Synthesis and Peripheral Vasodilator Activity of α-[1-(4-Piperidylamino)alkyl]benzyl Alcohols

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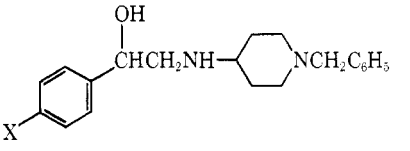
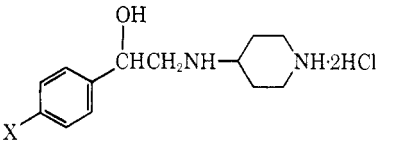
In a search for novel peripheral vasodilator agents related structurally to sympathomimetic phenethanolamines such as 4-hydroxy-α-{1-[(1-methyl-2-phenoxyethyl)amino]ethyl} benzyl alcohol (isoxsuprine) and α-[(butylamino)methyl]-4-hydroxybenzyl alcohol (bamethan), but containing a second amino group on the side chain, a series of α-[1-(4-piperidylamino)alkyl]-benzyl alcohols (Table I) were prepared.

Compds **12** and **13** were prepared by hydrogenolysis in the presence of 10% Pd/C of **4** and **6**, resp. Preparative details for all compounds are given in the Experimental Section.

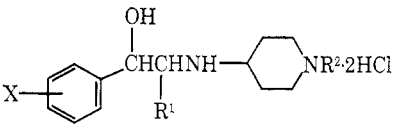


4, X = H
5, X = OH



12, X = H
13, X = OH

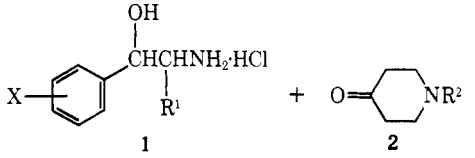
TABLE I



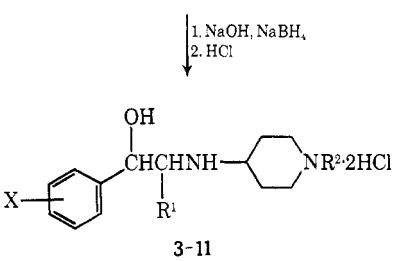
No.	X	R^1	R^2	Mp, °C dec	Yield, %	Formula[a]	Recrystn solvent[b]	Vasodilator potency[c]
3	H	H	CH_3	255–256	67	$C_{14}H_{24}Cl_2N_2O$	A	5.5
4	H	H	$CH_2C_6H_5$	295	66	$C_{20}H_{28}Cl_2N_2O$	B	2.0
5	*p*-HO	H	CH_3	210–211	53	$C_{14}H_{24}Cl_2N_2O_2$	C	11.0
6	*p*-HO	H	$CH_2C_6H_5$	214	26	$C_{20}H_{28}Cl_2N_2O_2$	C	5.1
7	*p*-HO	H	*n*-C_4H_9	201	49	$C_{17}H_{30}Cl_2N_2O_2$	C	13.9
8	*m*-HO	H	*n*-C_4H_9	227–229	49	$C_{17}H_{30}Cl_2N_2O_2$	A	5.0
9	*p*-HO	H	$CH_2CH_2OCH_3$	175–176	45	$C_{16}H_{28}Cl_2N_2O_3$	D	3.9
10	*p*-HO	CH_3	$CH_2CH_2OCH_3$	203–204	23	$C_{17}H_{30}Cl_2N_2O_3$	A	1.7
11	*p*-HO	H	$CH_2CH_2C_6H_5$	278	41	$C_{21}H_{30}Cl_2N_2O_2$	A	15.6
12	H	H	H	259	52	$C_{13}H_{22}Cl_2N_2O$	C	0.9
13	*p*-HO	H	H	*d*	15	$C_{12}H_{22}Cl_2N_2O_2$		2.1

[a] Compds **3, 4, 8, 10, 11,** and **12** were analyzed for C, H, N; **5, 6, 7, 9,** and **13** for C, H, N, Cl. The anal. results were within ±0.4% of the theor values. [b] A, aq 95% EtOH; B, MeOH–EtOH; C, MeOH–*i*-PrOH; D, EtOH. [c] Based on papaverine equal to 100 and isoxsuprine equal to 1000. [d] Amorphous.

