96. The Stereospecific Synthesis of all four Stereoisomers of 2-Amino-6-phenoxy-cyclohexanol[1])

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Dedicated to Professor *A. S. Dreiding* on the occasion of his 60th birthday

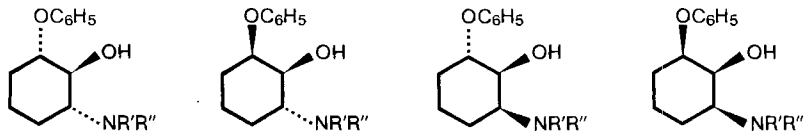
(4.1.79)

Summary

Epoxidation of 3-phenoxycyclohexene **5** with *m*-chloro-perbenzoic acid gave **6** and **7** in a ratio of 9:1. These two epoxides were heated with a series of amines to give the aminophenoxycyclohexanol derivatives **1** and **2** respectively; in all cases the reaction was regio- and stereospecific. Two methods based on the principle of neighbouring group participation were developed to synthesize the *cis*-amino alcohols **3** and **4**. In the first, the hydroxy group was used to introduce an amine function at the vicinal carbon atom. In the second method, the amino group served as the point of reference and the configuration of the adjacent alcohol function was inverted.

Introduction. – There are four possible stereoisomers of 2-amino-6-phenoxycyclohexanol *(Scheme 1)* and three of these isomers can be obtained in principle from a suitably constructed epoxide. Nucleophilic attack at an epoxide results in diaxial scission and it is often regiospecific [1]. For example both *trans*- and *cis*-3-methoxycyclohexane epoxides are cleaved almost exclusively at position 1 to give the corresponding *trans*-cyclohexanols [2]. Therefore reaction of the 3-phenoxycyclohexane epoxides **6** and **7** with an appropriate amine should lead to the isomers **1** and **2** respectively, whilst treatment of the amino epoxide **9** with sodium phenoxide should yield the isomer **3**. The all-*cis* isomer **4** could be prepared by inverting the configuration of the hydroxy group of isomer **1**.

Scheme 1



1 **2** **3** **4**

Note: only one racemic form is depicted

[1]) First presented at the Autumn Meeting of the Swiss Chemical Society, Lugano, October 1973.

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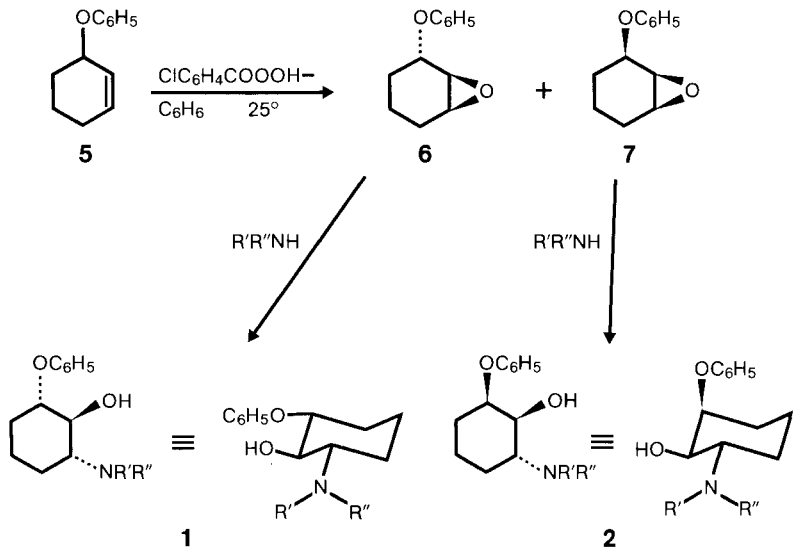
1. **Synthesis of isomers 1 and 2.** – Treatment of 3-phenoxycyclohexene **5** with *m*-chloro-perbenzoic acid gave two epoxides (*ca.* 9:1), which were separated by chromatography but their configuration could not be assigned unambiguously from the NMR. spectra. When the major isomer was heated with isopropylamine the single amino alcohol, isolated in 86% yield, was unequivocally the *trans*-isomer **1** with the three substituents equatorially located (NMR.)[2]). Therefore the starting epoxide must have been the *trans*-isomer **6**, assuming diaxial scission and that the cleavage of the epoxide was regiospecific. This was confirmed by heating the minor isomer with isopropylamine when a different amino alcohol was isolated. Its NMR. spectrum was compatible only with structure **2** in which the phenoxy group is axial. Similar results were obtained with ammonia and dimethylamine: in all cases the structures **1** and **2** represented the conformation of the *trans*- and *cis*-phenoxyamino alcohols obtained from **6** and **7** respectively. A recent patent described a similar sequence of reactions leading to **1**, but the configuration of the products was not published [3].

