Tetrahedron Vol 44, No 11, pp 3289 to 3294, 1988
Printed in Great Britain

0040-4020/88 $3.00 + 00
Pergamon Press plc

THE SYNTHESIS OF ANTIHYPERTENSIVE 3-(1,3,4-OXADIAZOL-2-YL)PHENOXYPROPANOLAMINES

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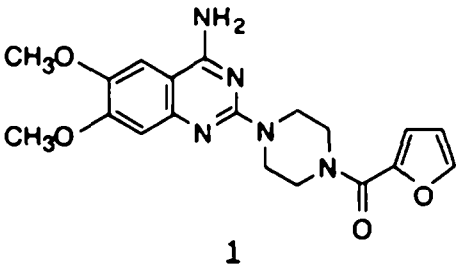
(*Received in USA* 20 *October* 1987)

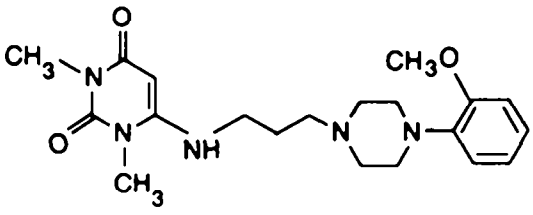
Abstract - The synthesis of 3-(1,3,4-oxadiazol-2-yl)phenoxypropanolamines **3** is described, including the enantioselective syntheses of **R**- and **S**-**3a**. The compounds **3** are of interest as antihypertensives with a specific α_1-receptor-blocking action.

The vasodilatation mediated by α_1-receptor blockade has been utilized for some time to treat hypertension. However, the older α-receptor antagonists had very pronounced side effects such as reflex tachycardia and orthostatic dysregulation. These were caused by the unspecific α-receptor blockade, which involved presynaptic α_2-receptors.

Newer α-receptor antagonists such as prazosin (**1**) or urapidil (**2**) selectively block α_1-receptors and thus have considerably fewer side effects.



