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SYNTHESIS AND ABSOLUTE CONFIGURATION OF SUBSTITUTED MORPHOLINES

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Abstract—We studied methods of stereospecific synthesis that enabled us to obtain variously substituted morpholinic compounds and to determine their absolute configuration. From a study of the chiroptical properties of synthetic N-[2-pyridyl-N-oxide] derivatives of optically active morpholines, it was possible to correlate the sign of the Cotton effect with the absolute configuration. This correlation agrees with that previously established for derivatives of the piperidine type. By evaluating the various contributions to the Cotton effect of substituents in positions 2 and 3, we established the absolute configuration of bicyclic compounds condensed in the two positions mentioned above.

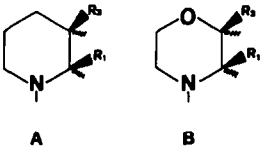
It is known that the pharmacological activity of many medicinal agents depends largely on their chirality, both from the pharmacokinetic point of view and as regards their interaction with specific receptors.

At present we are interested in stereochemical research on amino compounds, and have proposed correlations between their absolute configuration and the chiroptical properties of certain suitable derivatives obtained by introducing a chromophoric group on the N atom. The semi-empirical rules developed provide a good degree of reliability in cases where the condensation product obtained has a limited conformational freedom.

In the case of open-chain compounds the presence of an additional chromophoric group in the amine portion gives rise, in the derivatives examined, to a system that behaves like a homoconjugated chromophore whose geometry depends on the configuration and conformation of the molecule. Because of the very high value of the Cotton effect in such chromophoric systems, it has proved possible[1] to relate the shape of the CD curves to the absolute configuration of the amine. Starting with similar assumptions, the absolute configurations of some adrenergic compounds have recently been proposed.[2]

The possibility of correlating chiroptical properties and absolute configuration was subsequently extended[3] to chiral compounds in which the N atom is incorporated in a ring structure, and which therefore possess less conformational freedom compared with open-chain amines. It has been observed that in piperidine derivatives the sign of the Cotton effect of the corresponding N-[2-pyridyl-N-oxide] derivatives is related to the chirality of the molecule, independently of the nature of the substituent R and of its relative position with respect to the nitrogen. Thus, all monosubstituted piperidine compounds having the absolute configuration shown in A (Fig. 1) always show a negative Cotton effect.

Structures of the morpholine shown in B (Fig. 1) are closely related to the piperidine structures already considered, but whereas they offer considerable pharmacological interest, no correlations have been established between their chiroptical properties and their absolute configurations, and from the point of view of synthesis only methods for the preparation of racemic compounds have been reported.[4] The synthesis of morpholine derivatives in optically active form and the possibility of determining their absolute configurations, either by physical methods or by chemical correlations, constitute the subject of the present work.

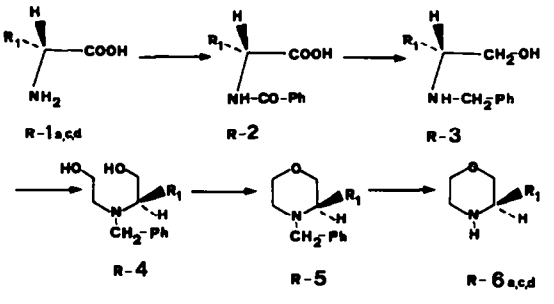


A B

Fig. 1

In the case of 3-substituted morpholines, the absolute configuration has been chemically established starting from the amino-acid **1**, which is converted into the corresponding N-benzylaminoalcohol **3**.[5–7] This latter gave N-benzylaminodiol **4** from which, after cyclisation with 70% H_2SO_4 to **5**, the amine **6** is obtained (Scheme 1).

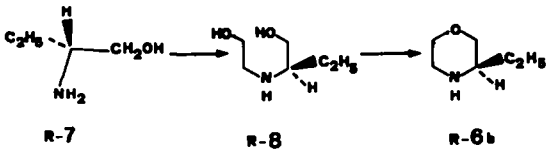
In this synthetic route, in order to avoid a double substitution of the nitrogen, protection of the amine function with a good leaving group was