Scheme 2

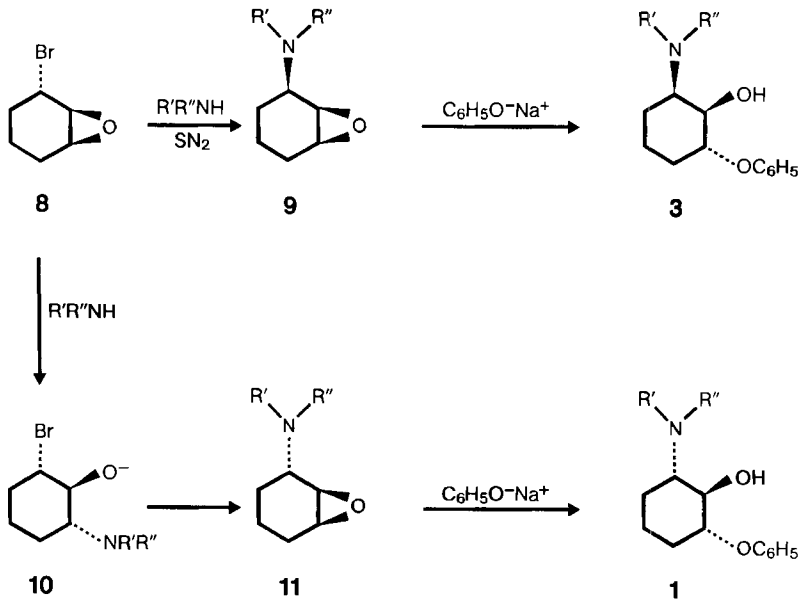


2. **Synthesis of isomer 3.** – a) *From the* cis-*amino epoxide* **9**. Treatment of the *cis*-amino-epoxide **9** with sodium phenoxide should lead, by analogy with the results described above, to the third isomer. The major problem, however, is to synthesize **9**. Two isomers could be formed when **8** reacted with an amine; displacement of bromide by an amine *via* an S_N2-mechanism will lead to the required *cis*-amino epoxide, whilst cleavage of the epoxide by the amine followed by cyclization of the halohydrin **10** will give the *trans*-amino epoxide **11**. These two compounds can be readily differentiated since reaction of **9** with sodium phenoxide will lead to a new amino alcohol **3**, whilst **11** will give the *trans*-

[2]) The salient features of the NMR. spectra of the compounds **1–4** are summarized in the *Table*.

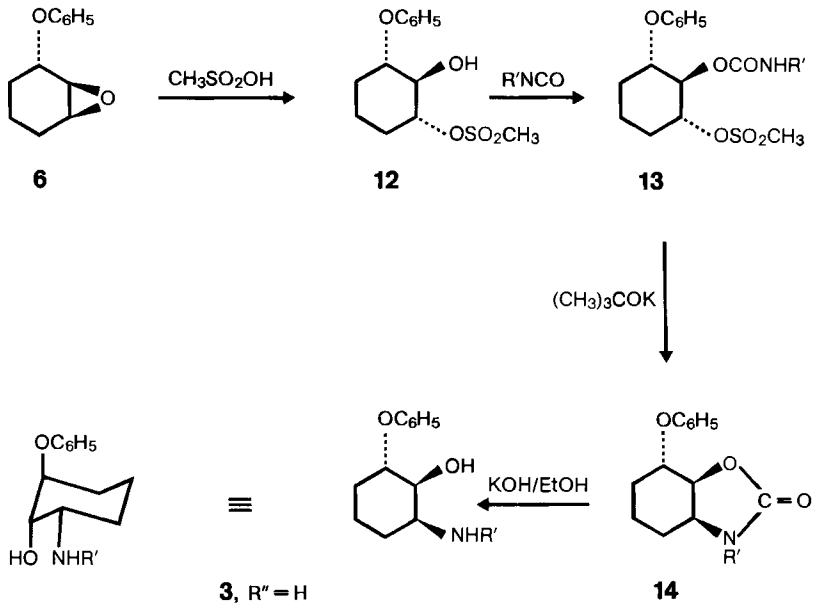
amino alcohol **1**. Epoxidation of 3-bromocyclohexene with *m*-chloro-perbenzoic acid yielded the *trans*-epoxide **8** which was then stirred for 5 days at RT. with piperidine. An amino epoxide was formed in 57% yield which was transformed into an amino alcohol with sodium phenoxide. The NMR. spectrum left no doubt that this was the *cis*-amino alcohol **3** and not the *trans*-isomer **1**, thus proving the configuration of the intermediate epoxides **8** and **9** (R′–R″=$(CH_2)_5$). Unfortunately, the results with other amines were not so encouraging. Either no reaction took place or mixtures of the halohydrin **10** and the *cis*-epoxide **9** were obtained. Thus both pathways can be followed, so the method is too limited to be practically useful.