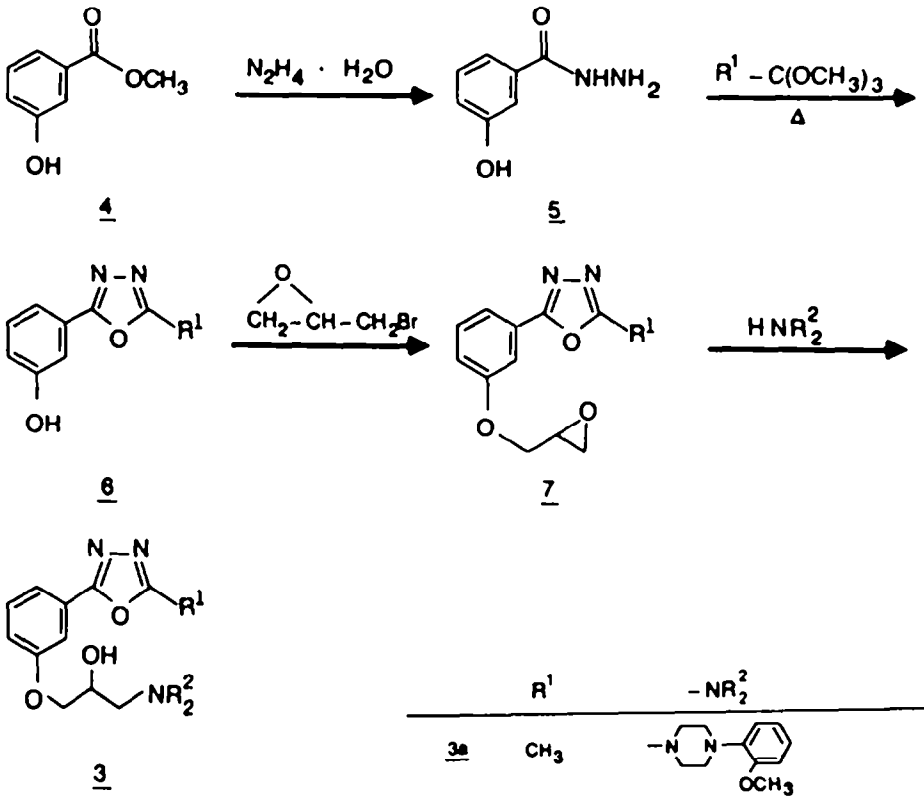
1



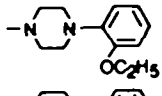
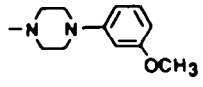
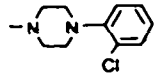
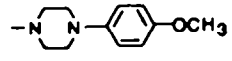
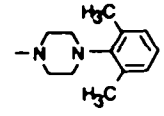
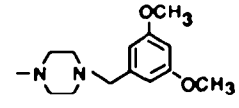
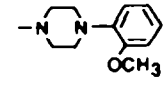
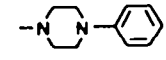
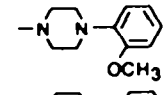
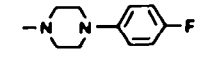
2

We have also been working on the development of selective α_1-sympatholytics, and have found, in the 3-(1,3,4-oxadiazol-2-yl)-phenoxypropanolamines **3**, a new class of compounds which have this type of action and whose synthesis is described here.[10]

This article is dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.



Scheme 1

	R^1	$-NR_2^2$
3a	CH_3	
b	CH_3	
c	CH_3	
d	CH_3	
e	CH_3	
f	CH_3	
g	CH_3	
h	H	
i	H	
j	$C(CH_3)_3$	
k	$C(CH_3)_3$	

Methyl 3-hydroxybenzoate (4) is treated with hydrazine hydrate in methanol to give the benzohydrazide 5 in good yield. Heating with orthocarboxylates[1] effects the ring closure to the 1,3,4-oxadiazole 6. The lower orthocarboxylates were used as solvents, whereas the reaction with the less readily accessible orthoesters of higher carboxylic acids was preferably carried out in propanol.

The 2,3-epoxypropoxybenzene 7 was synthesized by converting 6 with sodium hydride in DMSO or DMF into the phenolate, which was condensed with epibromohydrin. This method has the advantage over the reaction with potassium carbonate as base in acetone that only stoichiometric amounts are required of epibromohydrin, which is highly toxic. The ring opening of the epoxide 7 by heating with amines in ethanol or isopropanol gives good yields of the desired phenoxypropanolamines 3a-k.

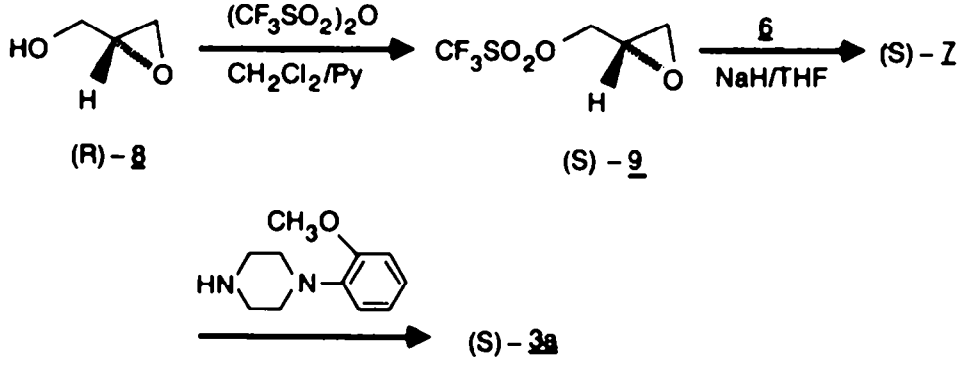
The compounds 3a-k have the 3-amino-2-hydroxypropoxy side-chain which is characteristic of β-receptor antagonists, but they have no β-sympatholytic activity, this being attributable to the aromatic and amine substitution which is unsuitable for the latter type of action. β-Sympatholytic activity is chiefly found in ortho-substituted phenoxypropanolamines[8], whereas α-sympatholytic properties are particularly marked in compounds 3 with meta-substitution.