R-1a,c,d R-2 R-3

R-4 R-5 R-6a,c,d

Scheme 1

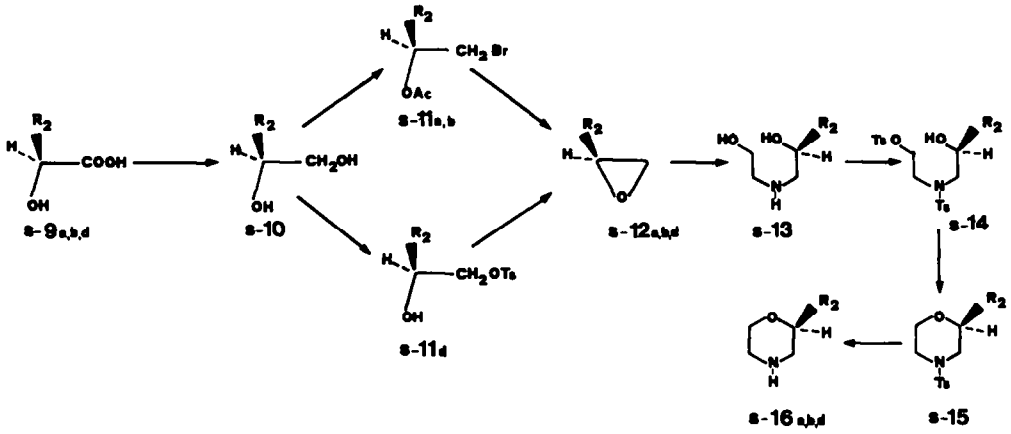


Scheme 2

preferred instead of using a large excess of the unprotected aminoalcohol in the reaction with ethylene oxide. Only in the preparation of **6b** (Scheme 2), the commercially available R-aminoalcohol **7** was directly reacted.

The synthesis of 2-substituted morpholines is performed (Scheme 3) starting from the chiral hydroxyacid **9**; this is transformed into the diol **10** from which the corresponding epoxide **12** is obtained[8-10] using the α-bromoacetyl derivative **11a,b**,[8] or the monotosylate **11d**.[10] By reaction with ethanolamine the epoxide can be converted into the amino-diol **13**, which is transformed into the ditosylate **14** which, without further purification, is cyclised in an alkaline medium to give the corresponding N-tosylmorpholine. From this, finally, the 2-substituted morpholine **16**, having a chirality identical to that of the epoxide used, is obtained.

Modification of the reaction scheme for the cyclisation of amino-diols **13** in contrast to those having structure **4** was necessary in order to avoid racemization of the chiral centre in the presence of the sulphuric acid.

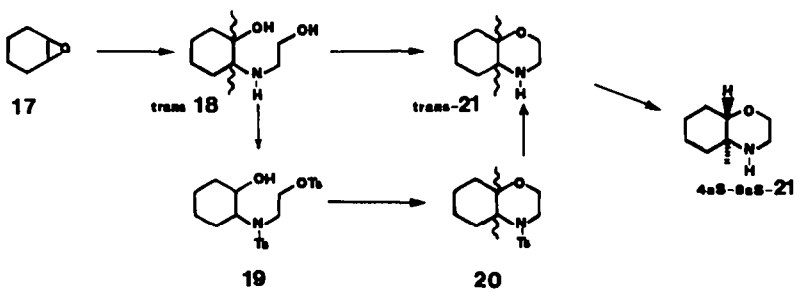


Scheme 3

A considerable degree of racemization occurs in the transformation of **15d** into **16d**, since the acidic hydrogen on the chiral centre exchanges easily in the strongly alkaline medium of the detosylation reaction. When the progress of the reaction is followed polarimetrically, it is observed, for the compound indicated above, that the optical activity decreases markedly as a function of time. The specific rotation of the optically pure **16d** was determined by resolving the racemic amine with the aid of dibenzoyltartaric acid.

In order to investigate what influence the simultaneous presence of the substituents in position 2 and 3 has on the chiroptical properties of the morpholine derivatives, we prepared (Scheme 4) the racemic *trans*-octahydro-1,4-benzoxazine **21**, starting from cyclohexene epoxide **17** which, on reaction with ethanolamine, gave the *trans*-amino-diol **18**. The latter was cyclised by the two different methods indicated in Schemes 2 and 3, in both cases giving the compound *trans*-RS-**21** as the only reaction product. In the cyclisation of similar compounds with 60% sulphuric acid, other authors[11] have recently observed the exclusive formation of the *trans*-morpholine derivative. The racemate was resolved using L-tartaric acid.

