Conformation of N-(β-Chloroethyl)-2-phenoxyethylamines in Relation to Adrenergic Blocking Activity[1]

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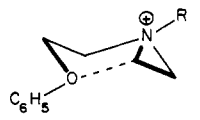
Previous rationalizations on the conformational requirements for adrenergic blocking activity of N-(β-chloroethyl)-2-phenoxyethylamines are briefly summarized. In order to test the validity of some earlier interpretations, the synthesis of *cis*- and *trans*-cyclopentane analogs of this class of blocking agents was accomplished. The *cis* isomer XII was obtained from intermediate VII whereas the *trans* isomer XXVII was secured either through the sequence XIII → XXI → XXIII → XXVII → XXII or through direct substitution of XXI by N-methyl-2-aminoethanol. Other routes were also explored, the results of which are discussed. It was shown that the new alkylating agents XII and XXVII are highly active adrenergic blockers surpassing the parent compound I by a factor of approximately 100. The results are taken as definitive evidence for the involvement of a folded conformation such as III at the receptor level. The conformational properties of these new drugs are briefly discussed.

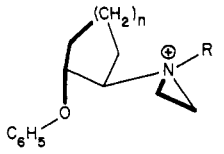
In previous papers dealing with the mechanism of action of adrenergic blocking β-haloalkylamines,[2-5] an attempt was made to relate physiological activity with the stereoelectronic properties of the chemically derived ethyleniminium ions (EI-ions). A particularly intriguing phenomenon lies in the complete loss of blocking activity when the ethereal oxygen of the 2-phenoxyethylamine I is replaced by a methylene group as in II.[6] An explanation for this striking anomaly was offered [2,3] and the conclusion was reached that the EI-ion derivable from I would be readily induced by the receptor sites to assume a conformation III in which the relative positions of the phenyl ring and the alkylating carbons precisely fit the required phenethylamine pattern normally conducive to alkylation of an anionic active site.[2] The lack of activity of II could then be ascribed to the large energy barrier opposing the existence of a conformation similar to III (methylene instead of an oxygen) and this because of the severe nonbonded interactions that would result from the eclipsing of methylene groups.

$C_6H_5OCH_2CH_2NRCH_2CH_2Cl$ I

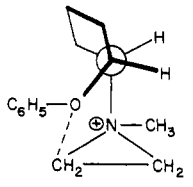
$C_6H_5CH_2CH_2CH_2NRCH_2CH_2Cl$ II



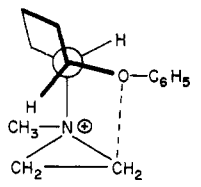
III



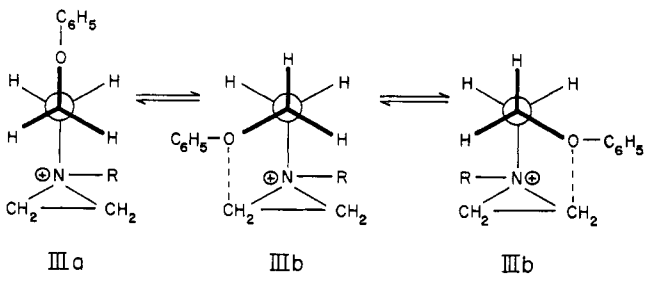
IV



XXIX



XXX



IIIa IIIb IIIb

The possibility that conformation III might contribute to the ground state structure was also recognized and in an attempt to provide information on this point, the kinetic behavior of a series of substituted N-(β-chloroethyl)-2-phenoxyethylamines was studied.[2] Although useful information was derived from these earlier studies, no concrete evidence for the existence of conformation III under pseudophysiological conditions could be adduced. It became clear that another approach to the problem of the postulated intervention of conformation III at the receptor level was required and to this end the exploitation of controlled stereochemical variables appeared to us as the next best method of investigation.

The use of rigid cyclic analogs of I suggested itself in such studies because of the possibility of fixing the distance separating the electrophilic carbons of the EI-ion and the ethereal oxygen of III. Assuming that an optimum distance between these two key moieties can be maintained in a suitable ring analog of III, then an improved level of adrenergic blocking activity should result because of the reduction in entropy demand for the "freezing" of III at the receptor level. Clearly, this will be true only as long as the inclusion of the ring necessary to fix the relative positions of the groups concerned does not interfere with binding onto the receptor surface. An answer to this question had to await experimental verification since no cyclic analog of

(1) This research was supported by a grant from the National Cancer Institute of Canada and represents a portion of the thesis submitted by P. Cooper in partial fulfillment of the requirements for the Ph.D. degree.

(2) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958).