Scheme 3



b) *From* t-*2-methanesulfonyl*-t-*6-phenoxy*-r-*1-cyclohexanol* **12**. The reaction between an epoxide and an organic isocyanate yields a 2-oxazolidinone [4] and is catalyzed by halides such as LiCl or LiBr [5]. Since 2-oxazolidinones can be hydrolyzed to *cis*-amino alcohols we tried this reaction with *trans*-phenoxycyclohexane epoxide **6** but obtained only complex mixtures. Subsequently, we found that the cleavage of the epoxide with lithium halide was not regiospecific and also that considerable amounts of the 1,2-diol had been formed from the intermediate urethane, indicating competition between *O*- and *N*-cyclization [6]. Treatment of **6** with methanesulfonic acid at 0° led to the hydroxymethanesulfonate **12** which reacted rapidly with benzoyl isocyanate to give the urethane **13** (R′=COC_6H_5) in 80% overall yield. This was cyclized with potassium *t*-butoxide in *t*-butyl alcohol to the 2-oxazolidinone **14** which was hydrolyzed directly to the *cis*-amino alcohol **3** (R′=R″=H) in an overall yield of 50% (from **13**). The *N*-substituted amino alcohols could also be prepared in good yield by using the appropriate alkyl isocyanate.

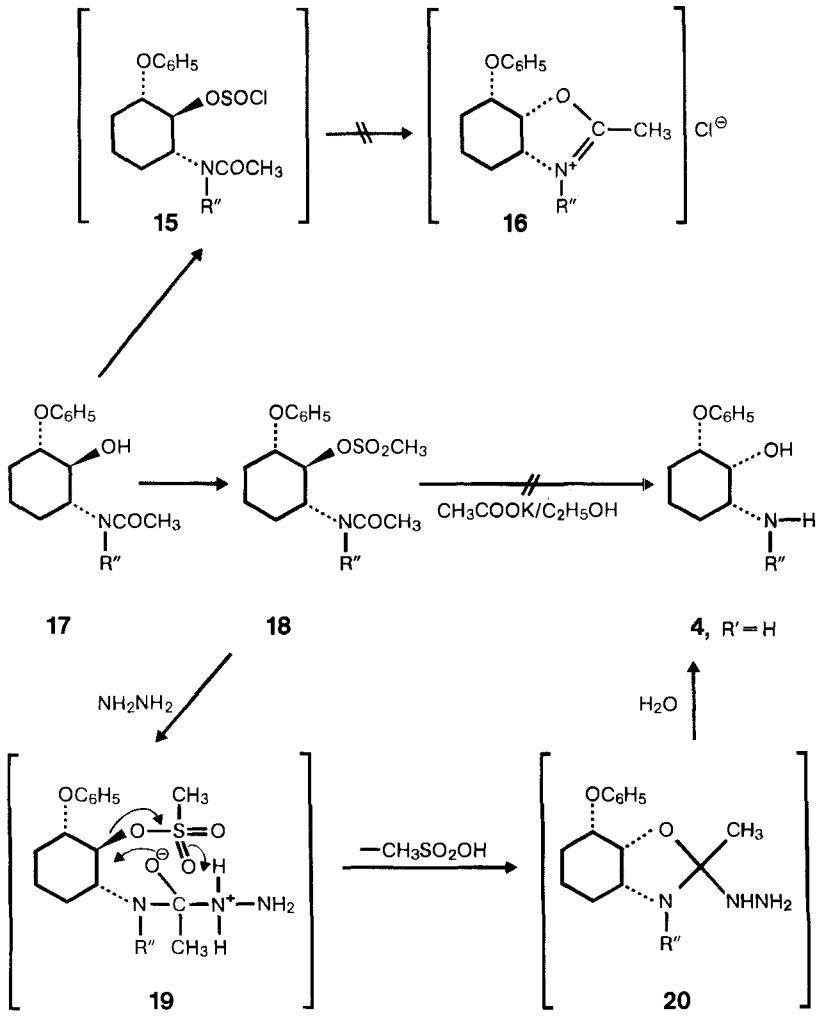
Scheme 4



3. **Synthesis of isomer 4.** – In principle, we could apply the sequence shown in *Scheme 4* to convert the *cis*-epoxide **7** to the all-*cis*-isomer **4**. Since only relatively small amounts of this epoxide were available we sought a method to invert the configuration of the hydroxy group in **1**. *trans*-2-Aminocyclohexanol may be transformed to the *cis*-isomer by treatment of the corresponding amide with thionyl chloride followed by hydrolysis of the intermediate *cis*-oxazoline hydrochloride [7]. The yields varied from 40–50% [7] to 95% [8] [9]. We therefore converted **1** (R′=R″=H) to the amide **17** (R″=H) and treated it with thionyl chloride under differing conditions, but we were unable to isolate either the oxazoline hydrochloride **16** (R″=H) or the all-*cis*-amine **4**. The NMR. spectrum of **17** showed that the three substituents were equatorial whereas rearrangements of the type presented in *Scheme 5* require an antiperiplanar orientation of the amide and ester groups [10]. Presumably the chlorosulfite ester **15** decomposed before the necessary transition state had been formed so that the internal displacement could not occur. Another standard method to invert the hydroxyl group in *trans*-amido alcohols is to heat the corresponding alkyl methane sulfonate with potassium acetate in ethanol [9] [10], but under these conditions **18** was recovered unchanged.