The morpholine derivatives synthesised are reported in Table 1; from these we prepared the corresponding N-[2-pyridyl-N-oxide] derivatives, whose chiroptical properties in methanol are shown



Scheme 4

Table 1 : physical constants and NMR data of morpholines

Morpholine	R_1	R_2	B.p. °C (mm Hg)	$[\alpha]_D$	NMR ($CDCl_3$ /TMS); δ(ppm)
R-(-)-6a[4c]	CH_3	H	131 (760)	-21.5 (neat)	3.80-2.70 (m,7H, CH_2-N-CH; CH_2-O-CH_2); 2.04 (s,1H, NH); 0.96 (d,3H, CH_3).
R-(-)-6b[4d]	C_2H_5	H	148 (760)	-2.8 (neat)	3.80-2.40 (m,7H, CH_2-N-CH; CH_2-O-CH_2); 1.92 (s,1H, NH); 1.40-1.08 (m,2H, $\underline{CH_2}$-CH_3); 0.86 (t,3H, CH_3).
R-(+)-6c	$CH(CH_3)_2$	H	150 (760)	+8.7 (neat) d=0.9755	3.90-3.06 (m,4H,CH_2-O-CH_2); 3.04 (s,1H, NH); 2.94-2.80 (m,2H, CH_2-N); 2.60-2.30 (m,1H, N-CH); 1.70-1.30(m,1H, $\underline{CH}$-CH_3); 0.96(d,3H,CH_3); 0.92(d,3H,CH_3).
R-(-)-6d	C_6H_5	H	76-7[a]	-45.8 (MeOH)	7.28 (s,5H,aromatic); 3.90-2.80 (m,7H, CH_2-O-CH_2;CH_2-N-CH); 1.92 (s,1H, NH).
S-(+)-16a[4c]	H	CH_3	130 (760)	+ 1 (MeOH)	[b] 4.00-3.64 (m,3H, CH_2-O-CH); 3.36-2.60 (m,5H, CH_2-N--CH_2; NH); 1.20 (d, 3H, CH_3).
S-(-)-16b[4c]	H	C_2H_5	155 (760)	-14.6 (neat)	3.90-2.30 (m,7H, CH_2-N-CH_2; CH_2-O-CH); 2.22(s,1H,NH); 1.60-1.06 (m,2H, $\underline{CH_2}$-CH_3); 0.94 (t,3H, CH_3).
S-(+)-16d[4e]	H	C_6H_5	138 (14)	+12.6[c](MeOH)	7.30 (s,5H,aromatic); 4.42(m,1H,O-CH-C_6H_5); 4.10-3.50 (m,2H, O-CH_2); 3.10-2.60(m,4H, CH_2-N-CH_2); 1.84 (s,1H,NH).
4aR-(+)-21	trans-octahydro-1,4-benzoxazine		(d)	+20.3 (MeOH)	3.90-3.40 (m,2H); 3.12-2.70 (m, 3H); 2.50-2.20 (m, 1H) 2.00-1.00 (m,broad, 8H); 1.60 (s,1H,NH).

(a) M.p.°C; crystallized from n-hexane; (b) spectrum of hydrochloride in CD_3OD; (c) optical rotation of amine obtained from resolution of racemate; compound from synthesis (scheme 3) shows $[\alpha]_D$ = +0.45 (c=30%,MeOH); (d) sublimed

in Table 2, compared to those of the piperidine derivatives previously studied. Some of the CD curves are shown in Fig. 2.

Comparison of these data shows that the shape of the CD curves for the morpholine-type derivatives is analogous to that of the corresponding piperidines.

The Cotton effect at higher wavelengths always has the same sign when the orientation of the substituent at the chiral centre (independently of the position of the latter with respect to the nitrogen) remains the same. In contrast, the position of the chiral centre and the nature of the substituent influence the amplitude of the Cotton effect which is much greater when the asymmetric carbon is adjacent to the nitrogen. This behaviour can be related to the fact that a substituent in this position, in its preferred equatorial conformation, severely limits the conformational freedom of the chromophore group linked to the nitrogen. In fact,

Table 2: UV and CD data for N-[2-pyridyl-N-oxide]-derivatives of morpholines and piperidines

from morpholines	R_1	R_2	UV λ max (nm)	UV log ε	CD λ max (nm)	CD $[\Theta]\cdot10^{-2}$	from piperidines	R_1	R_2	UV λ max (nm)	UV log ε	CD λ max (nm)	CD $[\Theta]\cdot10^{-2}$
R-(-)-6a	CH_3	H	320	3.28	323	- 63	R-(-)-22	CH_3	H	327	3.49	328	- 79
R-(-)-6b	C_2H_5	H	325	3.49	327	- 95	R-(-)-23	C_2H_5	H	332	3.53	332	-125
R-(+)-6c	$CH(CH_3)_2$	H	327	3.48	335	-146							
R-(-)-6d	C_6H_5	H	315	3.43	323	- 60	S-(-)-24	C_6H_5	H	315	3.36	332	- 14[a]
S-(+)-16a	H	CH_3	320	3.47	315	- 5	R-(-)-25	H	CH_3	328	3.50	323	- 11
S-(-)-16b	H	C_2H_5	320	3.46	318	- 9	R-(-)-26	H	C_2H_5	312	3.57	312	- 8
S-(+)-16d	H	C_6H_5	320	3.53	318	- 2	S-(+)-27	H	C_6H_5	325	3.53	323	- 43
4aR-(+)-21	trans-octahydro-1,4-benzoxazine		312	3.36	319	- 47	8aR-(+)-28	trans-decahydro-quinoline		320	3.08	325	- 10

