mole) in warm EtOH (250 ml) was run into a stirred solution of aminoguanidine nitrate (134 g, 0.975 mole) in 500 ml of H_2O and 750 ml of EtOH. A ppt was formed almost immediately. The suspension was warmed to about 70° to complete the reaction, then allowed to cool to room temp overnight. The ppt was filtered off, washed (H_2O, a little EtOH, and Et_2O), and suspended in 1.8 l. of H_2O. This stirred suspension was warmed at 80° for 30 min and filtered hot to give the guanylhydrazone, mp 228–229° dec, yield 213 g (72%). *Anal.* ($C_9H_{10}Cl_2N_4 \cdot HNO_3$) H, N, O. C: calcd, 35.08; found, 35.53.

The other guanylhydrazones in Table II were prepared similarly.

***N*-Amino-*N'*-phenethylguanidine Hydrochloride.**—*S*-Methylisothiosemicarbazide ·HI (44.3 g, 0.19 mole) was suspended in a mixture of abs EtOH (100 ml) and phenethylamine (23.5 g, 0.193 mole) and heated under gentle reflux until MeSH was no longer evolved. Removal of the EtOH *in vacuo* gave an orange–brown oil which was taken up in *n*-PrOH and diluted with Et_2O. A small crimson ppt was rejected. The filtrate was treated with ethanolic HCl to give a fine white crystalline solid, mp 140–146°, yield 38.7 g. (90%). Three recrystallizations from EtOH gave fine pale-cream plates, mp 156–157° (10.1 g). *Anal.* ($C_9H_{14}N_4 \cdot 2HCl$) C, H, Cl. N: calcd, 22.31; found, 22.78.

2,6-Dichlorophenethylguanidine Sulfate.—A mixture of 2,6-dichlorophenethylamine[12] (24 g, 0.125 mole), *S*-methylisothiouronium sulfate (17.7 g, 0.063 mole), 93% EtOH (50 ml), and H_2O (25 ml) was heated on a steam bath until the evolution of MeSH ceased. On cooling, a solid, mp 255–258°, crystd; yield 12.7 g. Trituration, first with hot H_2O, then with hot EtOH, gave a fine white powder, mp 258–260°, yield 10.4 g. *Anal.* ($C_9H_{11}Cl_2N_3 \cdot 0.5H_2SO_4$) C, H, Cl, N, O, S.

Acknowledgment.—The authors wish to thank Dr. H. Lehner and his staff for the microanalyses and ir spectra.

(12) β-(2,6-Dichlorophenyl)ethylamine · HCl, mp 283–286°) was prepared by catalytic reduction of 2,6-dichlorophenylacetonitrile, bp 134° (4 mm).

Synthesis and Norepinephrine Depleting Activity of Some Metaraminol Ethers

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A series of ethers of (1*R*,2*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) has been prepared. These compounds deplete the mouse heart of norepinephrine. The more potent members, *e.g.*, the ethyl and cyclopropylmethyl ethers, exhibited acute pressor effects in the dog while the *m*- and *p*-chlorobenzyl ethers of metaraminol were found to produce norepinephrine depletion without significant acute pressor action. Evidence is presented to show that the ethers are dealkylated *in vivo* to metaraminol.

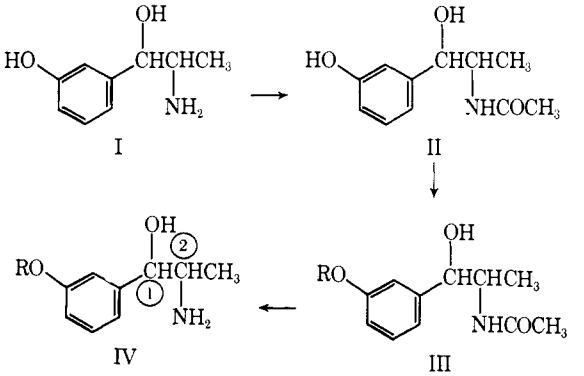
Metaraminol (I), (−)-erythro, appears to possess the attributes of a nearly ideal substitute adrenergic transmitter.[1,2] Thus metaraminol has a high intrinsic ability to enter and displace the normal transmitter norepinephrine from storage sites within the adrenergic neuron; it is released during stimulation of the sympathetic nervous system; it is not a substrate for monoamine oxidase; and it possesses considerably less transmitter potential than norepinephrine.