Fujinaga & Matsushima [11] have used hydrazine hydrate to hydrolyze amides. Assuming that the mechanism of this reaction is similar to the one established for the base-catalyzed hydrolysis of amides [6], we reasoned that treatment of **18** with hydrazine would lead to the tetrahedral intermediate **19** which would be ideally located to displace the adjacent mesylate and so form the cyclic compound **20** which could then be hydrolyzed to the required amino alcohol **4**. When **18** (R″=H) was heated with neat

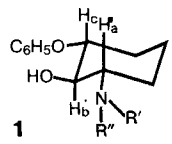
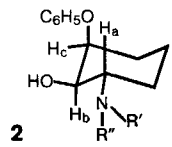
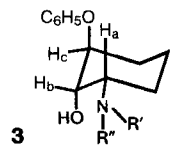
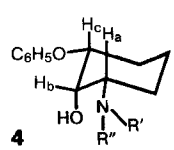
Scheme 5



hydrazine hydrate at 110° the pure all *cis*-amino alcohol **4** (R′ = R″ = H) was obtained. This new method was applied with equal success to *N*-substituted amides (**18** R″ = $CH(CH_3)_2$ and $CH_2C_6H_5$) and so does not seem to be limited by steric hindrance. In all cases the yields were good, generally above 75%.

We have therefore developed two methods to prepare *cis*-2-amino alcohols. In the first, the hydroxy group serves as the point of reference and the configuration at the adjacent carbon atom is inverted by *N*-attack of the urethane. In the second method the amine is used to reverse the configuration of the vicinal alcohol. Thus the two syntheses complement each other and so should be useful in stereochemical problems.

Table. *^{1}H-NMR. Data of Compounds* **1–4**

Isomer	R′	R″	Shifts in ppm			$w_{H_{1/2}}$(Hz)		J in Hz	
			H_a	H_b	H_c	H_a	H_c	J_{ab}	J_{bc}
 **1**	H*	H*	2.70	3.36	4.08	25	25	10	9
	H	$CH(CH_3)_2$	2.50	3.38	4.06	22	23	10	9
	CH_3	CH_3	2.30	3.53	4.11	23	22	10	9
 **2**	H*	H*	3.07	3.30	4.64	23	10	9	3
	H	$CH(CH_3)_2$	2.93	3.34	4.66	24	10	10	3
 **3**	H**	H**	4.05	4.45	4.70	16	12	5	4
	H	$CH(CH_3)_2$	3.07	3.79	4.52	17	13	5	4
		$-(CH_2)_5-$	2.51	4.05	4.65	16	9	4	4
	H	$CH_2C_6H_5$	3.12	3.90	4.60	13	14	5	3
 **4**	H*	H*	2.79	3.98	4.17	17	17	3	3
	H**	H**	4.00	4.43	4.82	13	12	4	4
	H	$CH(CH_3)_2$	2.68	4.04	4.16	17	14	2	2
	H	$CH_2C_6H_5$	2.56	3.78	4.15	18	8	2	3

All spectra were recorded at 100 MHz using TMS as internal standard (δ = Oppm). The spectra were measured in $CDCl_3$ at ca 30°, excepting those marked with * or ** which were determined in $CDCl_3$ at 55° and CF_3COOD respectively.

Experimental Part

General. The purity of the products as well as the progress of reactions were controlled by TLC. using 40 × 80 mm Polygram Sil G/UV_{254} (*Machery-Nagel*, Dürren). The plates were eluted with ether/petroleum ether (E/P) or acetone/benzene (A/B) or acetone/chloroform (A/C) using the proportions (*v/v*) given in the text. The spots were identified by a UV.-lamp and rendered visible by spraying with 5% $Na_2Cr_2O_7$-solution in H_2SO_4/H_2O 1:1 by *v/v* followed by heating to *ca.* 60°. After a product had been extracted, the organic phase was dried (Na_2SO_4) and evaporated on the rotatory evaporator *in vacuo* at *ca.* 40°. IR. spectra were recorded as *Nujol* mulls on a *Perkin-Elmer* Model 21 spectrometer; the position of the peaks is given in cm^{-1} using the following abbreviations for the intensities: br. broad, *s* strong, *m* medium. The NMR. spectra, unless otherwise indicated, were determined at 100 MHz in $CDCl_3$ and the chemical shifts (δ) are given in ppm relative to TMS. as internal standard. The following abbreviations are used: *s* singlet, *d* doublet, *d* × *d* doublet of doublets, *d* × *qa* doublet of quartets, *t* triplet, *m* multiplet. Only the significant peaks are given. All substances gave acceptable analyses, unless otherwise indicated. M.p. were determined on the *Koffler* block and are uncorrected.