The 3-amino-2-hydroxypropoxy side-chain has a centre of asymmetry at carbon atom 2. Of the two resulting enantiomeric ortho-substituted β-blockers, only the (S)-antipode has β-sympatholytic activity[9]. In order to establish whether the α_1-antagonistic activity of the oxadiazoles 3 depends in a similar manner on the absolute configuration of the molecule, we synthesized the two enantiomers of 3a.

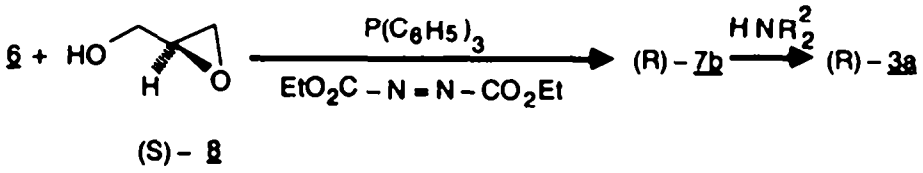
Since a number of C-3 synthons are now available in the form of pure enantiomers[2], it is easier to obtain stereoisomers of 3-amino-2-hydroxypropoxybenzenes on the laboratory scale by stereospecific synthesis than by racemate resolution.

The chiral C-3 synthon which we used was glycidol (8), both enantiomers of which can be prepared from allyl alcohol by Sharpless oxidation[3]. (R)-Glycidol can also be obtained from mannitol[4], and (S)-glycidol can be obtained by hydrolysis of (R)-glycidyl butyrate[5].

To synthesize (S)-3a (Scheme 2), (R)-8 was converted into (S)-trifluoromethanesulphonylglycidol[6] ((S)-9). The phenolate of 6b was prepared with sodium hydride in THF and was treated with (S)-9 at room temperature of give (S)-7b.



Scheme 2 Synthesis of (S)-7b and (S)-3a



Scheme 3 Synthesis of (R)-7b and (R)-3a

(R)-7b was prepared from 6b and (S)-8 by a Mitsunobu reaction using triphenylphosphine/diethyl azodicarboxylate (Scheme 3)[7]. The enantiomers of 3a obtained by both methods had an optical purity >95 %. This was established by ^{1}H NMR spectroscopy. Addition of 10 equivalents of (S)-1-(9-anthryl)-2,2,2-trifluoroethanol to a solution of the substance in chloroform resulted in the OCH_3 singlet in the spectrum of (R,S)-3a being split sufficiently to allow separate integration.

Examination of the α_1-sympatholytic activities of the two enantiomers showed no difference. Compound 3a in the form of the fumarate of the racemate, which has the generic name nesapidil, is undergoing detailed pharmacological testing by Knoll AG, Ludwigshafen, FRG. The results of the pharmacological investigations of this class of substances will be reported elsewhere.

EXPERIMENTAL PART

The melting points were determined using a Buchi apparatus and are uncorrected. The NMR spectra were recorded with a Varian XL 100 or Perkin-Elmer R 24 (tetramethylsilane as internal standard).

3-(1,3,4-Oxadiazol-2-yl)phenol (6a)
90 g (0.6 mol) 3-hydroxybenzohydrazide and 355.2 g (2.4 mol) triethyl orthoformate are refluxed for 22 hours. Excess orthoformate is removed by distillation, and the solid residue is recrystallized from ethanol. Yield 83 g (86%) colorless crystals, m.p. 215 - 216°C.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenol (6b)
is prepared in analogy to 6a with an excess of triethyl orthoacetate. Yield 94 g (89%) colourless crystals, m.p. 174 - 175°C.

3-(5-t-Butyl-1,3,4-oxadiazol-2-yl)phenol (6c)
is prepared in analogy to 6a with equimolar amounts of triethyl orthopivalate in 250 ml n-propanol. Yield 31 g (24%) colourless crystals, m.p. 148 - 149°C.