Crout[2] has reported that metaraminol has a significant antihypertensive effect in a few subjects given the drug orally in small dosages over several days. However, administration of metaraminol under certain conditions can produce acute pressor effects which makes testing of the compound for therapeutic utility precarious. The amino acid α-methyl-*m*-tyrosine, which is metabolized to metaraminol in animals,[3] has also been reported to be effective in lowering the blood pressure of hypertensive patients when administered intravenously.[4] However, the amino acid was not effective after oral administration. In addition central nervous system effects have been observed with α-methyl-*m*-tyrosine which have discouraged further clinical trials.

It seemed desirable, therefore, to develop other derivatives of metaraminol which would be susceptible to metabolic conversion into the phenolic amine without causing acute cardiovascular effects.

Chemistry.—The ethers reported in Table I were prepared from metaraminol (I), (−)-erythro, by the route outlined in Scheme I. The acetyl intermediates

SCHEME I



III were usually not isolated, but were hydrolyzed directly to the optically active ethers IV with NaOH.

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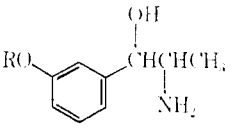
(1) For leading references to the substitute transmitter hypothesis, see: I. J. Kopin, *Annu. Rev. Pharmacol.*, **8**, 377 (1968); C. A. Stone and C. C. Porter, *Advan. Drug Res.*, **4**, 71 (1967).

(2) J. R. Crout, *Circ. Res.*, **18**, **19**, *Suppl.*, **I**, 120 (1966).

(3) A. Carlsson and M. Lindquist, *Acta Physiol. Scand.*, **54**, 87 (1962); P. A. Shore, D. Bushfield, and H. S. Alpers, *J. Pharmacol. Exp. Ther.* **146**, 194 (1964).

(4) D. Horwitz and A. Sjoerdsma, *Life Sci.*, **3**, 41 (1964); H. J. Holtmeier, A. vonKlein-Wisenberg, and F. Marongiu, *Deut. Med. Wochenschr.*, **91**, 198 (1966).

TABLE I: ETHERS OF (1*R*,2*S*)-α-(1-AMINOETHYL)-*m*-HYDROXYBENZYL ALCOHOL (METARAMINOL)