3-Phenoxycyclohexene **5**. 3-Bromocyclohexene (483.2 g, 3 mol) was added dropwise under N_2 to a stirred suspension of K_2CO_3 (455 g, 4.49 mol), phenol (310.6 g, 3.3 mol) and 1,2-dimethoxyethane (1.5 l), the temperature being maintained between 40–45° by an ice bath. The suspension was stirred overnight at 45°, cooled, filtered, and the residue rinsed with ether. The filtrate was washed with 0.5N NaOH

(4×200 ml), water (4×200 ml), dried and evaporated to give an oil which was distilled to give pure **5** 351.1 g (67.3%), b.p. 80–81°/0.6–0.5 Torr, n_D^{20} 1.547, TLC.: E/P 1:9. [12a]: b.p. 80°/0.03 Torr; [12b]: b.p. 71–73°/0.25 Torr.

trans- *and* cis-*1,2-Epoxy-3-phenoxycyclohexane* **6** *and* **7**. A solution of **5** (351 g, 2.01 mol) in benzene (500 ml) was added dropwise over 1 h to a stirred solution of *m*-chloro-perbenzoic acid (450 g, 2.2 mol) in benzene (3.5 l). The temperature was maintained at 25° by an ice-bath and after *ca.* 45 min the *m*-chlorobenzoic acid started to precipitate. The resulting suspension was stirred overnight at RT., filtered, the residue washed with benzene and the filtrate extracted successively with 5% $NaHSO_3$-solution (7×200 ml), 10% Na_2CO_3-solution (8×250 ml), and water (4×250 ml). The organic phase was dried and evaporated to give an oil (390 g) which was applied to a column of silica gel (5 kg) made up with petroleum ether. The column was eluted initially with petroleum ether then with increasing amounts of ether, fractions of 250 ml being collected. TLC.: initially E/P 2:8, later fractions E/P 1:1.

Fr.	1–10 E/P 0:10 to 1:9	2.1 g **5**+**6**
	11–52 E/P 1:9	280.0 g pure **6** (73.2%)
	53–70 E/P 1:9 to 1:1	1.45 g **6**+**7**
	71–75 E/P 1:1	34.0 g pure **7** (8.9%)
	76–79 E/P 1:1	8.57 g impure **7** (2.2%)

Distillation of fractions 11 to 52 afforded 243.2 g (63.6%) of pure **6**, b.p. 88–90°/0.3 Torr, m.p. *ca.* 25°, n_D^{21} 1.542. – NMR.: 3.15 (*m*, 2 H); 4.42 (*m*, 1H).

Fractions 71 to 75 were crystallized from ether/petroleum ether to give 25.5 g (6.7%) pure **7**, m.p. 50.5–51.5°. – NMR.: 3.24 (*m*, 1H); 3.34 (*d*×*d*, *J*=2 and 4 Hz, 1H); 4.55 (*m*, 1H).

1. ***cis*- and *trans*-Amino alcohols 1 and 2.** – Examples a) and c) illustrate the standard procedures.

a) t-*2-Amino*-t-*6-phenoxy*-r-*1-cyclohexanol* **1** *(R′=R″=H).* Water (25 ml) was carefully added to a mixture of liquid ammonia (150 ml), *t*-butyl alcohol (75 ml) and the *trans*-epoxide **6** (17 g, 90 mmol) contained in a stainless steel autoclave. This was heated at 90° for 18 h, cooled, and the majority of the ammonia allowed to evaporate at RT. for 3 h. The suspension was filtered, the residue washed well with ether and then dissolved in $CHCl_3$. The $CHCl_3$ was dried and evaporated to give an amorphous solid (13.3 g, 72%), m.p. 178–180°. Crystallization from ethanol gave pure **1** as glistening needles, m.p. 178–178.5°. Evaporation of the ether/ammonia filtrate gave a solid containing both monomeric and dimeric amino alcohols. TLC. A/B 4:6.

b) t-*2-Amino*-c-*6-phenoxy*-r-*1-cyclohexanol* **2** *(R′=R″=H).* As in a), but using the *cis*-epoxide **7**. Yield 84%, m.p. 159–160° from ether/$CHCl_3$.