(a) This value is corrected: the CD amplitude previously reported[3] was a misprint

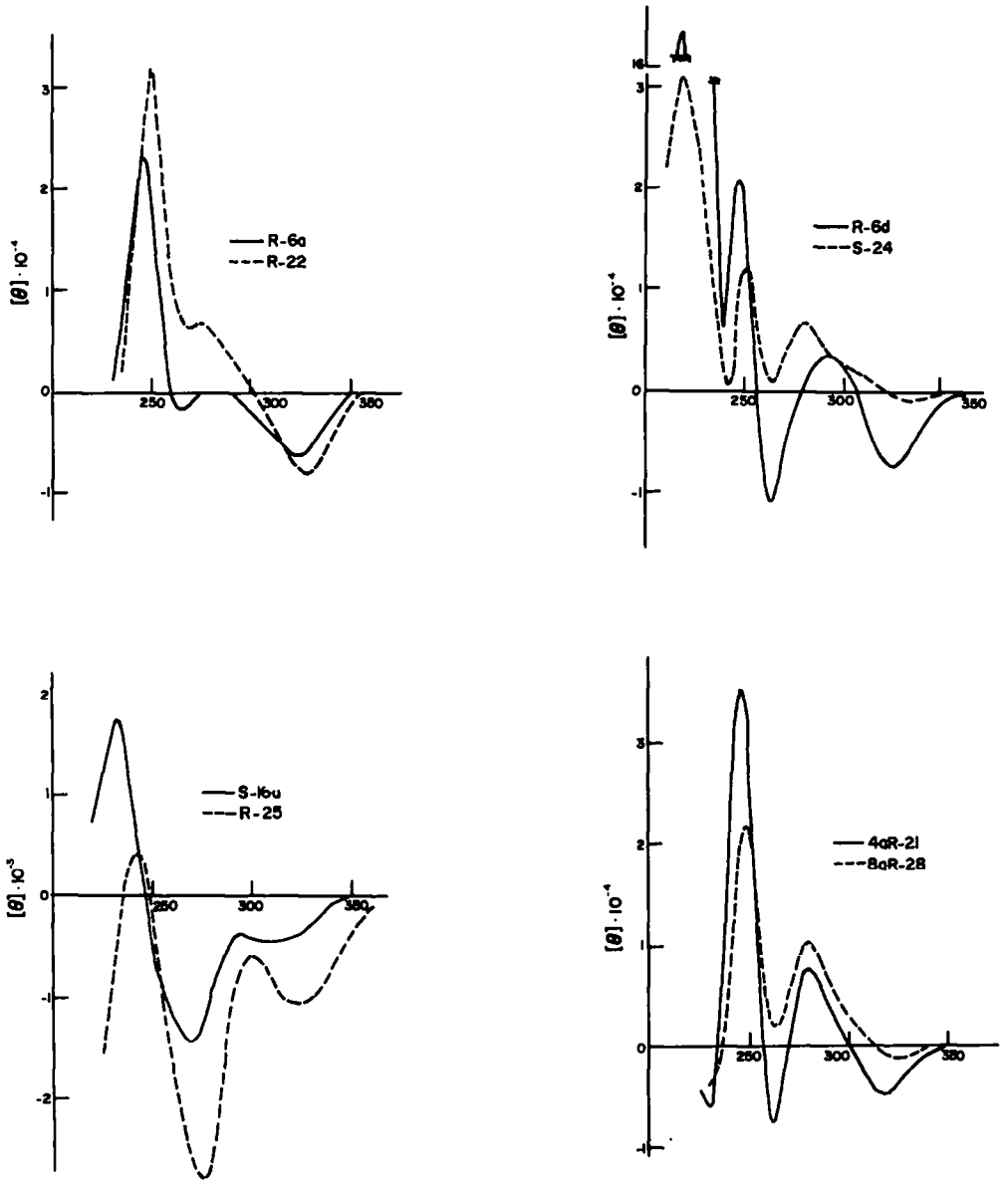


Fig. 2

as the bulk of the substituent on the carbon in the α position with respect to the nitrogen increases (e.g. Me, Et, i-Pr), one observes an increase in the absolute value of the amplitude. When the ring substituent is a chromophoric group (e.g. carboxyl, phenyl) the amplitude may depend, in addition to the bulk, on the contribution of the homoconjugated chromophore originating from the interaction of the two chromophores in those conformations in which the chromophores can assume suitable reciprocal positions in space.