No.	R	Method[a]	Mp, °C	Yield,[b] %	Formula	Analyses	Norepinephrine depletion ED_{50},[c] mg/kg	Norepinephrine depletion ED_{50}[d] as metaraminol, mg/kg	Relative dog pressor activity[e]
1	H						0.10	0.10	1.0
2		A	152.0–153.0	18.6	$C_{18}H_{19}NO_2 \cdot C_4H_4O_4$[f]	C, H, N	0.15	0.11	0.05
3	C_2H_5	B	145.0–146.0	34.7	$C_{11}H_{17}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.19	0.16	0.10
4	$(CH_3)_2CH$	D	125.5–126.5	22.6	$C_{12}H_{19}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.24	0.19	
5		C	141.0–144.0	46.8	$C_{14}H_{17}NO_2S \cdot C_4H_4O_4$[g]	C, H, N	0.30	0.19	<0.01
6	*m*-$FC_6H_4CH_2$	C	136.0–138.5	37.0	$C_{16}H_{18}FNO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.35	0.21	
7	*p*-$FC_6H_4CH_2$	C	147.0–148.5	27.1	$C_{16}H_{18}FNO_2 \cdot CH_4O_3S$[h]	C, H, S	0.39	0.24	
8	CH_3	B	153.4–154.4	48.8	$C_{10}H_{15}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.45	0.42	0.10
9	*m*-$ClC_6H_4CH_2$	D	117.0–120.0[i]	43.8[j]	$C_{16}H_{18}ClNO_2 \cdot CH_4O_3S$[k]	C, H, Cl	0.67	0.38	0
10	$C_6H_5CH(CH_3)$	D	189.4–190.4	14.4	$C_{17}H_{21}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.65	0.43	0
11	$C_6H_5CH_2$	D	160.0–162.0	53.5	$C_{16}H_{19}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.77	0.50	0
12		C	143.5–146.5	32.4	$C_{15}H_{18}N_2O_2 \cdot C_4H_4O_4$[g]	C, H, N	0.80	0.52	
13	*p*-$ClC_6H_4CH_2$	C	193.5–195.5[l]	38.0[k]	$C_{16}H_{18}ClNO_2 \cdot CH_4O_3S$[a]	C, H, Cl	0.85	0.49	0
14	$CH_3(CH_2)_2CH_2$	D	132.0–133.5	32.5	$C_{13}H_{23}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	0.90	0.67	
15	$CH_2{=}CHCH_2$	D	140.5–142.0	28.5	$C_{12}H_{17}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	1.0	0.81	0.08
16	*o*-$ClC_6H_4CH_2$	D	152.8–154.5	38.5	$C_{16}H_{18}ClNO_2 \cdot C_4H_4O_4$[g]	C, H, N	2.53	1.44	0
17	$C_6H_5CH_2CH_2$	D	134.5–136.5	20.1	$C_{17}H_{21}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	2.60	1.72	
18	*p*-$NCC_6H_4CH_2$	C[m]	123.0–126.0	8.2	$C_{17}H_{18}N_2O_2 \cdot CH_4O_3S$[n]	C, H, N	2.80	1.66	
19	*o*-$BrC_6H_4CH_2$	D	134.0–135.0	37.5	$C_{16}H_{18}BrNO_2 \cdot CH_4O_3S$[o]	C, H, N	3.36	1.67	
20	*o*-$CH_3C_6H_4CH_2$	D	129.0–130.5	22.2	$C_{17}H_{21}NO_2 \cdot CH_4O_3S$[p]	C, H, S	5.07	3.38	
21	*m*-$CH_3C_6H_4CH_2$	D	145.0–146.0	26.0	$C_{17}H_{21}NO_2 \cdot CH_4O_3S$[q]	C, H, N	~6.0	~4.0	
22	*p*-$CH_3C_6H_4CH_2$	C	204.0–206.0	27.1	$C_{17}H_{21}NO_2 \cdot CH_4O_3S$[q]	C, H, S	6.44	4.27	
23	$C_6H_{11}CH_2$[r]	D	131.8–135.8	7.2[s]	$C_{16}H_{23}NO_2 \cdot CH_4O_3S$[o]	C, H, N	~10	~6.3	0
24	C_6H_5	E	191.7–201.7	28.0[t]	$C_{15}H_{17}NO_2 \cdot CH_4O_3S$[o]	C, H, N	~51	~35	0
25	*p*-$CH_3OC_6H_4CH_2$	C	176.0–178.0	6.0[u]	$C_{17}H_{21}NO_3 \cdot CH_4O_3S$[q]	C, H, N	[v]		
26	(1*S*,2*R*)-CH_3[w,x]	B	149.9–152.9	40.6	$C_{10}H_{15}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	[y]		
27	(1*S*,2*R*)-$C_6H_5CH_2$[w,x]	D	155.7–156.7	32.1	$C_{16}H_{19}NO_2 \cdot C_4H_4O_4$[g]	C, H, N	[z]		

[a] Prepared by alkylation of the phenol II with the corresponding (A) tosylate, (B) dialkylsulfate, (C) chloride, (D) bromide, (E) diphenyliodonium chloride with 1 equiv of NaOMe as the base in the alkylation reaction in place of K_2CO_3. [b] Overall yield from the amide II. [c] Oral potency of metaraminol ethers in depleting the mouse heart of norepinephrine, 16 hr after administration. Doses calculated as base weight. Six groups of 5 mice per assay except for the *m*-chlorobenzyl ether, 9 groups of 5 mice. [d] Observed ED_{50}'s converted into an equimolar amount of metaraminol base. [e] Administered intraduodenally at 1.25 mg/kg. [f] Hydrogen maleate salt. [g] Methanesulfonate salt. [h] Softens at 113°. [i] Isolated as the hydrogen maleate salt, mp 155.8–157.5°, *Anal.* ($C_{16}H_{18}ClNO_2 \cdot C_4H_4O_4$) C, H, N. [j] Softens at 180°. [k] Isolated as the hydrogen maleate salt, mp 165.5–167.5°, *Anal.* ($C_{16}H_{18}ClNO_2 \cdot C_4H_4O_4$) C, H, N. [l] Acetamido group removed by acid hydrolysis, see Experimental Section. [m] Cyclohexylmethyl. [n] Isolated as the hydrogen maleate salt, mp 165.5–167.5°, *Anal.* ($C_{16}H_{25}NO_2 \cdot C_4H_4O_4$) C, H, N. [o] Isolated as the hydrogen maleate salt, mp 157.0–159.0°, *Anal.* ($C_{15}H_{17}NO_2 \cdot C_4H_4O_4$) C, H, N. [p] Isolated as the hydrogen maleate salt and purified as the methanesulfonate salt. [q] Data not reported because this ether gave a significant metaraminol value when assayed by the *o*-phthalaldehyde method.[14] [r] (+)-Erythro configuration, prepared from (1*S*,2*R*)-α-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol[5] by the same procedure used to prepare the (1*R*,2*S*)-enantiomers. [s] $[\alpha]^{25}D$ (+) 23° (*c* 2, H_2O). [t] No effect at 0.5 mg/kg. [u] $[\alpha]^{25}D$ (+) 18° (*c* 2, H_2O). [v] No effect at 0.7 mg/kg.