(3) B. Belleau, *J. Med. Pharm. Chem.*, **1**, 327 (1959).

(4) B. Belleau, *ibid.*, **1**, 343 (1959).

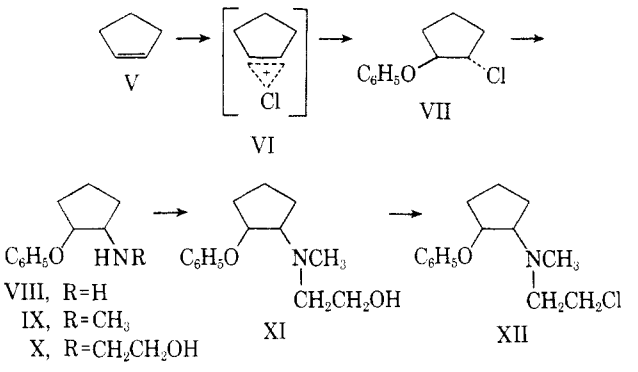
(5) B. Belleau and D. J. Triggle, *ibid.*, **5**, 636 (1962).

(6) G. E. Ullyot and J. F. Kerwin, "Medicinal Chemistry," Vol. II, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, Inc., New York. N. Y., 1956, p. 242.

I of the type under consideration had as yet been described.

Theoretical as well as practical considerations led us to select for our studies the general structural type IV which provides for the existence of *cis* and *trans* isomers in which the distance separating the ring carbons of the EI-ion and the ethereal oxygen may be varied appreciably depending on the size of the carrier ring. The choice of the latter may be restricted only to those rings that are smaller than cyclohexyl because the conformational lability of the higher membered rings would seriously complicate any interpretation of the pharmacological data. Even though the cyclopentane ring is conformationally flexible,[7] its somewhat flatter geometry and relatively small dimensions as compared to cyclohexane made it an acceptable choice for preliminary studies of the effect of annellation on adrenergic blocking activity of EI-ions of type IV. The greater accessibility of appropriate cyclopentane derivatives as opposed to lower homologs was also of some importance in directing the choice of structural type for pharmacological studies. It is the purpose of this communication to describe the synthesis of *cis*- (XII) and *trans*-2-phenoxy-N-methyl-N-(β-chloroethyl)cyclopentylamine (XXVII) and to report on their adrenergic blocking activity.

Synthesis of XII and XXVII.—The starting material for the synthesis of the *cis* isomer XII was *trans*-2-phenoxycyclopentyl chloride (VII). The latter was conveniently prepared by the reaction of cyclopentene (V) with *t*-butyl hypochlorite and phenol. Since a cationic species such as VI is undoubtedly involved as an intermediate in this reaction, the assignment of the *trans* configuration to VII poses no special theoretical problem. Reaction of the chloride VII with methylamine gave the expected amine IX in pure form. The *cis* configuration can be safely assigned to the latter



on the basis of the well known course (SN2) of such displacement reactions.[8] Treatment of the chloride VII with 2-aminoethanol afforded the *cis* amino alcohol X which was methylated to the tertiary amine XI by reaction with formaldehyde and formic acid.[9] Reaction of XI with thionyl chloride finally gave *cis*-2-phenoxy-N-methyl-N-(β-chloroethyl)cyclopentylamine (XII).

Efforts were next directed at the preparation of the *trans* isomer XXVII. Several routes were explored which often led to interesting incidental observations. In one attempt, 2-phenoxycyclopentanone (XIII) was converted to the Schiff base XIV by reaction with benzylamine and thence hydrogenated to the N-benzyl derivative XV. Catalytic hydrogenolysis of the latter led to *cis*-2-phenoxycyclopentylamine (VIII). No evidence for the formation of the *trans* amine XXIV was obtained. The configuration assignment to VIII is based on direct comparisons (infrared, crystalline derivatives) with the *trans* isomer XXIV whose configuration is known with certainty (see below). It seems clear that hydrogenation of XIV involves attack of the molecule from the least hindered side. In an analogous fashion, 2-phenoxycyclopentanone oxime (XVI) was reduced by lithium aluminum hydride to the *cis* amine VIII. In another attempt to secure the *trans* isomer XXIV, the oxime XVI was oxidized with peroxytrifluoroacetic acid to the corresponding 2-phenoxy-1-nitrocyclopentane (XVIII) which gave rise again to the *cis* amine VIII when reduced with lithium aluminum hydride. Attempts to epimerize the nitro derivative XVIII according to Zimmerman and Nevins[10] led to degradation of the compound. The *cis* configuration can be assigned to XVIII on the basis of the expectable course of the protonation of the *aci*-nitro intermediate XVII. It would be expected[10] that protonation of XVII would occur from the least hindered side of the molecule to give the product of kinetic control.

