145° (0.07 mm), mp 49–52°; fumarate, mp 162–163°. *Anal.* ($C_{17}H_{25}NO_6$) C, H, N.

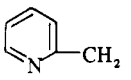
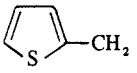
1-*tert*-Butylamino-3-[*o*-(2-pyridylmethyl)phenoxy]-2-propanol Fumarate (37). To a soln of 8.5 g (0.152 mole) of KOH in 350 ml of H_2O were added 25 g (0.135 mole) of *o*-(2-pyridylmethyl)phenol[5] and 40 g (0.433 mole) of epichlorohydrin. The mixt was stirred at room temp for 6 hr, then extd with C_6H_6. The C_6H_6 layer was treated with 5 g of decolorizing charcoal, washed (H_2O), and evapd *in vacuo*. To a soln of the residual oil in 70 ml of MeOH were added 10 g (0.147 mole) of *tert*-$BuNH_2$ and 0.5 g of H_2O. The mixt was allowed to stand at room temp for 72 hr and evapd *in vacuo*. The residual oil was extd with 5% HCl. The aq layer was made alk with NaOH and the isolated oil was extd with C_6H_6. The ext was treated with 5.0 g of decolorizing charcoal, then washed with H_2O. After drying (K_2CO_3), C_6H_6 was removed *in vacuo*. The oily residue yielded 8.5 g (27.5%) of the fumarate, mp 196–200°. *Anal.* ($C_{21}H_{28}N_2O_4$) C, H, N.

1-*tert*-Butylamino-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]-2-propanol Hydrochloride (26a, 26b). To a soln of 77 g (0.308

Table II



IX

No.	R^4	R^2	R^3	Mp, °C	Crystn solvent	Formula[a]	PA_2 value[c]
37		H	*tert*-Bu	196–200	MeOH–Et_2O	$C_{19}H_{26}N_2O_2 \cdot 0.5C_4H_4O_4$[b]	8.57 (n = 12)
38		H	*tert*-Bu	161–162	EtOH–C_6H_6	$C_{18}H_{25}NO_2S \cdot HCl$	8.00 (n = 4)
39			Piperidyl	157–158	Me_2CO–EtOH	$C_{19}H_{25}NO_2S \cdot HCl$	8.09 (n = 4)
40		H	*i*-Pr	95–97	EtOH–C_6H_6	$C_{17}H_{23}NO_2S \cdot HCl$	8.04 (n = 4)
41		H		153–154	EtOH–C_6H_6	$C_{20}H_{27}NO_2S \cdot HCl$	7.44 (n = 3)
42		CH_3	$(CH_2)_2OH$	117–118	Me_2CO–EtOH	$C_{17}H_{23}NO_3S \cdot HCl$	7.53 (n = 3)
43				231–232	MeOH	$C_{19}H_{26}N_2O_2S \cdot 2HCl$	6.95 (n = 3)

[a] See Table I, footnote *a*. [b] Fumaric acid. [c] See Table I, footnote *g*.

mole) of 1,2-epoxy-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]propane in 230 ml of MeOH were added 27 g (0.369 mole) of *tert*-$BuNH_2$ and 3 ml of H_2O. The mixt was allowed to stand at room temp for 48 hr and then evapd *in vacuo*. The residual oil was extd with 10% HCl. The aq layer was made alk with NaOH and the sepd oil was extd with C_6H_6. The ext was dried (K_2CO_3) and concd *in vacuo*, and the residue was distd to give 89 g (89.5%) of 1-*tert*-butylamino-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]-2-propanol, bp 180–186° (0.07 mm).

Anhyd HCl (12.5 g, 0.342 mole) was introduced into a chilled soln of 89 g (0.276 mole) of 1-*tert*-butylamino-3-[*o*-(tetrahydrofurfuryloxy)phenoxy]-2-propanol in 270 ml of $CHCl_3$. After 2 hr, white cryst ppts were filtered, dried *in vacuo*, and recrystd twice from MeOH-*i*-Pr_2O to give 39 g of one of the racemic diastereoisomers of the product, mp 118°. *Anal.* ($C_{18}H_{29}NO_4 \cdot HCl$) C, H, N.

The filtrate was evapd to dryness *in vacuo*. The solid residue was collected and recrystd twice from MeOH-*i*-Pr_2O to give 37 g of the other racemate, mp 151–154°. *Anal.* ($C_{18}H_{29}NO_4 \cdot HCl$) C, H, N.

References

(1) M. Nakanishi, H. Imamura, T. Nakamura, and T. Kimura, *Yakugaku Zasshi*, in press.
(2) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, 11, 1009 (1968).
(3) (a) F. Troxler (Sandoz Ltd.), Swiss Patent 469,002 (1969); *Chem. Abstr.*, 71, 70493 (1969); (b) G. E. Moore and S. R. O'Donnel, *J. Pharm. Pharmacol.*, **22**, 180 (1970); (c) J. Giudicelli, H. Schmitt, and J. R. Boissier, *J. Pharmacol. Exp. Ther.*, **168**, 116 (1969); (d) C. F. Schwender, S. Farber, C. Blaum, and J. Shavel, Jr., *J. Med. Chem.*, 13, 684 (1970); (e) R. D. Robson and H. R. Kaplan, *J. Pharmacol. Exp. Ther.*, **175**, 157 (1970); (f) B. Levy and W. Wasserman, *Brit. J. Pharmacol.*, 39, 139 (1970); (g) C. Goldenberg, R. Wandestrick, F. Binon, and R. Charlier, *Chim. Ther.*, **5(4)**, 285 (1970).
(4) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *J. Med. Chem.*, **12**, 638 (1969).
(5) Ch. J. Morel and W. G. Stoll, *Helv. Chim. Acta*, **33**, 516 (1950).
(6) K. Takagi, I. Takayanagi, and K. Fujie, *Chem. Pharm. Bull.*, 6, 716 (1958).
(7) J. M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).
(8) M. S. K. Ghouri and T. J. Haley, *J. Pharm. Sci.*, **58**, 511 (1969).
(9) J. R. Boissier, R. Ratouis, C. Dumont, P. H. Derible, and J. P. Lavaux, *J. Med. Chem.*, **13**, 971 (1970).
(10) W. R. Kirner, *J. Amer. Chem. Soc.*, **50**, 1955 (1928).
(11) Agripat S. A., French Patent 1,484,502 (1967); *Chem. Abstr.*, 68, 95502 (1968).