In one case (III, R = $CH_2C_6H_5$) the amide was isolated and characterized. Since this sequence of reactions would not be expected to affect the configuration of either of the two asymmetric centers in metaraminol, the ethers IV were assumed to have erythro stereochemistry. This assignment was confirmed by nmr measurements which showed the expected erythro spin coupling constant of 3.5–4.0 Hz for the hydrogens situated on C-1 and C-2[5] of several of the ethers.[6,7] Presence of the threo isomer could not be detected by nmr. In addition, the benzyl ether IV (R = $CH_2C_6H_5$) underwent catalytic hydrogenolysis to a phenol identical with metaraminol. Therefore the ethers have the same absolute configuration as metaraminol, 1R,2S.[7,8]

Metaraminol (I) could be alkylated directly to IV (R = $CH_2C_6H_5$) in excellent yield with benzyl bromide and NaOH in DMSO.[9] However, material prepared by this direct route did not have a satisfactory melting point or analysis. An attempt to prepare the *p*-cyanobenzyl ether (IV, R = *p*-$NCC_6H_4CH_2$) by this method

(5) See formula IV for numbering.

(6) Amino alcohols with the erythro (ephedrine) configuration have been reported to have J_{H_1,H_2} = 2.5–4.3 Hz while those having the threo (pseudoephedrine) configuration have J_{H_1,H_2} = 8–9.6 Hz: P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967); R. H. Uloth, J. R. Kirk, W. A. Gould, and A. A. Larsen, *ibid.*, **9**, 88 (1966); G. G. Lyle and L. K. Keefer, *J. Org. Chem.*, **31**, 3921 (1966); J. D. Hyne, *Can. J. Chem.*, **39**, 2563 (1961).

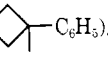
(7) W. S. Saari, A. W. Raab, and E. L. Engelhardt, *J. Med. Chem.*, **11**, 1115 (1968).

(8) Absolute configuration convention of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(9) Selective O-alkylation of tyrosine has been successful by this procedure: S. L. Solar and R. R. Schumaker, *J. Org. Chem.*, **31**, 1996 (1966).

led to isolation of only the O,N-dialkylated metaraminol derivative.

Reaction of cyclopropylmethyl tosylate[10] with II and anhydrous K_2CO_3 in acetone followed by NaOH hydrolysis gave the cyclopropylmethyl ether IV in low yield. The appearance of the ether CH_2 as a doublet centered at 3.87 ppm (2 H, J = 7 Hz) in the nmr spectrum and the presence of a complex cyclopropyl H multiplet at 0.5 ppm indicated that the cyclopropylmethyl group had remained intact during this sequence of reactions.

Solvolysis of cyclopropylmethyl tosylate in a number of solvents has been reported to give mainly unrearranged cyclopropylmethyl products. However under the same conditions, 1-phenylcyclopropylmethyl tosylate undergoes a rearrangement which leads to 1-phenylcyclobutyl products.[10] Reaction of 1-phenylcyclopropylmethyl tosylate with II was investigated with the aim of preparing the phenylcyclobutyl ether (IV, R = ). Unfortunately no pure products could be isolated.

The phenyl ether (IV, R = C_6H_5) was prepared by alkylation of the Na salt of II with diphenyliodonium chloride.[11]

Testing Methods

Norepinephrine and Metaraminol Determinations.—Female mice (Carworth CF 1) were given metaraminol or the ethers listed in Table I orally, except as noted, in aq solutions. Doses were calculated as base weight, mg/kg of body weight. After 16 hr the animals were sacrificed by decapitation, the hearts were excised immediately and chilled at 0° until assayed, not more than 1 hr later. The hearts, in pools of 5, were homogenized in $HClO_4$. The extracts, after purification by Al_2O_3 chromatography,[12] were assayed for norepinephrine[13] and for metaraminol.[14] Results are reported as concentration of amine, either norepinephrine or metaraminol, in the hearts divided by the concn of norepinephrine in the hearts of untreated mice. The metaraminol ethers were assayed by the *o*-phthalaldehyde method[14] before use, and were found to contain insignificant quantities of metaraminol.