Chemistry.—Compds **3–11** were obtained by a reductive alkylation of α-(1-aminoalkyl)benzyl alcohols



1 **2**



3-11

(**1**) with 1-alkyl-4-piperidones (**2**) using $NaBH_4$ as a reducing agent in a manner similar to a procedure previously described.[1]

(1) R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968).

Pharmacology.—The peripheral vasodilator effects of the compounds in dogs were determined by an assay method which measured blood flow through a carotid artery. This method is described in the Experimental Section, and the results are shown in Table I as potency comparisons with papaverine and isoxsuprine. In this assay none of the compounds exhibited sufficient peripheral vasodilator activity for further consideration as clinically effective drugs. The peripheral vasodilator effect ranged from less than 1 to 16% the activity of papaverine and only 0.1 to 1.6% the activity of isoxsuprine.

Experimental Section

Chemistry.—All melting points were obtained in a Mel-Temp apparatus and are reported uncor. Satisfactory ir spectra were recorded for all new compds using a Perkin-Elmer Model 21 spectrophotometer. All elemental anal. results for the compounds were within ±0.4% of the theor values.

α-(1-Aminoalkyl)benzyl Alcohols and 1-Alkyl-4-piperidones.—Except as reported below these compds were commercial chemicals or were known compds prepd as previously described.

1-(2-Methoxyethyl)-4-piperidone (**14**) was prepd from 2-

methoxyethylamine and ethyl acrylate using a 3-step procedure described by Balyard and McElvain[2] for the synthesis of 1-alkyl-4-piperidones. The intermediate *N,N*-bis(β-carboxethoxyethyl)-β-methoxyethylamine boiled at 111° (0.05 mm). The last 2 steps, the cyclization and decarboxylation, were done consecutively without isolation of the intermediate 3-carbethoxy-1-(2-methoxyethyl)-4-piperidone. The final product, a colorless liquid, boiled at 72–73° (0.5 mm). *Anal.* ($C_8H_{15}NO_2$) C, H, N.

α-[1-(1-Alkyl-4-piperidylamino)alkyl]benzyl Alcohols (3–11).—$NaBH_4$ (0.125 mole) was added in small portions over 2 hr to a stirred mixt of *dl*-α-(1-aminoalkyl)-4-hydroxybenzyl alcohol·HCl (0.025 mole), KOH (0.025 mole), and 1-alkyl-4-piperidone (0.177 mole) in 100 ml of MeOH. The reaction mixt was maintained at about 5° by means of an ice bath during the addn. After the addn the mixt was stirred for 1 hr at 20° and then acidified to pH 4 with 4 *N* HCl in EtOH. The mixt was filtered to remove pptd inorg salts and then evapd to an oil. The residual oil was triturated with boiling *i*-PrOH. The resulting white cryst prod was filtered off and recrystd (see Table I).

α-[1-(4-Piperidylamino)alkyl]benzyl Alcohols (12 and 13).—A soln of α-[(1-benzyl-4-piperidylamino)methyl]benzyl alcohol·2HCl (**4** or **6**) (0.085 mole) in 125 ml of aq 80% EtOH was hydrogenated for 6 hr at 3 atm using 5 g of 10% Pd/C as catalyst. The catalyst was removed by filtration, and the filtrate was evapd. The residue was recrystd (Table I).

Pharmacology Assay Method.—The test substances were assayed in anesthetized dogs on the vascular bed supplied by the carotid artery. In this prepn a constant flow (peristaltic) blood pump was interposed between the proximal and distal segments of the right carotid artery. Prior to drug treatment blood flow rate was set to result in a mean perfusion pressure approximately equal to systemic arterial blood pressure. Perfusion pressure was measured distal to the pump. Drug injections were made into the blood stream distal to the pump. Vasodilation was indicated by a decrease in perfusion pressure. Potency comparisons with papaverine were determined from plots of log molar dose *vs.* decrease in perfusion pressure. In this assay isoxsuprine was approximately 10 times more active than papaverine. The results reported in Table I are based upon the arbitrary assignment of papaverine potency at 100.

(2) N. W. Bolyard and S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 922 (1929).