An entry into the *trans* series of amines was finally discovered when it was observed that 2-phenoxycyclopentanone (XIII) was reduced by lithium aluminum hydride to a mixture of *cis* and *trans* alcohols XIX and XX in a ratio of 66:34 (as ascertained by vapor phase chromatography). Substitution of the bulkier reagent lithium tri-*t*-butoxyaluminum hydride for lithium aluminum hydride changed the *cis*, *trans* isomer ratio to 90:10. Configuration assignments were made through comparison (v.p.c. and derivatives) with a specimen of *trans*-2-phenoxycyclopentanol (XIX) prepared by treating cyclopentene oxide (XXVIII) with phenol in the presence of boron trifluoride. The steric course of this reaction follows from the earlier work of Winstein and Henderson.[11] The *cis* alcohol XX was purified as the crystalline tosylate XXI which reacted with sodium azide to give *trans*-2-phenoxycyclopentyl azide (XXIII). The configuration assignment to the latter follows from the well established course of such substitution reactions.[8] Catalytic hydrogenation of the azide XXIII afforded the pure *trans*-2-phenoxycyclopentylamine (XXIV) which was different (infrared, crystalline derivatives) from the amine VIII obtained as described.

The *trans* amine XXIII thus obtained was converted to the N-formyl derivative XXV and thence to the N-methyl analog XXVI by reduction with lithium aluminum hydride. The *trans* amine XXVI differs in its properties from the N-methylamine IX prepared from *trans*-2-phenoxycyclopentyl chloride (VII). Reaction of XXVI with ethylene oxide gave the *trans*-amino alcohol XXII which finally afforded the desired *trans*-N-methyl-N-(β-chloroethyl)-2-phe-

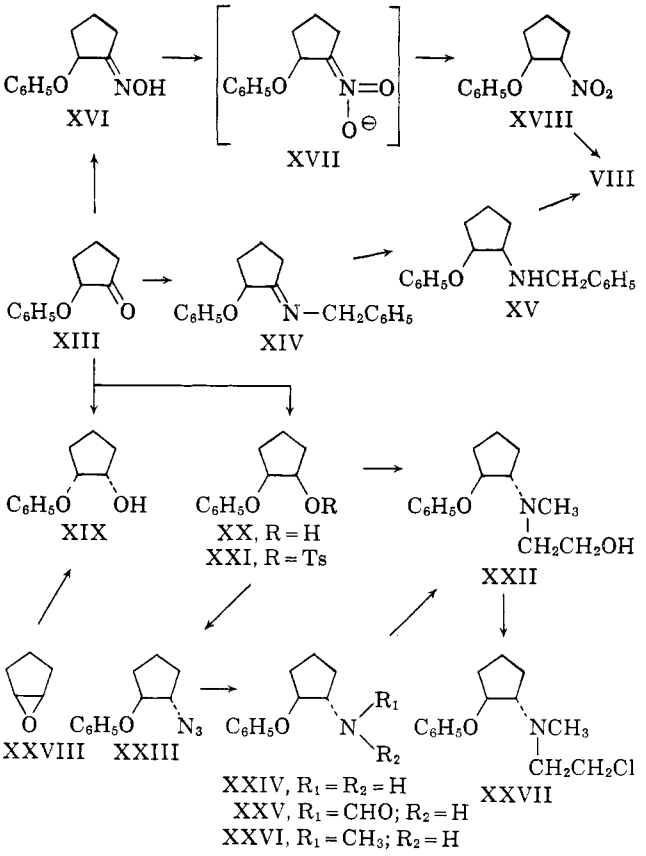
(7) W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 36.

(8) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book, Inc., New York, N. Y., 1962, p. 118.

(9) "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., p. 723.

(10) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957).

(11) S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943).



noxycyclopentylamine (XXVII) when treated with thionyl chloride. A shorter route to the intermediate amino alcohol XXII consisted in treating the *cis* tosylate XXI with N-methyl-2-aminoethanol. The product proved to be identical with the one obtained by the stepwise procedure.

It was previously shown[3] that the rate of formation and the rate of hydrolysis of EI-ions is a function of the relative basicity of the participating nitrogen of β-chloroethylamines. In order that the pharmacological properties of the alkylating agents XII and XXVII may be interpreted in terms of their steric properties, it was necessary to determine the dissociation constants of two isomeric amines of the above cyclopentane series. The final products XII and XXVII being unstable under the usual conditions for titration, the two isomeric primary amines VIII and XXIV were used instead. The respective pK_a values (in 50:50 ethanol–water) for these *cis–trans* isomers were 8.88 and 8.53. Previous experience[3] suggests that the difference is too small to affect significantly the relative abilities of XII and XXVII to generate active EI-ions which in addition must be of comparable stabilities.