c) t-*2-Isopropylamino*-t-*6-phenoxy*-r-*1-cyclohexanol* **1** *(R′=H, R″=CH(CH₃)₂).* The *trans*-epoxide **6** (9.5 g, 50 mmol), *t*-butyl alcohol (25 ml), and isopropylamine (43 ml, 0.5 mol) were heated at 130° overnight in an autoclave. The solvent was evaporated and the residue (11.02 g, m.p. 77–79°) crystallized from ether/petroleum ether to give the pure product 10.65 g (86%), m.p. 78–79°, TLC. E/P 2:8.

d) t-*2-Dimethylamino*-t-*6-phenoxy*-r-*1-cyclohexanol* **1** *(R′=R″=CH₃).* As in c), but using dimethylamine. Yield 73%, m.p. 54–55° from $CHCl_3$/petroleum ether.

e) t-*2-Isopropylamino*-c-*6-phenoxy*-r-*1-cyclohexanol* **2** *(R′=H, R″=CH(CH₃)₂).* As in c), but using the *cis*-epoxide 7. Yield 90%, m.p. 66–67° from ether/petroleum ether.

f) t-*2-Benzylamino*-t-*6-phenoxy*-r-*1-cyclohexanol* **1** *(R′=H, R″=C₇H₇).* A solution of **6** (19.0 g, 0.1 mol) in 109 ml benzylamine (1 mol) was heated under reflux for 5 h, the benzylamine distilled in high vacuum and the residue crystallized from ether/petroleum ether to give 19.3 g (65%) of glistening white needles, m.p. 81–83°.

2. ***cis*-Amino alcohol 3.** – trans-*3-Bromo-1,2-epoxycyclohexane* **8**. This was prepared from 3-bromocyclohexene (16.1 g, 0.1 mol) and *m*-chloroperbenzoic acid (24.4 g, 0.11 mol) in the same way as **6** and **7**. The crude product was distilled to give pure **8**, 13.1 g (74%), b.p. 71–72°/11 Torr, n_D^{23} 1.514. – NMR.: 3.26 (*m*, 1H); 3.39 (*d*×*d*, *J*=1.5 and 3 Hz, 1H); 4.47 (*m*, 1H); see [13].

cis-*1,2-Epoxy-3-piperidino-cyclohexane* **9** *(R′=R″=(CH₂)₅).* A mixture of epoxide **8** (54.2 g, 306 mmol), piperidine (62 ml, 612 mmol) and benzene (100 ml) was stirred at RT. for 24 h, the precipitate filtered, the solid washed with benzene,, and the filtrate concentrated to approximately the original volume. This was stirred at RT. for another 24 h, the precipitate removed as above and the reaction continued until TLC. (E/P 1:1) showed that the starting material had disappeared (5 days). The reaction seemed to become blocked unless the piperidinium hydrobromide was periodically removed, whereas

carrying out the reaction at higher temperatures led to mixtures. A total of 43.52 g (86%) of piperidinium hydrobromide, m.p. 238–240° was recovered. Benzene and piperidine were evaporated and the residual oil distilled to give 31.6 g (57%) of **9**, b.p. 77–79°/0.6 Torr, n_D^{21} 1.499. Analysis showed the presence of 1.4% Br. – NMR.: 2.3–2.9 (*m*, 5 H); 3.08 (*m*, 1 H); 3.24 (*d*×*d*, *J* = 4 and 1 Hz, 1 H).

t-*6-Phenoxy*-c-*2-piperidino*-r-*1-cyclohexanol* **3** (*R′* = *R″* = $(CH_2)_5$). A mixture of **9** (10.59 g, 58.4 mmol), sodium phenoxide (13.6 g, 117 mmol) and 1,2-dimethoxyethane (50 ml) was refluxed under N_2 for 20 h. The solvent was evaporated, the residue dissolved in benzene and water, the benzene layer washed with 0.5N NaOH (2× 100 ml), 10% $NaHCO_3$-solution (2× 100 ml), water (2× 100 ml), dried and evaporated to give a white solid, 13.62 g (84%). Crystallization from benzene/petroleum ether gave the pure product as prisms, 7.85 g (49%), m.p. 120–121°.

t-*2-Mesyloxy*-t-*6-phenoxy*-r-*1-cyclohexanol* **12**. The *trans*-epoxide **6** (38 g, 0.2 mol) in dry ether (30 ml) was added over 10 min to an ice-cold solution of methanesulfonic acid (16.2 ml, 0.25 mol) in dry ether (40 ml). The clear solution was stirred for 15 min, diluted with 50 ml ether, washed with water until neutral, dried and evaporated to give a waxy solid (54.34 g, 95%). This was sufficiently pure for the reaction with the isocyanate. A small sample was recrystallized from ether/CH_2Cl_2 to give pure **12**, m.p. 102.5–105° (dec.). TLC. E/P 1:1. – IR.: 3555*s* sharp (OH); 1160*s* and 1170*s* (OMs). – NMR.: 2.9 (*s*, 1H); 3.1 (*s*, 3 H); 3.78 (*t*, *J* = 9 Hz, 1H); 4.1 (*m*, 1 H); 4.52 (*d*× *qa*, *J* = 5, 9 and 11 Hz, 1 H).

