(*c* 0.208, 0.0114), $[\phi]_{600}$ +247, $[\phi]_{589}$ +247, $[\phi]_{339}$ +8400, $[\phi]_{304}$ −8400, $[\phi]_{280}$ −646, $[\phi]_{255}$ −7100, (*a* = +168, midpoint 324 mμ).

Registry No.—**4,** 13866-15-4; **5,** 13961-88-1; N-acetyl derivative of (+) **5,** 13866-26-7; **7,** 13866-17-6; **13a,** 13866-18-7; **13b,** 13866-19-8; **13c,** 13866-20-1; HCl salt **14a,** 13866-25-6; **15,** 13866-21-2; **16,** 13866-22-3; N-acetyl derivative of **16,** 13866-24-5; N-benzylidene-(+)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol, 13866-23-4.

Synthesis and Stereochemistry of Amino Alcohols and Derivatives in the 2-Amino-α-phenylcyclohexanemethanol Series

J. SZMUSZKOVICZ AND L. L. SKALETZKY

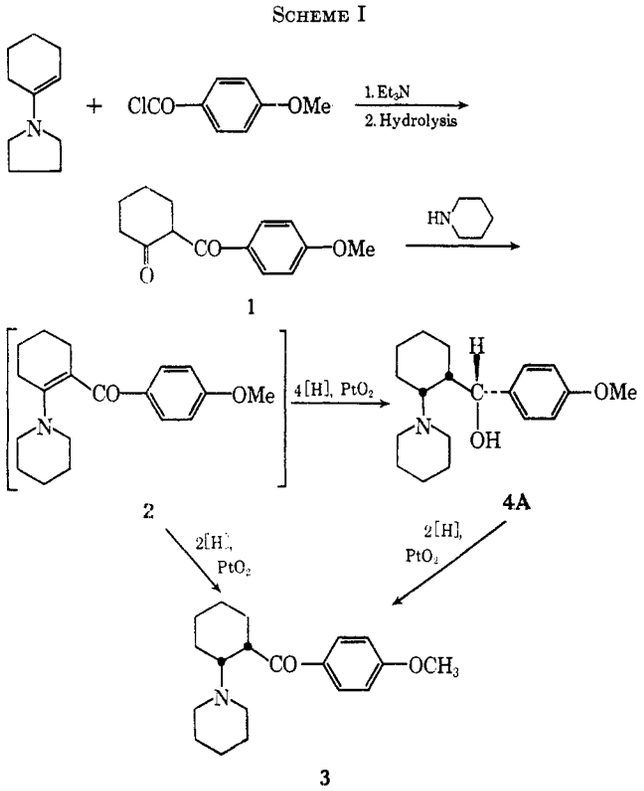
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received April 10, 1967

Synthesis of the four amino alcohols, racemates **4A, 4B, 4C,** and **4D** of 2-(piperidino)-α-(*p*-methoxyphenyl)-cyclohexanemethanol, was accomplished as shown in Schemes I and II. The stereochemistry of these four racemates was determined by chemical transformations, nmr and infrared techniques, and the conformations assigned as α′, β, γ, and δ, respectively (Table I and Figure 1). Racemates **4A** and **4B** were also correlated with octahydrobenzoxazinones **8A** and **8B** (Scheme III and Table II). An interesting behavior of octahydrobenzoxazinone **8A** was noted: it isomerized to **8B** with trifluoroacetic acid without decarboxylation (Schemes III and IV). The relative stabilities of **4A, 4B, 4C,** and **4D** were further examined by synthesis of the corresponding methyl ethers **10A, 10B, 10C,** and **10D** and interconversions in this series (Scheme V). Conformations were assigned to these ethers (Figures 2 and 3). Several miscellaneous reactions of amino alcohols **4A** and **14** are described (Scheme VI).

Stimulated by the finding that amino alcohols such as piperidino alcohol **4** showed interesting diuretic activity, we embarked upon a synthetic and stereochemical investigation of this class of compounds.[1]

SCHEME I



The preparation of the required starting materials, 2-benzoylcycloalkanones, is illustrated in the case of 2-(*p*-methoxybenzoyl)cyclohexanone (**1**; see Scheme I above).