Adrenergic Blocking Activity of XII and XXVII.[12]— The *cis* and *trans* isomers XII and XXVII were evaluated for antiadrenergic activity in cats by measuring their effect on the pressor response to injected epinephrine and norepinephrine and by determining their effect on the response of the nictitating membrane to these amines and to electrical stimulation of the superior cervical nerve. Epinephrine and norepinephrine were administered intravenously at doses of 8 γ/kg., a dose which results in an increase of blood pressure of about 90–100 mm. The magnitude and the duration of the pressor responses were recorded. The nictitating membrane contraction was recorded mechanically and a square wave stimulator supplying pulses of 2 v. at a frequency of 20 stimuli/sec. was employed for electrical stimulation of the superior cervical nerve. The *trans* isomer was tested at dose levels of from 0.5 to 8 mg./kg. in two cats. Inhibition of the epinephrine pressor response first appeared following the 2 mg./kg. dose. At this dose the response was approximately 50% inhibited with little effect on the norepinephrine response. At 4 mg./kg. the epinephrine response was completely reversed and the norepinephrine response was about 67% inhibited. At 8 mg./kg. the *trans* isomer reversed epinephrine and inhibited norepinephrine about 75%. The epinephrine-induced contraction of the nictitating membrane and the contraction of the membrane to electrical stimulation were not inhibited at any of these doses. Due to the limited amount of material available, the *cis* isomer was tested in only one cat at doses of 1 and 2 mg./kg. Doses of 1 mg./kg. resulted in about a 40% inhibition of the epinephrine pressor response with no effect on the norepinephrine response. Doses of 2 mg./kg. resulted in approximately a 70% inhibition of the epinephrine response and almost a 50% inhibition of the norepinephrine response. It would appear that the two isomers are approximately equipotent. In one comparable experiment phenoxybenzamine[13] was administered in doses up to 8 mg./kg. Inhibition of the epinephrine pressor response began at about 4 mg./kg., but even at 8 mg./kg. there was only approximately a 20% inhibition. No effect on the nictitating membrane response to epinephrine or electrical stimulation was observed. These compounds, therefore, appeared to be more potent than phenoxybenzamine. Further confirmatory experiments would, of course, have to be run if statistical evaluations were to be carried out.

Discussion

It seems clear on the basis of the results discussed in the preceding section that forcing conformation III to become a ground state property of the molecule as in IV (where $n = 1$) leads to a considerable increase in adrenergic blocking activity. It can be safely concluded that XII and XXVII are considerably more potent than the parent compound I ($R = C_2H_5$).[6] The conclusion is permissible that this large increase in activity over that of I as well as phenoxybenzamine must be the consequence of a lowered entropy demand in the formation of the active conformation III at the receptor level. We consider these observations as constituting definitive evidence for the involvement at the receptor level of a conformation such as III which uniquely reproduces the distance relationships characteristic of the phenethylamine pattern.[2]

Although one might have expected the two isomers XII and XXVII, being geometrical isomers, to differ in potency, the fact that the distance separating the ring carbons of the EI-ion and the ethereal oxygen does not markedly differ in the two isomers provides little

(12) Dr. M. Pindell, Director of Pharmacological Research, Bristol Laboratories, Syracuse, N. Y.

(13) N-Benzyl-N-(β-chloroethyl)-2-phenoxyisopropylamine (ref. 6); this drug is about 20 times more potent than Dibenamine.[R]

justification for such an expectation.[14] The Newman projections XXIX and XXX for the active species, respectively, derivable from XII and XXVII, clearly illustrate this point. The preferred conformation for either XXIX or XXX must be that in which the bulky EI-ion substituent (which should approach the *t*-butyl group in effective bulk) is fixed exclusively in the pseudoequatorial orientation and the smaller ethereal oxygen in either the pseudoaxial (as in this *cis* isomer XXIX) or pseudoequatorial orientation (as in the *trans* isomer XXX).[15] A Newman projection IIIb of conformation III clearly illustrates the steric relationships with XXIX and XXX. The high potencies of the latter two serves to eliminate conformation IIIa as contributing to adrenergic blocking activity in the open chain series. More subtle information on the geometrical requirements for blocking activity in cyclic analogs of I may be obtained through the use of lower ring homologs of XII and XXVII.