*(*t-*2-Mesyloxy*-t-*6-phenoxy)*-r-*1-cyclohexyl)*N-*benzoyl-carbamate* **13** (*R′* = COC_6H_5). A solution of benzoyl isocyanate (6 g, 41 mmol) in 1,2-dichloroethane (20 ml) was added over 15 min to a stirred solution of the hydroxymesylate **12** (9.13 g, 31.9 mmol) in 1,2-dichloroethane (20 ml). After stirring for 1 h at RT., precipitation commenced and 5 min later the mixture solidified. The solid mass was filtered off and washed well with ether to give a white solid 11.23 g (81%), m.p. 165–167° (dec.). An aliquot was recrystallized from ether/CH_2Cl_2 to give the analytical sample, m.p. 167–169° (dec.). – IR.: 3325*s* and 3335*s* (NH), 1780*s*, 1690*m* (CO), 1180*s* (OMs). – NMR.: 3.0 (*s*, 3 H); 4.30 (*m*, *J* = 4.5, 9 and 10.5 Hz, 1 H); 4.72 (*m*, *J* = 4.5, 9.5 and 10.5 Hz, 1 H); 5.24 (*qa*, *J* = 9 and 9.5 Hz, 1 H); 8.35 (*s*, 1 H).

c-*2-Amino*-t-*6-phenoxy*-r-*1-cyclohexanol* **3** (*R′* = *R″* = *H*). Potassium *t*-butoxide (27 g, 0.241 mol) was added to a stirred suspension of the above carbamate (25.6 g, 59 mmol) in *t*-butyl alcohol (500 ml) at 60°. Within 5 min the solid had dissolved and 10 min later precipitation commenced. The suspension was stirred for 5 h at 60°, cooled to *ca.* 35° and NaOH (12 g, 300 mmol) in water (10 ml) added. The clear solution was stirred overnight at 70° and the solvent evaporated. The residue was partitioned between ether and 2N HCl, the ether phase separated, the acid layer extracted once with 50 ml ether and the combined aqueous phases basified with 8N NaOH. The precipitate was collected, washed well with water until the filtrate was neutral and crystallized from ethanol to give pure **3** (R′ = R″ = H), 6.1 g (50%), m.p. 164–166°.

c-*2-Alkylamino*-t-*6-phenoxy*-r-*1-cyclohexanol* **3** (*R′* = *H*, *R″* = *alkyl*). The following experiments illustrate the general procedure.

*(*t-*2-Mesyloxy*-t-*6-phenoxy)*-r-*1-cyclohexyl*-N-*benzyl-carbamate* **13** (*R′* = $CH_2C_6H_5$). The hydroxymethanesulfonate **12** (12.24 g, 42.7 mmol) was dissolved in 1,2-dichlorethane (50 ml) and benzyl isocyanate (6.85 g, 51.5 mmol) added. The clear solution was left overnight at RT. (no precipitation) and then stirred at 70° for 2 h. The solvent was evaporated and the residue crystallized from ethanol to give 15.25 g (85%) product, m.p. 131–132.5°. Recrystallization from ethanol gave the analytical sample as fine needles, m.p. 132–134°. – IR.: 3300*s* sharp (NH), 1700*s* br. (CO), 1180*ms* (OMs). – NMR.: 2.9 (*s*, 3 H); 4.16 (*m*, *J* = 4.5, 9 and 24 Hz, 3 H); 4.60 (*m*, *J* = 4.5, 9 and 11 Hz, 1 H); 5.10 (distorted *t*, *J* = 9 Hz, 2 H).

3-Benzyl-c-*3a,4,5,6,7,*-c-*7a-hexahydro*-r-*7-phenoxy-3*H-*benzoxazol-2-one* **14** (*R′* = $CH_2C_6H_5$). The above carbamate (164.12 g, 0.391 mol) was dissolved in *N,N′*-dimethylformamide (500 ml) and added to a stirred solution of potassium *t*-butoxide (174.5 g, 1.56 mol) in the same solvent (1 l). TLC. (A/C 1:9) showed that the reaction was instantaneous. The contents were poured onto a mixture of ice (1 kg) and conc. hydrochloric acid (500 ml), stirred for 15 min and the precipitate filtered off. The white solid was washed with water, dissolved in CH_2Cl_2, washed again with water until neutral, dried and evaporated to give a solid, 109.11 g (86%). This was crystallized from ether/CH_2Cl_2 to give brilliant clusters, 101.3 g (80%), m.p. 106–107°. – IR.: 1750*s* and 1740*s* (CO). – NMR.: 3.8 (*m*, 1 H); 4.56 (*m*, 1 H); 4.07 and 4.73 (*qa*, J_{AB} = 14 Hz, 2 H).