2,3-Epoxypropoxy-3-(1,3,4-oxadiazol-2-yl)benzene (7a)
1.6 g of a 55% suspension of sodium hydride in liquid paraffin (36 mmol) is suspended in 50 ml anhydrous DMSO, and 5.8 g (36 mmol) of 6a, dissolved in 50 ml DMSO, is added dropwise. Then 5 g (36 mmol) epibromohydrin is added dropwise, and the mixture is stirred at room temp. for 7 h. The solvent is removed by distillation in vacuo, the residue is added to 500 ml brine, and the mixture is extracted by shaking several times with methylene chloride or diethyl ether. The combined organic phases are dried over Na_2SO_4 and concentrated. The solid residue is recrystallized from toluene/hexane. Yield 4.2 g (53%) colourless crystals, m.p. 80 - 82°C. - ^{1}H NMR ($CDCl_3$): 8.7 (s, 1H, oxadiazole proton); 7.0 - 8.0 (m, 4H, aromatic protons); 4.0 (dd, 1H), 4.35 (dd, 1H), 3.35 (m, 1H), 2.8 (m, 1H), 2.9 (m, 1H) epoxypropyl protons.

2,3-Epoxypropoxy-3-(5-methyl-1,3,4-oxadiazol-2-yl)benzene (7b)
is prepared in analogy to 7a. Yield 5.7 g (69%) colourless crystals, m.p. 56°C.

2,3-Epoxypropoxy-3-(5-butyl-1,3,4-oxadiazol-2-yl)benzene (7c)
is prepared in analogy to 7a. Yield 7.7 g (78%) pale yellow oil.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (3a)
7.6 g (33 mmol) 7b and 6.4 g (33 mmol) 2-methoxyphenylpiperazine in 50 ml ethanol are stirred under reflux for 17 h. The solvent is removed in a rotary evaporator, the oily residue is taken up in methylene chloride, and the solution is washed with water, dried over Na_2SO_4 and concentrated. The oily residue is either crystallized directly or the hydrochloride is precipitated from ethanol/diethyl ether with ethereal hydrochloric acid, washed with isopropanol and dried at 80°C in vacuo. Yield 11.2 g (68%) colourless crystals, m.p. 205 - 206°C. Analysis: calculated for $C_{23}H_{28}N_4O_4 \cdot 2HCl$ (497). C 55.5; H 6.1; N 11.3; Cl 14.3; found: C 55.4; H 6.2; N 11.4; Cl 14.0%.

The following are obtained in analogy to 3a:

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(2-ethoxyphenyl)-1-piperazinyl]-2-propanol (3b)
Yield 14.6 g (87%) colourless crystals, m.p. 200 - 202°C. Analysis: calculated for $C_{24}H_{30}N_4O_4 \cdot 2HCl$ (511). C 56.4; H 6.3; N 11.0; Cl 13.9; found: C 56.3; H 6.3; N 11.1; Cl 13.8%.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(3-methoxyphenyl)-1-piperazinyl]-2-propanol (3c)
Yield 10.1 g (72%) colourless crystals from ethanol, m.p. 125 - 127°C. Analysis: calculated for $C_{23}H_{28}N_4O_4$ (424). C 65.1; H 6.6; N 13.2; found: C 64.9; H 6.6; N 13.3%.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(2-chlorophenyl)-1-piperazinyl]-2-propanol (3d)
Yield 12.5 g (73%) colourless crystals, m.p. 216 - 218°C. Analysis: calculated for $C_{22}H_{25}N_4O_3Cl \cdot H_2O$ (519.9). C 50.6; H 5.6; N 10.8; Cl 20.5; found: C 49.7; H 6.5; N 11.0; Cl 20.8%.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(4-methoxyphenyl)-1-piperazinyl]-2-propanol (3e)
Yield 9.9 g (71%) colourless crystals, m.p. 166 - 168°C from ethanol. Analysis: calculated for $C_{23}H_{28}N_4O_4$ (424.5). C 65.1; H 6.6; N 13.2; found: C 65.1; H 6.6; N 13.5%.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(2,6-dimethylphenyl)-1-piperazinyl]-2-propanol (3f)
Yield 12.3 g (81%) colourless crystals, m.p. 187 - 188°C. Analysis: calculated for $C_{24}H_{30}N_4O_3 \cdot HCl$ (459). C 62.8; H 6.8; N 12.2; Cl 7.8; found: C 62.6; H 6.7; N 12.2; Cl 8.5%.