Experimental[16]

***trans*-2-Phenoxycyclopentyl Chloride (VII).**—To a solution of 1.3 g. of *p*-toluenesulfonic acid and 68 ml. (52.4 g., 0.77 mole) of cyclopentene in 100 ml. of dry benzene was added while stirring 20 g. (0.10 mole) of *t*-butyl hypochlorite. After the heat of the reaction had subsided, a solution of 10 g. (0.1 mole) of phenol in 100 ml. of benzene was added. The mixture was cooled to 25° and an additional 100 ml. (1.13 moles) of cyclopentene was added followed by a solution of 117 g. (1.14 moles) of phenol in 150 ml. of benzene. Over a 3-hr. period, there was added while stirring 126 g. (1.16 moles) of *t*-butyl hypochlorite. The mixture was then extracted several times with 10% aqueous sodium hydroxide and then washed with water. The organic phase was dried and evaporated *in vacuo* to give a liquid which was distilled *in vacuo* yielding 129 g. (35%) of colorless liquid, b.p. 59–64° (0.2 mm.), $n^{25}D$ 1.5370, *d* 1.12. Both the infrared and n.m.r. spectra agreed with the expected structure even though it was not possible to obtain a satisfactory empirical analysis.

Anal. Calcd. for $C_{11}H_{13}ClO$: C, 67.1; H, 6.67; Cl, 18.0. Found: C, 70.9; H, 6.42; Cl, 15.1.

N-Methyl-*cis*-phenoxycyclopentylamine (IX).—A solution of 7 g. (0.036 mole) of chloride VII and 2.6 g. (0.084 mole) of methylamine in 10 ml. of dioxane was heated in a Parr bomb at 180° for 20 hr. The mixture was mixed with 50 ml. of 10% aqueous hydrochloric acid and extracted with ether. Evaporation of the ether gave 3.3 g. of crude starting chloride VII (47% recovery). The aqueous phase was made strongly alkaline and extracted with ether. The extract was dried and evaporated to give a liquid which was distilled *in vacuo* at 121–128° (9 mm.), yielding 2.2 g. of the amine IX. It was characterized as the crystalline hydrochloride, m.p. 134–136° after recrystallization from acetone–2-propanol.

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.3; H, 7.97; N, 6.15. Found: C, 63.0; H, 7.89; N, 6.28.

N-(β-Hydroxyethyl)-*cis*-2-phenoxycyclopentylamine (X).—A mixture of 28 g. (0.14 mole) of the chloride VII and 28 g. (0.46 mole) of 2-aminoethanol was heated under reflux and under nitrogen for 20 hr. The solution was poured into excess dilute hydrochloric acid and extracted with ether. The aqueous phase was made strongly alkaline and extracted with ether. The extract was dried and evaporated and the residue crystallized from benzene. There was obtained 4.5 g. (14.5%), m.p. 66–68° unchanged by further recrystallizations.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.68; N, 6.33. Found: C, 70.6; H, 8.66; N, 6.17.

N-Methyl-N-(β-hydroxyethyl)-*cis*-2-phenoxycyclopentylamine (XI).—A mixture of 3 g. (0.013 mole) of amino alcohol X, 2.7 g. (0.052 mole) of 90% formic acid, and 2.4 ml. (0.032 mole) of 40% aqueous formaldehyde was heated at 115° for 12 hr. Excess 50% aqueous sodium hydroxide was added and the cooled solution extracted with chloroform. The extract was dried and evaporated, and the residue was distilled *in vacuo* to yield 2.35 g. (77%) of colorless viscous oil, b.p. 180 (0.2 mm.), $n^{23}D$ 1.5405. It was characterized as the hydrochloride which after recrystallization from acetone–2-propanol had m.p. 152–154°.

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: C, 61.8; H, 8.15; N, 5.16. Found: C, 61.3; H, 8.22; N, 5.39.

N-Methyl-N-(β-chloroethyl)-*cis*-2-phenoxycyclopentylamine Hydrochloride (XII).—To a solution of 0.5 g. (0.002 mole) of XI in 5 ml. of dry chloroform was added 5 ml. of chloroform saturated with dry hydrogen chloride. The mixture was cooled to 0° while 0.5 ml. (0.007 mole) of thionyl chloride was added portionwise over a 5 min. period. The solution was stirred 15 min. at 0°, then stored 1 hr. at room temperature, and then heated under reflux for 1 hr. Evaporation *in vacuo* left an oil which was taken up in hot acetone–ethyl acetate. After standing several months at 25°, the compound crystallized and after recrystallization from acetone–2-propanol had m.p. 158–158.5°.

Anal. Calcd. for $C_{14}H_{21}Cl_2NO$: C, 57.8; H, 7.28. Found: C, 57.5; H, 7.50.