According to the general procedure for acylation of enamines,[2] treatment of 1-cyclohexen-1-ylpyrrolidine with *p*-methoxybenzoyl chloride afforded the desired compound **1.**

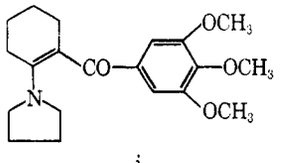
The next step, condensation of a 1,3-diketone with a secondary amine, is illustrated in the case of 2-(*p*-methoxybenzoyl)cyclohexanone (**1**) and piperidine (Scheme I), which gave the intermediate vinylogous amide (**2**). The ultraviolet spectrum of unpurified compound **2** in ether was compatible with the vinylogous amide structure and showed λ_{max} 264 mμ (*a* = 47.98) and 321 (7.41);[3] moreover, the nmr spectrum of the sample of **2** in carbon tetrachloride showed no absorption in the vinyl hydrogen region. Hydrogenation of **2** in ethanol in presence of platinum oxide gave the *cis*-alcohol **4A**[4] (see Scheme I and II), one of the two possible *cis* racemates. In some cases this type of amino alcohol could be prepared without isolation of the 1,3-diketone, but the yields were erratic.[5]

Preparation of the Four Amino Alcohol Racemates 4A, 4B, 4C, 4D and Assignment of *cis, trans* Configurations.—On treatment with trifluoroacetic acid (TFA), *cis*-alcohol **4A** was easily converted in 72%

(1) The pharmacological results of tests of a large number of compounds belonging to this class, only a few of which are described here, will be published elsewhere.

(2) See review of Enamines by J. Szmuszkovicz, *Advan. Org. Chem.*, **4,** 1 (1963).

(3) The ultraviolet spectrum (in ether) of the crystalline vinylogous amide (i) obtained from the condensation of 2-(3,4,5-trimethoxybenzoyl)-cyclohexanone with pyrrolidine showed λ_{max} 262 mμ (*a* = 33.26; ε 11,500) and 358 (*a* = 15.90; ε 5500).



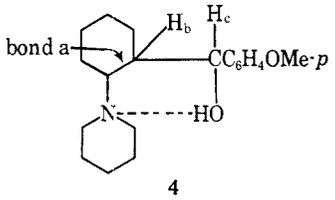
i

(4) Capital letters after Arabic numerals designate specific diastereoisomers of the structure in question.

(5) *Cf.* R. D. Campbell and J. A. Jung, *J. Org. Chem.*, **30,** 3711 (1965), who have shown that the reaction of 1-cyclohexen-1-yl morpholine with various benzoyl chlorides gives rise to 2,2-diacylcyclohexanones.

TABLE I

CONFORMATIONAL ANALYSIS OF **4A**, **4B**, **4C**, AND **4D**[a,b]