From what has been said it emerges that in the pyridyl-N-oxide derivatives of amino-compounds whose nitrogen atom is incorporated in a ring structure the greatest contribution to the amplitude of the Cotton effect is made by the substituent that lies nearest to the N atom. Consequently, in the bicyclic compounds **28** and **21**, which can be considered similar to disubstituted piperidine and morpholine derivatives having opposite configurations at the two chiral centres in position 2 and 3, the shape of the CD curve is related to the configuration of the substituent at the chiral centre adjacent to the nitrogen. This confirms the 8aR configuration already attributed by other authors[12] to (+)-*trans*-decahydroquinoline **28**, and establishes as 4aR the absolute configuration of (+)-*trans*-octahydro-1,4-benzoxazine **21**.

EXPERIMENTAL

Microanalyses were conducted by Dr. A. Reho, Istituto di Chimica Farmaceutica with a Hewlett-Packard Model 185 CHN analyzer.

The mps, determined with a Tottoli apparatus, are not corrected. Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. CD and UV spectra were recorded in methanol with Cary 61 dichograph and with Cary 15 spectrophotometer, respectively (cells of

Table 3: Physical constants and NMR data for R-4 compounds

Compound	R_1	Formula	$[\alpha]_D$ (EtOH)	N % calcd.	found	NMR ($CDCl_3$/ TMS): δ (ppm)
R-(-)-4a	CH_3	$C_{12}H_{19}NO_2$	- 73.4	6.69	6.52	7.28(s,5H,aromatic); 3.84-2.30(m,9H) 3.10(s,2H,2OH); 0.90(d,3H,CH_3).
R-(+)-4c	$CH(CH_3)_2$	$C_{14}H_{23}NO_2$	+ 23	5.90	5.90	7.26(s,5H,aromatic);3.86-2.28(m,9H); 3.00-2.70(broad.2H,2 OH);2.00-1.60(m,1H, $\underline{CH}(CH_3)_2$);1.04(d,3H,CH_3);0.87(d,3H,CH_3).
R-(-)-4d	C_6H_5	$C_{17}H_{21}NO_2$	- 89.5	5.16	5.39	7.40-7.05(m,10 H,aromatic);4.10-2.30 (m,9H);3.23(s,2H,2 OH).

10 mm and concentrations about 0.01 mg/ml). NMR spectra were recorded with a Varian HA 100 spectrometer in $CDCl_3$, unless otherwise indicated, using TMS as internal standard; chemical shifts are expressed in δ (ppm).

General procedure for the preparation of N-*benzyl-amino-diols* R-**4(a,c,d)**. The N-benzyl-aminoalcohols **3** (prepared by known methods[5-7]) (1 mole) were stirred with ethylene oxide (1 mole) in the presence of phenol (1 mole)[13] in a stoppered probe at room temp for 3 hr. The resulting soln was made alkaline with NaOH and was extracted with $CHCl_3$. Evaporation of solvent gave high boiling oils which were distilled in an air bath at 140–160° (external temp). Physical constants and NMR data of compounds **4a,c,d**, are reported in Table 3.

General procedure for preparation of N-*benzyl*-3-*substituted morpholines* R-**5(a,c,d)**. Compounds **4** were heated in a sealed tube with 70% w/w H_2SO_4 (molar ratio 1 mole/750 ml) at 140° for 15 hr.[4a] The soln was cooled and made alkaline with NaOH. After filtration of the salt, the aqueous soln was extracted with ether. Distillation of the residue obtained from the organic solvent gave required compounds **5(a,c,d)**. Physical constants and NMR data are reported in Table 4.

General procedure for preparation of 3-*substituted-morpholines* R-**6(a,c,d)**. Compounds **5a,c** were hydrogenated in a stainless steel autoclave in the presence of 10% Pd/C (about 25 m.moles/0.5 g of catalyst) for 2 hr at 60–80 atm and 80°. In the case of **5d** hydrogenation was performed at room temp and 1 atm for 12 hr. After filtration, 10 ml of conc HCl was added and the soln was evaporated under vacuum. The residue was treated with 20% NaOHaq and continuously extracted with ether. After distillation of the solvent, liquid morpholines **6a,c** and solid **6d** were obtained.