***cis*-2-Phenoxycyclopentylamine (VIII). (A) From the Schiff Base XIV.**—The starting 2-phenoxycyclopentanone (XIII) was prepared according to the literature.[17] A mixture of 2 g. (0.011 mole) of ketone XIII and 1.24 ml. (0.011 mole) of benzylamine was heated at 70° for 3 min., ethanol (25 ml.) was added, and the solution was hydrogenated over Adam's catalyst and 50 p.s.i. (3.5 kg./cm.²) of hydrogen for 3 hr. The catalyst was removed and 10 ml. of concentrated hydrochloric acid added. Hydrogenation was resumed over 10% palladium-on-carbon as the catalyst. After 15 hr., the catalyst was removed and the solution was taken to dryness *in vacuo*. The residue was dissolved in water and the solution extracted with ether. The aqueous phase was made strongly alkaline, extracted with ether, and the extract dried and evaporated to yield an oil which was distilled *in vacuo* yielding at about 200° (bath temp.) (18 mm.) 0.75 g. of colorless liquid. It was converted to the hydrochloride which crystallized from methanol–acetone, m.p. 197–199°.

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 61.8; H, 7.55; N, 6.56. Found: C, 61.8; H, 7.51; N, 6.59.

(B) From the Oxime XVI.—A solution of 1.3 g. (0.068 mole) of 2-phenoxycyclopentanone oxime (m.p. 105–107°) in 20 ml. of dry ether was added dropwise over 1 hr. to a stirred suspension of 0.5 g. (0.013 mole) of lithium aluminum hydride in 50 ml. of ether and the mixture heated under reflux for 1 hr. It was then carefully decomposed with water and aqueous sodium hydroxide solution, the precipitated salts filtered off, and the filtrate evaporated *in vacuo*. Distillation of the residue afforded 1.06 g. (88%) of colorless liquid b.p. (bath) 170° (18 mm.). It was identical (infrared spectrum and melting point of the hydrochloride) with the amine prepared by method A.

(C) From 2-Phenoxy-1-nitrocyclopentane (XVIII). Preparation of XVIII.—Oxidation of the oxime XVI to the nitro analog XVIII was carried out by the method of Emmons and Pagano.[18] A refluxing mixture of 5.15 g. (0.027 mole) of the oxime XVI, 0.55 g. of urea, 21 g. of disodium hydrogen phosphate, and 50 ml. of acetonitrile was treated over a 30-min. period with a quantity of peroxytrifluoroacetic acid prepared from 1.47 ml. of 90% hy-

(14) This can be easily seen with Barton molecular models; recent work by F. V. Brutcher, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959), and by F. V. Brutcher and W. Bauer, Jr., *ibid.*, **84**, 2233 (1962), made it apparent that in four-center reactions such as *trans* diaxial E_2 eliminations, the cyclopentane ring resembles the cyclohexane ring if the envelope conformation is assumed. It is now recognized that simple substituted cyclopentanes are more stable in the envelope rather than the half-chair conformation (see ref. 8, pp. 250–251). On that basis, the distance separating the oxygen and nitrogen atoms in the *cis* isomer XII is found to be only about 18% shorter than in the *trans* isomer XXVII. Moreover, because of free rotation about the carbon–nitrogen bonds, the difference in the respective distances separating the oxygen atom and one alkylating carbon in the two isomers can be made even smaller.

(15) In projections XXIX and XXX, the actual difference in the distances indicated by broken lines is of the order of 10% as can be seen with Barton molecular models (see ref. 14).

(16) All melting points were taken in open capillaries and are corrected. Infrared spectra were recorded with a Perkin–Elmer Infracord spectrophotometer. The n.m.r. spectra were recorded using a Varian instrument, Model V-4302, operating at 60 Mc./sec. Vapor phase chromatographic analysis were performed with a Pye apparatus equipped with an Apiezon column. Microanalyses were by Midwest Microlab, Indianapolis, Ind., and A. Castagne of the National Research Council of Canada.

(17) M. Mousseron, R. Jacquier, and A. Fontaine, *Bull. Soc. Chim. France*, 774 (1952).

(18) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

drogen peroxide and 9.1 ml. of trifluoroacetic anhydride in 15 ml. of acetonitrile. The mixture was heated under reflux for 1 hr. and the solvent removed *in vacuo*. The residue was extracted with ether, and the extract was washed with water and saturated sodium bicarbonate solution. The ether was dried and evaporated, and the residue was distilled *in vacuo* yielding at 130° (bath) (0.05 mm.) 4.03 g. (72%) of yellowish liquid; λ_{max} (liq. film) 1530 (NO_2 stretch) and 1225 cm.$^{-1}$ (aromatic ether).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.32. Found: C, 63.5; H, 6.10.