1-[3-(5-Methyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(3,5-dimethoxybenzyl)-1-piperazinyl]-2-propanol (3g)
Yield 10.5 g (59%) colourless crystals, m.p. 198 - 199°C. Analysis: calculated for $C_{25}H_{32}N_4O_5 \cdot 2HCl$ (541.5). C 55.5; H 6.3; N 10.3; Cl 13.2; found: C 54.7; H 6.6; N 10.1; Cl 13.3%.

1-[3-(1,3,4-Oxadiazol-2-yl)phenoxy]-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (3h)
Yield 3.6 g (22%) colourless crystals, m.p. 208 - 210°C. Analysis: calculated for $C_{22}H_{26}N_4O_4 \cdot 1.5\ HCl \cdot 1.5\ H_2O$ (492). C 53.7; H 6.2; N 11.4; found: C 53.2; H 6.5; N 11.0%.

1-[3-(1,3,4-Oxadiazol-2-yl)phenoxy]-3-(4-phenyl-1-piperazinyl)-2-propanol (3i)
Yield 10.9 g (87%) colourless crystals, m.p. 136 - 138°C from isopropanol. Analysis: calculated for $C_{21}H_{24}N_4O_3$ (380.5). C 66.3; H 6.3; N 14.7; found: C 66.1; H 6.5; N 14.6%.

1-[3-(5-t-Butyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (3j)
Yield 11.4 g (62%) colourless crystals, m.p. 202 - 204°C. Analysis: C 55.9; H 6.7; N 10.2; Cl 15.7; found: C 55.9; H 6.8; N 10.4; Cl 15.0%.

1-[3-(5-t-Butyl-1,3,4-oxadiazol-2-yl)phenoxy]-3-[4-(4-fluorophenyl)-1-piperazinyl]-2-propanol (3k)
Yield 3.7 g (21%) colourless crystals, m.p. 188 - 190°C. Analysis: calculated for $C_{25}H_{31}N_4O_3 \cdot 2HCl \cdot 0.5\ H_2O$ (536.5). C 55.9; H 6.3; N 10.4; Cl 13.3; found: C 56.1; H 6.4; N 10.5; Cl 14.1%.

(S)-2,3-Epoxypropoxy-3-(5-methyl-1,3,4-oxadiazol-2-yl)benzene ((S)-7b)
A solution of 2.50 g (14.5 mmol) 6 in 10 ml THF was added dropwise at room temp. to a suspension of 0.37 g (15 mmol) NaH in 50 ml THF. After stirring for 30 min, 3.0 g (14.5 mmol) 9, dissolved in a little THF, was added, and the mixture was stirred overnight and then poured onto ice, and the mixture was extracted with ethyl acetate. The organic phase was washed twice with 1N NaOH and once with water, and dried over Na_2SO_4. Removal of the solvent in vacuo resulted in 3.2 g crude (S)-7b. - The (S)-3a synthesized from this had an optical rotation $[\alpha]_D^{23}$ of + 11.5° (c = 1.23, CH_3OH).

(R)-2,3-Epoxypropoxy-3-(5-methyl-1,3,4-oxadiazol-2-yl)benzene ((R)-7b)
9.9 g (56 mmol) 6 and 5.0 g (67 mmol) (S)-8 and 17.6 g (67 mmol) triphenylphosphine were mixed in 100 ml THF and, while cooling in ice, 11.7 g (67 mmol) diethyl azodicarboxylate was added. The mixture was stirred at room temp. overnight, the solvent was removed by distillation, the residue was taken up in ether, and the solution was filtered. The filtrate was concentrated to crystallization, and the crystals were filtered off with suction and dried. 5.8 g crude (R)-7b was obtained. - The (R)-3a prepared from this had an optical rotation $[\alpha]_D^{23}$ of -11.6° (c = 1.24, CH_3OH).

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