Absolute Configuration of the Optical Isomers of Salbutamol

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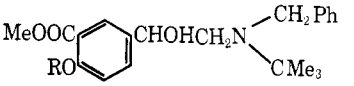
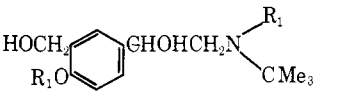
The synthesis and biological properties of the β-sympathomimetic amine, salbutamol (**4**), have been described.[1] This compound is more selective for β_2 receptors than previously known drugs and therefore it was of interest to test each enantiomer to ascertain if the activity resided mainly in the (*R*)-(−) configuration as is the case with other drugs which act at adrenoreceptors.[2]

Attempted resolutions of salbutamol, or any phenolic precursor, were unsuccessful.[3] However, when the phenolic group of the intermediate ester **1** was protected as the benzyl ether **2** then resolution was efficiently achieved with either (+)- or (−)-di-*p*-toluoyltartaric acid. In each case only one isomer formed a crystalline



1, R = H
2, R = $PhCH_2$



3, R_1 = $PhCH_2$
4, R_1 = H

salt and the antipode was recovered from the mother liquors in good yield and reasonable optical purity.

Neutralization of the purified salts liberated the resolved bases **2** which on reduction with LAH followed by catalytic debenzylation gave the required isomers **4**. The (+) and (−) forms were both characterized as their acetate salts.

The β-adrenoreceptive activities of these isomers were compared with those of the racemic compound on the β_1 receptors[4] of the isolated atria of the guinea pig and on the β_2 receptors[4] of the intact trachea of the guinea pig (Table I). In the latter test[5] the (−) isomer was approximately equiactive with the racemate and 80 times more potent than the (+) isomer. A similar pattern was shown in the much weaker effects on the force of contraction of the electrically driven left atrium.[6] However, both isomers were much less active than the racemate in increasing the rate of contraction of the spontaneously beating right atrium.[7] Although this result has been verified on several occasions, the very low order of activity precludes any useful interpretation of the apparent synergism in the racemate.[8]

TABLE I
BIOLOGICAL ACTIVITY OF THE ENANTIOMERS OF SALBUTAMOL

	Biological test[a]		
Compound	Trachea (β_2)	Left atrium (β_1)	Right atrium (β_1)
Racemate	4.3	15,000[b]	1,000
(−) Isomer	6.6	15,000[b]	10,000[b]
(+) Isomer	423	Inactive	100,000[b]

[a] These results represent the ratio of the amount of drug required to produce an equivalent response to a unit of isoprenaline. [b] Denotes partial agonist activity.

Comparison of the CD spectra of the salbutamol isomers with that of (*R*)-(−)-octopamine[9] showed that (−)-salbutamol had the *R* configuration. Both levorotatory compounds showed a clear negative Cotton effect at 276–280 nm. At lower wavelengths, 220–230 nm, the curves tended toward a further negative peak although this is somewhat masked by the high aromatic absorption.

(1) D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, A. C. Ritchie, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," Methuen and Co., London, 1964, pp 282–343.

(3) Similar difficulties in resolving phenolic amines have been described see A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, **52**, 678 (1969).

(4) (a) A. M. Lands, A. Arnold, J. P. McAuliff, F. P. Luduena, and T. G. Brown, Jr., *Nature (London)*, **214**, 597 (1967); (b) A. M. Lands, F. P. Luduena, and H. J. Buzzo, *Life Sci.*, **6**, 2241 (1967).

(5) For pharmacological method see J. B. Farmer and R. A. Coleman, *J. Pharm. Pharmacol.*, **22**, 46 (1970).

(6) For pharmacological method see J. R. Blinks, *J. Pharmacol. Exp. Ther.*, **151**, 221 (1966).

(7) For pharmacological method see J. W. Black, W. A. M. Duncan, and R. G. Shanks, *Brit. J. Pharmacol. Chemother.*, **25**, 577 (1965).

(8) A more detailed pharmacological evaluation of these isomers will be submitted for publication elsewhere by J. B. Farmer and R. J. Marshall.

(9) (a) V. Erspamer, *Nature (London)*, **169**, 375 (1952); (b) T. Kappe and M. D. Armstrong, *J. Med. Chem.*, **7**, 569 (1964).