Reduction of XVIII.—A solution of 3 g. (0.014 mole) of XVIII in 30 ml. of dry ether was added over a 45-min. period to a suspension of 1.5 g. (0.037 mole) of lithium aluminum hydride in ether. After stirring for 3 hr., the mixture was decomposed with water and dilute alkali and worked up in the usual way. Distillation of the crude amine fraction gave 1.1 g. (44%) of pure VIII, b.p. 175° (bath) (19 mm.). It was identical in every respect (infrared spectrum and melting point of the hydrochloride) with the *cis* amine obtained by methods A and B.

***cis*-2-Phenoxycyclopentanol (XX). (A) By Reduction with Lithium Aluminum Hydride.**—A solution of 5 g. (0.028 mole) of 2-phenoxycyclopentanone (XIII) in 60 ml. of dry ether was added over a 1-hr. period to a stirred suspension of 2 g. (0.05 mole) of lithium aluminum hydride in 100 ml. of ether. After heating under reflux for 2 hr., the mixture was decomposed and worked up in the usual manner to give 5 g. of the expected alcohol (no carbonyl absorption in the infrared). Analysis of this material by v.p.c. (at 167°; 40 ml./min. of argon) revealed two components in a ratio of 66:34 (retention time 18 min. and 21 min., respectively). The isomeric alcohols were separated and characterized as their crystalline tosylates (prepared in the usual manner at 0° for 2 days and 22° for 2 days). The crude mixture of tosylates had m.p. 80–90°. Recrystallization from 2-propanol gave the pure *cis* **tosylate** XXI (6.3 g. from 5 g. of alcohol mixture), m.p. 98–100°.

Anal. Calcd. for $C_{18}H_{20}O_4S$: C, 65.2; H, 6.06. Found: C, 65.1; H, 6.20.

From the mother liquors, there was isolated 1.6 g. of the isomeric ***trans*-2-phenoxycyclopentanol *p*-toluenesulfonate,** m.p. 45–48°, identical (infrared spectrum and mixture melting point) with an authentic sample prepared subsequently.

(B) By Reduction with Lithium Tri-*t*-butoxyaluminum Hydride.—To a stirred suspension of 25 g. (0.1 mole) of lithium tri-*t*-butoxyaluminum hydride in 50 ml. of dry Diglyme was added over a 40-min. period a solution of 8 g. (0.045 mole) of 2-phenoxycyclopentanone in 30 ml. of Diglyme. The mixture was stirred for 2 hr. and then poured on ice-cold dilute hydrochloric acid. It was worked up in the usual way and the product distilled *in vacuo* at 85° (10 mm.), 8.7 g. (100%) of crude *cis* alcohol XX was collected. Analysis by v.p.c. as described previously indicated the presence of only 10% of the *trans* isomer. The *cis* isomer was converted to the same crystalline tosylate XXI (80%), m.p. 98–100°, as described in A.

***trans*-2-Phenoxycyclopentanol XIX and its Tosylate.**—A benzene solution of cyclopentene oxide (XXVIII) was prepared from 175 g. of 2-bromocyclopentanol in 690 ml. of benzene and 300 g. of powdered potassium hydroxide followed by distillation of the benzene–cyclopentene oxide mixture. The distillate of benzene–cyclopentene oxide was added dropwise over a 20-min. period to a stirred solution of 140 g. of purified phenol in 200 ml. of benzene containing 10 ml. of boron trifluoride etherate. The mixture was washed several times with 5% aqueous sodium hydroxide, then dried and evaporated. The residue was distilled *in vacuo* to give 44 g. (25% yield) of colorless viscous oil, b.p. 80–90° (0.005 mm.). The product was converted to the tosylate in the usual manner to give 60 g. (66% yield) of crude crystalline material. Recrystallization from 2-propanol gave 47 g. of colorless crystals, m.p. 48–49.5°.

Anal. Calcd. for $C_{18}H_{20}O_4S$: C, 65.2; H, 6.06. Found: C, 65.0; H, 6.17.

***trans*-2-Phenoxycyclopentyl Azide (XXIII).**—To a solution of 2.8 g. (0.043 mole) of sodium azide in 200 ml. of Carbitol containing 35 ml. of water was added 6.65 g. (0.02 mole) of *cis*-2-phenoxycyclopentyl tosylate (XXI). The mixture was slowly heated to 95° and maintained at that temperature for 24 hr. It was then worked up in the usual manner to give an oil which was distilled *in vacuo* at 100° (0.5 mm.), yielding 3.7 g. (90%) of colorless oil. It exhibited a strong peak at 2120 cm.$^{-1}$ in the infrared as expected for an alkyl azide.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.0; H, 6.43; N, 20.8. Found: C, 65.2; H, 6.34; N, 20.9.