Physical constants and NMR data are reported in Table 1. R-(+)-**6c**-picrolonate: m.p. 240° (dec), crystals from EtOH. (Found: C, 52.25; H, 6.11; N, 18.13 Calc. for $C_{17}H_{23}N_5O_6$: C, 51.90; H, 5.89; N, 17.80%) R-(−)-**6d**: m.p. 76–7°, crystals from hexane (Found: C, 73.42; H, 8.17; N, 8.56 Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%).

*R-(−)-N-(β-Hydroxyethyl)-2-amino-1-butanol-***8**. Ethylene oxide (2.2 g) was added at 0° to a soln of R-(−)-**7** (15 g) in water (50 ml). The resulting soln was stirred at room temp for 1 day. Water and the excess of starting material were removed under vacuum. The residue was purified by distillation and R-(−) **8** was obtained (4.7 g): $[\alpha]_D = 17.85°$ ($c = 2.8\%$, MeOH), b.p. 138° (12 mm Hg). [lit.:[4d] 138–40°/12 mm Hg on racemic

Table 4: Physical constants and NMR data of R-5 compounds

Compound	R_1	Formula	B.p.°C (mmHg)	$[\alpha]_D$	N% calcd.	found	NMR ($CDCl_3$/ TMS); δ (ppm)
R-(-)-5a	CH_3	$C_{12}H_{17}NO$	140 (14)	-73.4(EtOH)	7.32	7.19	7.26(s,5H,aromatic);4.10-2.98(m,6H, CH_2OCH_2,$\underline{CH_2}C_6H_5$);2.60-2.00(m,3H, CH_2NCH);1.04(d,3H,CH_3).
R-(-)-5c	$CH(CH_3)_2$	$C_{14}H_{21}NO$	162 (14)	-99.2(MeOH)	6.39	6.28	7.28(s,5H,arom.);3.86-3.24(m,4H,CH_2OCH_2); 3.54(q,2H,$\underline{CH_2}C_6H_5$,ν_A4.14,ν_B2.95,J_{AB}[13] cps);2.70-2.48(m,1H,NCH);2.40-2.00(m,3H, CH_2N,$\underline{CH}CH_3$);1.00(d,3H,CH_3);0.96(d,3H,CH_3).
R-(-)-5d	C_6H_5	$C_{17}H_{19}NO$	85-7[(a)]	-54 (MeOH)	5.53	5.72	7.50-7.10(m,10 H,aromatic);3.84-2.08(m,9H).

(a) M.p.°C;crystallized from dichloromethane-n.hexane

Table 5: Physical constants and NMR data of S-13 compounds

Compound	R_2	Formula	m.p.°C	$[\alpha]_D$	NMR (TMS); δ (ppm)
S-(+)-13a[4c]	CH_3	$C_5H_{13}NO_2$	130 (2)	+ 23.7(MeOH)	($CDCl_3$):4.14(s,3H,2 OH,NH);3.96-3.82(m,1H, CH_3-CH);3.64(t,2H,CH_2OH);2.70(t,2H,CH_2CH_2N); 2.60-2.40(m,2H,$CHCH_2N$);1.16(d,3H,CH_3).
S-(+)-13b[4c]	C_2H_5	$C_6H_{15}NO_2$	143 (2)	+ 22.3($CHCl_3$)	($CDCl_3$):3.84(s,3H,2 OH,NH);3.70-3.40(m,3H, CH_2OH,CHOH);2.84-2.40(m,4H,CH_2NCH_2);1.60-1.30(m,2H,CH_3CH_2);0.96(t,3H,CH_2CH_3).
S-(+)-13d	C_6H_5	$C_{10}H_{15}NO_2$	88-90[a]	+ 2.6(MeOH)	(CD_3OD):7.40-7.15(m,5H,arom.);4.80(s,3H, 2 OH,NH);4.85-4.60(m,1H,CHC_6H_5);3.60(t,2H, NCH_2CH_2OH);2.80-2.60(m,4H,CH_2NCH_2).

(a) M.p.°C;crystallized from methanol-ether

compound] NMR: 3.90–3.30 (m, 7H, CH_2OH, CH_2OH, NH); 2.90–2.40 (m, 3H, CH_2N, CHN); 1.60–1.30 (m, 2H, CH_3—CH_2); 0.96 (t, 3H, CH_2CH_3).

R-(−)-3-Ethyl-morpholine **6**. R-(−)-**8** (6.9 g) was reacted with 70% w/w H_2SO_4 in the same manner described for the preparation of compounds **5a,c,d**. Physical properties are reported in Table I.