Sympathomimetic Actions.—The sympathomimetic actions of the compounds were assessed in anesthetized dogs. The initial study was made to determine whether pressor effects resulted early after iv administration.

Mongrel dogs of either sex were anesthetized with vinbarbital (50 mg/kg, iv) and artificially respired. A Walton–Brodie strain gauge was sutured to the right ventricle to measure myocardial contractility. Femoral arterial pressure and heat rate were monitored continuously during the experiment. The metaraminol ethers were given in doses of 0.05, 0.25, and 1.25 mg/kg iv in the order stated every 15 min, and metaraminol was tested at 0.1 of the above doses. Epinephrine (1.0 μg/kg) was given alternately with the above to assure that the preparation responded to sympathomimetic stimulation. A minimum of 2 animals were studied with each compound.

In order to determine whether sympathomimetic actions could be obtained after a longer interval than observed in the above experiments, additional studies were made after intraduodenal administration of some of these compounds. In these studies, the animals were anesthetized with pentothal (10 mg/kg) and barbital (250 mg/kg); bretylium (2.5 mg/kg, iv) was given 30 min before the test compounds to prevent inordinate increases in heart rate during the 6-hr period of continuously recording heart rate and blood pressure.

Results and Discussion

All of the metaraminol ethers of Table I having the 1R,2S configuration ((−)-erythro) were found to deplete the mouse heart of norepinephrine to some extent. The two ethers prepared in the 1S,2R series ((+)-erythro), **26**, and **27**, were essentially inactive in this respect.[15] The cyclopropylmethyl ether **2** was the most active compound of the series being almost as potent as metaraminol (**1**).

The methyl (**8**) and *m*-chlorobenzyl (**9**) ethers are compared with metaraminol in Table II for their ability to deplete norepinephrine from the hearts of mice. In addition, the concentration of metaraminol, as determined by the relatively specific method of Shore and Alpers,[14] is also tabulated. These data show that as the concentration of norepinephrine in the heart decreases, the amount of metaraminol increases, strongly suggesting that norepinephrine depletion produced by

TABLE II
INHIBITION OF METARAMINOL ETHERS BY SKF-525A

Compound	No.	Dose, mg/kg, po	SKF-525A,[a] 35 mg/kg ip	Heart norepi fract of normal[b]	Heart metaraminol fract of normal norepi[b]
Methyl ether	8	0	0	1.000	
		0	+	1.063	
		0.5	0	0.321	
		0.5	+	0.945	
				0.092[c]	
m-Chlorobenzyl ether	9	0	0	1.000	
		0	+	1.052	
		1.5	0	0.296	0.364
		1.5	+	0.813[d]	0.136
				0.052[c]	0.031[c]
Metaraminol	1	0	0	1.000	
		0	+	1.052	
		0.4	0	0.255	0.386
		0.4	+	0.230[e]	0.405
				0.052[c]	0.031[c]

[a] Given 45 min before metaraminol or the ether. [b] Sixteen hours after administration of metaraminol or the ether; three groups of 5 mice/treatment. [c] Standard deviation. [d] $p < 0.001$. [e] $p > 0.25$.

(10) D. D. Roberts, *J. Org. Chem.*, **30**, 23 (1965); J. W. Wilt and D. D. Roberts, *ibid.*, **27**, 3430 (1962).

(11) F. M. Beringer, A. Brierly, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, **75**, 2708 (1953).

(12) A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Ther.*, **138**, 360 (1962).

(13) C. C. Porter, J. A. Totaro, and A. Burcin, *ibid.*, **150**, 17 (1965).

(14) P. A. Shore and H. S. Alpers, *Life Sci.*, **3**, 551 (1964).

(15) For a discussion of norepinephrine depletion by the threo isomers of α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol, see ref 7, 16, and 17.

(16) M. L. Torchiana, C. C. Porter, and C. A. Stone, *Arch. Int. Pharmacodyn. Ther.*, **174**, 118 (1968).

(17) N. F. Albertson, F. C. McKay, H. E. Lape, J. O. Hoppe, W. H. Selberis, and A. Arnold, *J. Med. Chem.*, **13**, 132 (1970).

the *m*-chlorobenzyl ether is related to its conversion *in vivo* into metaraminol.