c-*2-Benzylamino*-t-*6-phenoxy*-r-*1-cyclohexanol* **3** (*R′* = *H*, *R″* = $CH_2C_6H_5$). A mixture of 8N KOH (195 ml, 1.56 mol), oxazolidinone **14** (101.3 g, 0.313 mol) and ethanol (850 ml) was refluxed under N_2 overnight and the solvent evaporated. The residue was dissolved in CH_2Cl_2/water, the organic layer washed

until neutral and the solvent dried and evaporated to give a solid, 91.26 g (98%) which was crystallized from ether to give the pure amino alcohol, 85.44 g (92%), m.p. 74.5–78.0°.

3. **The all-cis amino alcohol 4.** – The following experiments illustrate the general technique.

N-*(*t*-2-Hydroxy-*c*-3-phenoxy-*r*-1-cyclohexyl)acetamide* **17** *(R″ = H).* The *trans*-amino alcohol **1** (R′ = R″ = H) (18.25 g, 88.1 mmol) was added in portions to acetic anhydride (100 ml, 1 mol) and the suspension then heated to 80–85° until the solid had dissolved (*ca.* 10 min). The clear solution was cooled to RT., benzene (200 ml) added to the precipitate and the solid collected and washed with benzene until the odour of acetic anhydride was no longer apparent. The solid was recrystallized from CH_2Cl_2/ether/methanol to give the pure amide, 17.23 g (78.5%), m.p. 157–158°. A further 2.46 g of the amide could be obtained from the acetic anhydride/benzene filtrate by cautiously basifying with 8N NaOH, stirring for 1 h until the odour of acetic anhydride had disappeared and filtering the solid. Total yield 19.69 g (90%). – IR.: 3250*m-s*, 3200*m-s*, 3100*m* (NH,OH), 1665*s*, 1640*s*, 1580*s* (CONH). – NMR.: 1.95 (*s*, 3 H); 3.5–3.9 (*m*, 3 H); 4.1 (*m*, 1H); 6.3 (*d*, *J* = 7 Hz, H).

N-*(*t*-2-Mesyloxy-*c*-3-phenoxy-*r*-1-cyclohexyl)acetamide* **18** *(R″ = H).* The above amide (24.9 g, 0.1 mol) was suspended in 500 ml 1,2-dichloroethane and cooled to −25°. Triethylamine (139 ml, 1 mol) followed by methane sulfonyl chloride (39.2 ml, 0.5 mol) in 150 ml 1,2-dichloroethane were added slowly and then stirred at −25° for 30 min. Icecold 2N HCl (1 l) and CH_2Cl_2 were added, the organic phase separated, washed with cold 10% $NaHCO_3$-solution (2 × 250 ml), ice-water, dried and evaporated at RT. to give a solid 32.6 g. This was triturated with petroleum ether to give **18**, 32.13 g (98%), m.p. 143–148° of sufficient purity for the next step. An aliquot was crystallized from ether/CH_2Cl_2 to yield the analytical sample m.p. 158–161°. – IR.: 3280*s* sharp (NH), 1660, 1650*s*, 1640*s*, 1560*s* (CONH), 1170*s* (OMs). – NMR.: 2.05 (*s*, 3 H); 3.00 (*s*, 3 H); 4–4.7 (*m*, 3 H); 6.25 (*d*, *J* = 8 Hz, 1 H).

c-2-Amino-c-6-phenoxy-r-1-cyclohexanol **4** *(R′ = R″ = H).* The preceeding methanesulfonate (31.2 g, 96 mmol) was stirred with hydrazine hydrate (300 ml, 98%) and the temperature gradually increased to 110°. After 15 min the solid had dissolved, and 30 min later a precipitate started to appear. The reaction mixture was stirred for a total of 90 min, cooled, the solid collected and washed with water. Crystallization from ethanol/CH_2Cl_2 gave the required product as fine needles, 16.6 g (80%), m.p. 178–179°, mixed up with **1** (R′ = R″ = H) 155–180°.

c-2-Isopropylamino-c-6-phenoxy-r-1-cyclohexanol **4** *(R′ = H, R″ = C_3H_7).* From **1** (R′ = H, R″ = $CH(CH_3)_2$) in 58% overall yield, white needles from CH_2Cl_2, m.p. 139–140°.

c-2-Benzylamino-c-6-phenoxy-r-1-cyclohexanol **4** *(R′ = H, R″ = $CH_2C_6H_5$).* From **1** (R′ = H, R″ = $CH_2C_6H_5$) in 69% overall yield, white solid from ethanol, m.p. 124.5–125.5°.

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