S-(−)-1-Bromo-2-acetoxy-butane **11b**. The reaction was conducted as described for the preparation of S-(−)-**11a**,[8] starting from S-(−)-**10** (3.6 g). S-(−)-**11b** was obtained 5.5 g B.p. 76–77° (14 mm Hg); $[\alpha]_D = -21.5°$ (neat, d = 1.345). [lit:[14] b.p. 75–7° (15 mm Hg) on racemic compound] NMR: 5.05–4.70 (m, 1H, CH); 3.50–3.35 (m, 2H, CH_2—Br); 2.08 (s, 3H, CH_3CO); 1.67 (q, 2H, CH_3CH_2); 0.93 (t, 3H, CH_2—CH_3).

General procedure for the preparation of aminodiols S-**13(a,b,d)**. The epoxides **12** (1 mole) were added dropwise to a cooled soln of ethanolamine (4 mole) in water. The soln was stirred at room temp for 5 hr. After removal of water and ethanolamine the residue was distilled under vacuum. Physical constants and NMR data are reported in Table 5. Compound S-(+)-**13d**: Found C, 66.35; H, 8.73; N, 7.51. Calc. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73%).

General procedure for the preparation of N,O-di-p. *toluensulphonates* S-**14(a,b,d)**. Tosyl chloride (2 moles) was added to a stirred soln of **13** in dry pyridine at 0°. After 1 day at room temp the soln was poured on ice. The aqueous soln was extracted with $CHCl_3$, washing with 2 N HCl and H_2O. The residue obtained from the organic solvent was used without further purification.

General procedure for the preparation of N-p-*toluen sulphonyl-morpholines* S-**15(a,b,d)**. Powdered NaOH (1 mole) suspended in the smallest amount of MeOH was added to a stirred soln of **14** (1 mole) in $CHCl_3$. After about 30 min water was added and the organic layer, dried on Na_2SO_4, was removed under vacuum. The residue was purified by column chromatography on silica and crystallised from MeOH. Physical constants and analytical data are reported in Table 6.

General procedure for the preparation of 2-*substituted morpholines* S-**16(a,b,d)**. Na (10 moles) was added portionwise to a warmed soln of **15** (1 mole) in n-amyl alcohol. The soln after 3 hr refluxing was cooled and water was added. The two layers were separated: aqueous soln was extracted with ether and this with 2 N HCl; the alcoholic soln was directly extracted with 2 N HCl. The collected acidic solns were made alkaline and continuously extracted with ether. By distillation **16a,b,d** were obtained. Physical constants and NMR data are reported in Table 1.

trans RS—N-(β-*Hydroxyethyl*)-2-*amino*-1-*cyclohexanol* -**18**. The reaction was performed as described above for the preparation of **13**. *Trans* **18** was obtained in 94%

Table 6 : Physical constants and analytical data of S-15 compounds.

Compound	R_2	Formula	M.p.°C	$[\alpha]_D$	elemental analyses					
					calcd.%			found%		
					C	H	N	C	H	N
S-(+)-15a	CH_3	$C_{12}H_{17}NO_3S$	82-4	+25.9 (MeOH)	56.46	6.71	5.49	56.31	6.60	5.28
S-(+)-15b	C_2H_5	$C_{13}H_{19}NO_3S$	73-5	+37 ($CHCl_3$)	57.98	7.11	5.20	58.16	7.00	5.14
S-(+)-15d	C_6H_5	$C_{17}H_{19}NO_3S$	105-7	+6.6 (MeOH)	64.34	6.03	4.41	64.27	5.91	4.19