Further evidence that metabolism is a necessary prerequisite for depletion of norepinephrine by the metaraminol ethers is the finding that pretreatment with diethylaminoethyl 2,2-diphenylvalerate (usually known as SKF-525A), which inhibits drug-metabolizing enzymes,[18] blocked the norepinephrine-releasing action of the methyl and *m*-chlorobenzyl ethers (Table II). The activity of metaraminol was not influenced by pretreatment with SKF-525A. These results demonstrate that metabolism must occur for the methyl and *m*-chlorobenzyl ethers to be active and in addition, indicates that a microsomal drug metabolizing enzyme system is involved.

The low activity of the phenyl ether **24**, the least active member of the series, is most likely a reflection of the metabolic stability of the diphenyl ether function. The reluctance of diphenyl ethers to undergo metabolic cleavage has been noted previously[19] and is consistent with the view that microsomal O-dealkylation is best understood as a hydroxylation reaction at a saturated C adjacent to O.[20,21] The small amount of norepinephrine depletion observed with the phenyl ether in the mouse is for the most part probably due to release by metaraminol formed by cleavage of the ether bond following an aromatic hydroxylation.[22] Metaraminol was detected in the mouse heart after administration of the phenyl ether.

Following iv administration of metaraminol at 0.005, 0.025, and 0.125 mg/kg to the anesthetized dog, there was a rapid, almost instantaneous, dose-dependent rise in arterial pressure. The pattern of response following injection of the methyl ether **8** was similar to that of metaraminol but was obtained at tenfold higher doses (0.05–1.25 mg/kg). The response also differed from that of metaraminol in that it developed more gradually and reached a maximum 2–3 min after the injection. This delayed response is consistent with the gradual formation of metaraminol from the ether in a relatively slow dealkylation step.

Pressor responses of similar magnitude were also obtained with the cyclopropylmethyl (**2**), ethyl (**3**), and allyl (**15**) ethers. No significant acute sympathomimetic actions were obtained with the other ethers tested at this dose level (Table I). Of the more active norepinephrine-depleting agents listed in Table I, the aliphatic ethers uniformly exhibited greater pressor activity than the benzyl ethers. However, in other experiments in anesthetized dogs, the intraduodenal administration of metaraminol (0.125 mg/kg) and its benzyl ether (**11**) (10 mg/kg) caused definite increases in blood pressure and heart rate. Under similar conditions the *m*-chlorobenzyl (**9**) and *p*-chlorobenzyl (**13**) ethers were without effect.[26] This apparent dichotomy that some ethers exhibiting pressor responses are less potent depletors of norepinephrine (higher ED_{50} values) than other ethers which are not pressor under the same conditions (compare **8** with **5**, **15** with **5**, **9**–**11** and **13** (Table I) and **11** with **9**[26]) is resolved when it is recalled that the ED_{50} values are a measure of the extent of conversion into metaraminol after 16 hr, not the rate of conversion. The pressor responses observed with the aliphatic ethers therefore are probably due to a relatively rapid conversion of these ethers into metaraminol. However an alternate explanation that the simple intact aliphatic ethers have more sympathomimetic action *per se* than the benzyl ethers cannot be excluded at this time.

(18) The effects of SKF-525A on the metabolism of drugs has been reviewed by J. R. Gillette, *Fortschr. Arzneimittelforsch.*, **6**, 49, (1963).

(19) H. G. Bray, S. P. James, W. V. Thorpe, and M. R. Wasdell, *Biochem. J.*, **54**, 547 (1953).

(20) B. B. Brodie, J. R. Gillette, and B. N. LaDu, *Annu. Rev. Biochem.*, **27**, 427 (1958).

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(22) Nuclear hydroxylation of diphenyl ether[23] and cleavage of the diphenyl ether function in thyronine[24] and thyroxine[25] has been reported.

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Experimental Section

All melting points, determined on a Uni-Melt Thomas-Hoover capillary melting point apparatus are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra of all new compounds were consistent with the proposed structures. Nmr spectra were obtained in DOH with a Varian A60-A spectrophorometer using the DOH band at 4.65 ppm as an internal standard. Optical rotations were determined with a Zeiss photoelectric precision polarimeter.