***trans*-2-Phenoxycyclopentylamine (XXIV).**—The azide XXIII (3.7 g.) was hydrogenated under 31.5 kg./cm^2 of hydrogen in a solution of 3.5 ml. of concentrated hydrochloric acid in 100 ml. of methanol and over 1 g. of 10% palladium-on-charcoal. After 24 hr. the catalyst was removed, the solvent evaporated *in vacuo*, and the residue crystallized from 2-propanol to give 2.6 g. (66%) of the amine hydrochloride, m.p. 167–168°. A mixture melting point with the *cis* amine hydrochloride VIII gave a large depression (m.p. 142–183°).

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.8; H, 7.55; N, 6.56. Found: C, 61.6; H, 7.56; N, 6.51.

N-Formyl-*trans*-2-phenoxycyclopentylamine (XXV).—The amine hydrochloride XXIV was converted to the free base in 100% yield in the usual manner. A solution of 4 g. (0.018 mole) of the free base in 20 ml. of purified ethyl formate containing one drop of ethylene glycol was heated in a nickel bomb at 120° for 48 hr. Evaporation of the solution to dryness *in vacuo* gave an oil which crystallized from acetone to give 3.65 g. (100%) of white needles, m.p. 105–108°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.3; H, 7.41; N, 6.82. Found: C, 70.2; H, 7.26; N, 6.82.

N-Methyl-*trans*-2-phenoxycyclopentylamine (XXVI).—A solution of 3.3 g. (0.016 mole) of XXV in 500 ml. of dry ether was added dropwise over a 0.5-hr. period to a stirred slurry of 4 g. (0.1 mole) of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred for 12 hr. after which time water and aqueous sodium hydroxide were added to decompose the excess reagent. After working up in the usual manner, an oil was obtained which was distilled *in vacuo* at 135° (20 mm.), 2.85 g. (94%) of colorless oil was collected. It was characterized as the **hydrochloride** which crystallized from acetone, m.p. 105–109°, unchanged by further recrystallizations.

N-Methyl-N-(β-hydroxyethyl)-*trans*-2-phenoxycyclopentylamine (XXII). (A) From N-Methyl-*trans*-2-phenoxycyclopentylamine (XXVI).—A mixture of 1.1 g. of the N-methyl amine XXVI, 0.30 of ethylene oxide, and a trace of phenol was heated in a sealed tube at 50° for 24 hr., then at 95° for 24 hr., and finally at 150° for another day. Distillation of the mixture *in vacuo* gave 1 g. (90%) of the tertiary amine, b.p. 114° (0.05 mm.). Neither the picrate nor the hydrochloride could be induced to crystallize. The base was redistilled and a center cut taken for analysis.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.48; H, 8.93; N, 5.95. Found: C, 71.25; H, 8.81; N, 5.85.

(B) By Direct Substitution of *cis*-2-Phenoxycyclopentyl Tosylate (XXI).—A solution of 1 g. (0.003 mole) of the *cis* tosylate XXI in 10 ml. of purified N-methyl-2-aminoethanol was heated at 65° for 24 hr., then at 125° for another 24 hr., and finally at 145° for 20 hr. The excess solvent amine was removed *in vacuo* and the residue shaken with 20% aqueous sodium hydroxide. The insoluble oil was collected and distilled *in vacuo* to give 0.4 g. of colorless oil, b.p. 114° (0.05 mm.). The infrared spectrum of this product (XXII) was identical with that of the amine prepared by method A but was entirely different in the 850 to 1000 cm.$^{-1}$ region from the spectrum of the *cis* isomer XI.

N-Methyl-N-(β-chloroethyl)-*trans*-2-phenoxycyclopentylamine Hydrochloride (XXVII).—A solution of 0.4 g. of the tertiary amino alcohol XXII in 10 ml. of dry chloroform was treated at 0° first with dry hydrogen chloride (until acid to congo red) and then with 0.26 g. of thionyl chloride in 5 ml. of chloroform. The mixture was allowed to stand 12 hr. and then heated under reflux for 30 min., after which time it was decolorized with Norit, filtered, and evaporated to dryness *in vacuo*. The viscous pale yellow residue resisted all attempts at crystallization. It was dried under high vacuum at 80° before analysis.

Anal. Calcd. for $C_{14}H_{21}Cl_2NO$: C, 57.8; H, 7.28; N, 4.82. Found: C, 57.4; H, 7.68; N, 4.71.