Table 7. NMR data of N-[2-pyridyl-N-oxide]-derivatives of morpholines

N-[2-pyridyl-N-oxide]-derivatives of	NMR ($CDCl_3$/ TMS); δ (ppm)
R-(-)-6a	8.30-8.15(1H,H-6 pyridine); 7.28-7.18(1H,H-4 pyridine); 6.98-6.80(2H,H-3,5 pyridine);4.65-4.40 (m,1H,CHCH$_3$); 4.05-3.45(m,5H); 3.04-2.80(m,1H); 1.12(d,3H,CH$_3$).
R-(-)-6b	8.20-8.05(1H,H-6 pyridine); 7.32-7.08(1H,H-4 pyridine); 6.90-6.70(2H,H-3,5 pyridine); 4.56--4.30(m,1H,CHC$_2$H$_5$); 4.04-3.40(m,5H); 3.10-2.90(m,1H); 2.10-1.20(m,2H,CH$_3$CH$_2$);0.84(t,3H,CH$_3$)
R-(+)-6c	8.16-8.00(1H,H-6 pyridine); 7.30-7.06(1H,H-4 pyridine); 6.88-6.64(2H,H-3,5 pyridine); 4.45-4.20 (m,1H,CH-isoC$_3$H$_7$); 4.00-3.00(m,6H); 2.60-2.25(m,1H); 0.95(d,3H,CH$_3$); 0.76(d,3H,CH$_3$).
R-(-)-6d	8.24-8.08(1H,H-6 pyridine); 7.40-7.04(m,5H,aromatic); 7.00-6.46(m,3H,pyridine); 4.96-4.78(m, 1H,CHC$_6$H$_5$); 4.25-3.62(m,5H); 2.90-2.60(m,1H).
S-(+)-16a	8.20-8.05(1H,H-6 pyridine); 7.32-7.08(1H,H-4 pyridine); 6.95-6.72(2H,H-3,5 pyridine); 4.00-3.70 (m,5H); 3.00-2.35(m,2H); 1.24(d,3H,CH$_3$).
S-(-)-16b	8.22-8.08(1H,H-6 pyridine); 7.34-7.10(1H,H-4 pyridine); 6.95-6.72(m,2H,H-3,5 pyridine); 4.00--3.50(m,5H); 3.00-2.40(m,2H); 1.70-1.40(m,2H,CH$_3$CH$_2$); 1.02(t,3H,CH$_3$).
S-(+)-16d	8.20-8.05(1H,H-6 pyridine); 7.50-7.00(m,6H,H-4 pyridine,aromatic);6.90-6.65(2H,H-3,5 pyridine); 4.80(double d,1H,CHC$_6$H$_5$, J=10cps,J=3cps); 4.20-3.80(m,4H); 3.10-2.60(m,2H).
4aR-(+)-21	8.30-8.14(1H,H-6 pyridine); 7.36-6.85(m,3H,pyridine); 4.20-2.70(m,6H); 2.10-0.80(m,8H).

yield: b.p. 125° (0.05/mm Hg); the NMR spectrum shows that three protons exchange with D_2O. (Found: C, 59.99; H, 10.58; N, 8.63. Calc. for $C_8H_{17}NO_2$:C, 60.35; H, 10.76; N, 8.88%).

trans-RS-N-p-*Toluensulphonyl-octahydro*-1,4-*benzoxazine*-**20**. RS-**18** was transformed in *trans* **19** and then cyclised to RS-**20** as described above: m.p. 130–2°, crystals from MeOH (Found: C, 61.12; H, 7.26; N, 4.48. Calc. for $C_{15}H_{21}NO_3S$: C, 61.00; H, 7.17; N, 4.74%).

trans-RS-*Octahydro*-1,4-*benzoxazine*-**21**. RS-**20** was detosylated to RS-*trans* **21** as described above; hydrochloride: m.p. 270–2°, crystals from EtOH—Et_2O (Found: C, 53.95; H, 9.39; N, 7.65. Calc. for $C_8H_{15}NOCl$: C, 54.08; H, 9.08; N, 7.88%). *Trans* RS-**21** was also obtained from direct cyclisation of *trans* **18** with 70% H_2SO_4 w/w (identical physical constants and NMR spectrum).

trans 4aS-(−)-*Octahydro*-1,4-*benzoxazine*-**21**. Compound RS-**21** was resolved by crystallisation from water of the L-(+) tartaric acid salt; 4aS-(−)-**21** was obtained. Physical constants and NMR data for the antipode are reported in Table 1.

General procedure for the preparation of N-[2-*pyridyl*-N-*oxide*]-*morpholino derivatives*. The substituted morpholines (1 m.mole) were reacted with 2-fluoropyridine-N-oxide (1.2 m.moles) in the presence of $NaHCO_3$ (1 m.mole) in water (5 ml) or in a mixture (1:1) of H_2O—EtOH (5 ml) at room temp for 3 days. The rn mixture was then extracted with CH_2Cl_2. In the case of reaction conducted in hydroalcoholic medium, the soln was before concentrated under vacuum. From evaporation of the organic solvent highly viscous oils than can be stored in the dark at 0° were obtained. They were purified by double microdistillation under high vacuum and on the distilled products were immediately determined NMR, UV and CD spectra (Tables 2 and 7). In the NMR spectra the protons of the pyridine ring show a pattern in agreement with the data previously reported.[15] Only N-[2-pyridyl-N-oxide] derivative of **21**, after distillation, solidified: m.p. 76–78°. (Found: C, 66.60; H, 7.82; N, 12.13. Calc. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96%).

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