General Method for the Synthesis of Metaraminol Ethers. (1*R*,2*S*)-α-(1-Aminoethyl)-*m*-methoxybenzyl Alcohol Hydrogen Maleate (IV, R = CH_3).—A stirred mixture of 15 g (0.061 mole) of (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol hydrate,[27] 30 g of K_2CO_3, 13.2 g of Me_2SO_4, and 500 ml of Me_2CO was heated at reflux for 8 hr. After cooling, inorganic salts were removed by filtration. The filtrate was concd under reduced pressure to an oily residue which was then heated at reflux for 24 hr with 50 ml of 10% NaOH and 15 ml EtOH. The reaction mixture was concd under reduced pressure to remove most of the EtOH. H_2O was added to bring the total vol to about 100 ml. After satg with NaCl, the crude product was extracted into three 100-ml portions of EtOAc. The EtOAc extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The residue (13 g) was dissolved in EtOH, treated with 15 g of maleic acid, and the hydrogen maleate salt of the MeO derivative precipitated with Et_2O.[27] An analytical sample was obtained by recrystallization from EtOH–Et_2O; $[\alpha]^{25}D$ −24° (*c* 2, H_2O).

Some of the metaraminol ether hydrogen maleate salts prepared by this route were found to contain significant amounts (as much as 1–2%) of a phenolic contaminant, probably metaraminol.[28] This impurity could not be removed completely by repeated recrystallization or by conversion into the base and reformation of the hydrogen maleate salt. The methanesulfonate salts, however, could be obtained essentially free of contaminating phenol.[29]

(1*R*,2*S*)-α-[1-Acetamidoethyl]-*m*-benzyloxybenzyl Alcohol (III, R = $C_6H_5CH_2$).—A mixture of 7.5 g (0.030 mole) of (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol hydrate,[7] 15 g of K_2CO_3, 6.9 g of benzylbromide, and 200 ml of Me_2CO was stirred 24 hr at reflux. After cooling, the reaction mixture was filtered free of inorganic material and most of the Me_2CO removed under reduced pressure. H_2O was added to the residue and the precipitate dried to give 8.2 g (83.1%) of the benzyl ether, mp 137.0–140.0°. Recrystallization from EtOAc–hexane gave an analytical sample, mp 138.0–140.0°. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

(1*R*,2*S*)-α-(1-Aminoethyl)-*m*-benzyloxybenzyl Alcohol Hydrogen Maleate (IV, R = $C_6H_5CH_2$). A.—A solution of 8.2 g (0.0274 mole) of (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-benzyloxybenzyl alcohol in 100 ml of EtOH and 100 ml of 10% NaOH was heated at reflux for 24 hr and then concentrated under reduced pressure to remove most of the EtOH. The residue was dissolved

(26) These results will be reported in more detail in other publications from these laboratories.

(27) Yields and physical constants are recorded in Table I.

(28) Assayed by the fluorometric method of ref 14.

(29) An acid-catalyzed decomposition of the dibasic maleic acid salts during recrystallization may account for formation of the phenol since no significant amounts of contaminant were observed during purification of the monobasic methanesulfonic acid salts.

in a minimum quantity of warm EtOH and converted into the hydrogen maleate salt,[27] $[\alpha]^{25}D$ −15° (c 2, H_2O), as described for the Me ether.

B.—A solution of 2.1 g (0.012 mole) of $PhCH_2Br$ in 10 ml of DMSO was added slowly to a stirred mixture of 2.0 g (0.012 mole) of (1*R*,2*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) in 100 ml of DMSO and 6.0 ml of 2 *N* NaOH at 85°. After addition was complete, the reaction mixture was stirred at 85° for an additional 2 hr and then poured into 500 ml of ice H_2O. After saturating with NaCl, and extracting with four 200-ml portions EtOAc, the organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was converted into the hydrogen maleate salt and recrystallized (EtOH–Et_2O) to give 3.2 g (72%) of product, mp 150.0–154.0°. Repeated recrystallization did not improve the melting point. *Anal.* ($C_{16}H_{19}NO_2 \cdot C_4H_4O_4$)H; C: calcd, 64.32, found 65.16, 65.15.

(1*R*,2*S*)-α-(1-Aminoethyl)-*m*-(4-cyanobenzyloxy)benzyl Alcohol Methanesulfonate (IV, R = $CH_2C_6H_4CN$).—The intermediate (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-(4-cyanobenzyloxy)-benzyl alcohol was prepared by the general method using 9.2 g (0.0405 mole) of (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol hydrate,[7] 7.6 g (0.050 mole) of *p*-cyanobenzyl chloride, and 30.4 g of K_2CO_3 in Me_2CO (500 ml). A solution of 6 g (0.0185 mole) of the amide in EtOH (50 ml) was converted into the corresponding amine by heating 4 hr at reflux with 1 *N* HCl (100 ml). After removing most of the EtOH under reduced pressure, the residue was neutralized with excess satd $NaHCO_3$ solution. The product was extracted into EtOAc, dried (Na_2SO_4), filtered, and concentrated to 4 g of a yellow oil. The crude product was converted into the methanesulfonate salt in the usual manner. When purification proved difficult, the salt was reconverted into the free base with dil NaOH and EtOAc extraction. The 1.7 g of recovered oil was chromatographed on 85 g of silica gel. Elution with $CHCl_3$ then 10–50% MeOH–$CHCl_3$ removed 0.7 g of side products. The desired ether (0.7 g) was eluted from the column with MeOH (900 ml). The methanesulfonate salt was prepared in the usual manner and recrystallized from *i*-PrOH–Et_2O to give an analytical sample.[27]

(1*R*,2*S*)-α-[1-(4-Cyanobenzylamino)ethyl]-*m*-(4-cyanobenzyloxy)benzyl Alcohol Methanesulfonate.—A solution of 3.0 g (0.020 mole) of *p*-cyanobenzyl chloride in 20 ml of DMSO was added slowly to a stirred solution of 3.4 g (0.020 mole) of (1*R*,2*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) in 200 ml of DMSO and 8.0 ml of 2 *N* NaOH at 85°. After stirring 2.5 hr at 85°, the reaction mixture was poured into 1 l. of ice H_2O and extracted with EtOAc (4 × 200 ml). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was converted into the methanesulfonate and recrystallized from *i*-PrOH–Et_2O to give 0.8 g (16.2%) of product, mp 194.5–196.5°. *Anal.* ($C_{25}H_{23}N_3O_2 \cdot CH_4O_3S$) C, H, N.

Hydrogenolysis of (1*R*,2*S*)-α-(1-Aminoethyl)-*m*-benzyloxybenzyl Alcohol.—The free base (1.3 g, 5.06 mmoles), liberated from 2 g of the hydrogen maleate salt of the benzyl ether, was hydrogenated in 25 ml of EtOH with a 5% Pd–C catalyst at atmospheric pressure until 1 equiv of H_2 was taken up. After filtering and concentrating under reduced pressure, the crude product was converted into a fumarate salt (0.86 g), mp 192–195° dec. Further recrystallization (MeOH–EtOAc) gave 0.70 g (61.5%) of the pure fumarate salt of metaraminol, mp 199–200° dec, $[\alpha]^{25}D$ − 22.3° (c 2, H_2O). This product was identical by mmp and nmr with an authentic sample of metaraminol fumarate, mp 200–201° dec, prepared from metaraminol.

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Agonists–Antagonists Derived from Desomorphine and Metopon

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N-Phenethyl, -3-methyl-2-butenyl, and -cyclopropylmethyl derivatives (**3b**, **c**; **4c**, **d**; and **5a**, **b**) of normetopon, nordesomorphine, and 5-methyldihydronormorphine (**3a**, **4b**, and **5**, R = H) have been synthesized and evaluated for analgetic activity (mice) as well as for physical dependence capacity and properties of antagonism (monkeys). Marked separation of favorable and undesirable pharmacologic properties has been achieved in some instances.

It is well documented that the substitution of such radicals as allyl, 3-methyl-2-butenyl, and cyclopropylmethyl for Me on the N of morphine, levorphanol, and certain 6,7-benzomorphans confers a combination of agonist (analgetic) and antagonist properties that renders these molecules much less prone to abuse without markedly impairing their analgetic effectiveness.[1] Similar substitution of phenethyl is known to increase analgetic potency five- to tenfold with some decrease in abuse liability.[1,2] Consequently, we wish to report the preparation and some pharmacologic properties of *N*-3-methyl-2-butenyl- and -cyclopropylmethylnordesomorphine (**4c, d**); *N*-3-methyl-2-butenyl- and -phenethylnormetopon (**3c**, **b**); and *N*-cyclopropylmethyl and -phenethyl derivatives (**5a**, **b**) of the corresponding 6-carbinol. Desomorphine (**4a**)[3] was chosen as a base structure, because it is 10 times more potent than morphine with a rapid onset of action;[4] metopon (**1**)[5] is 3 times as active as morphine after parenteral administration and is very effective orally.[1,4,5]

Nordesomorphine (**4b**), the starting material for **4c**, **d**, was obtained in 20–30% yield by demethylation of the *O*-acetyl derivative of **4a** by either the von Braun method[6] or with diethyl azodicarboxylate.[7] Reaction of **4b** with cyclopropylcarbonyl chloride followed by reduction of the resultant amide with LAH gave **4d**.[8] Compound **4c** resulted from direct alkylation[9] of **4b** with 1-bromo-3-methyl-2-butene.

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