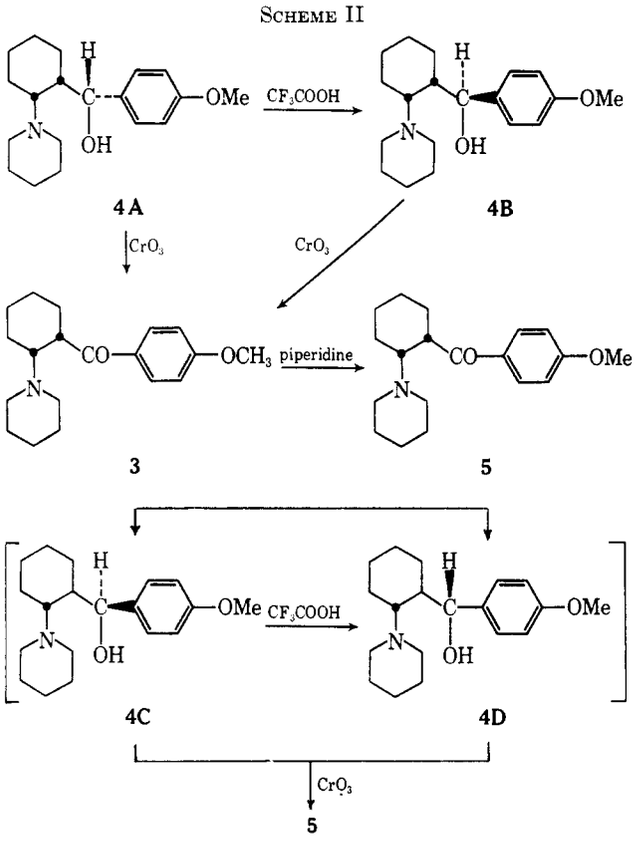
4

Configuration	Conformational designation	Stereochemistry about cyclohexane ring	Configuration of side-chain asym center	Conformation of piperidine	Dihedral angle H_b–C–C–H_c, deg	Predicted splitting[d]	Steric interference of *p*-methoxyphenyl and cyclohexane hydrogens	Obsd splitting and conformational assignment
A	α	*cis*	*threo*	Equatorial	~60	Small doublet (2.5 cps)	Very severe	
	α'	*cis*	*threo*	Axial	~30	Doublet	Less severe	Singlet[e]
B	β	*cis*	*erythro*	Equatorial	~180	Doublet	No	Doublet, J = 10 cps
	β'	*cis*	*erythro*	Axial	~90	Singlet	No	
C	γ	*trans*	*erythro*	Equatorial	~180	Doublet	No	Doublet, J = 9 cps
	γ'	*trans*	*erythro*	Axial	No H bonding	No H bonding		
D	δ	*trans*	*threo*	Equatorial	~60	Small doublet (2.5 cps)	Yes	Broad, could easily be
	δ'	*trans*	*threo*	Axial	No H bonding	No H bonding		doublet ~2–3 cps

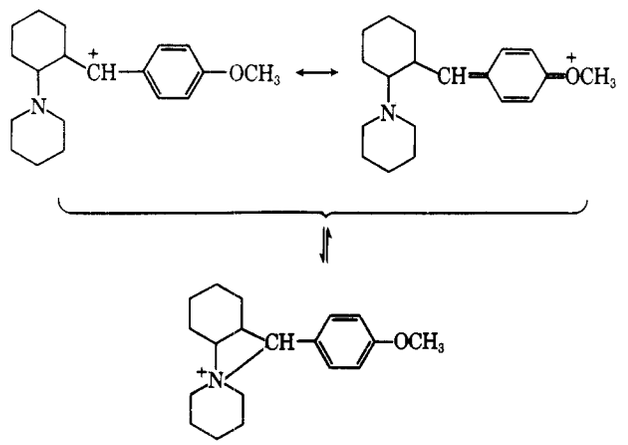
[a] Alcohols **4A, 4B, 4C,** and **4D** all showed hydrogen-bonded hydroxyl in carbon disulfide solution and the absorption did not shift in the range of about 0.5 M down to infinite dilution. We therefore conclude that the hydroxyl is intramolecularly hydrogen bonded to the nitrogen and the conformational analysis is that of a rigid molecule. [b] *erythro* is the configuration in which *p*-methoxyphenyl and bond a are superimposed and H_b and H_c are superimposed; *threo* is when *p*-methoxyphenyl and bond a are not superimposed and H_b and H_c are superimposed.[c] [c] D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, p 332. [d] See ref 8. [e] See text for further explanation.

yield (Scheme II) to *cis*-alcohol **4B.**[6] Alcohols **4A** and **4B** probably approached equilibrium proportions in this experiment through the carbonium ion intermediate and **4B** appears to be the more thermodynamically stable epimer. The assignment of configuration to **4B** is made on steric grounds. Examination of Dreiding or Courtauld models (see analysis in Table I) discloses that steric interference of the *p*-methoxyphenyl group with hydrogens of the cyclohexane ring occurs in structure **4A** but not in structure **4B.** Alcohols **4A** and **4B** belong to the *cis* series (cyclohexane ring) since both were oxidized by means of Jones reagent[7] to the same *cis*-ketone **3** (Scheme II), which was previously obtained (Scheme I) by hydrogenation of the vinylogous amide **2** with 1 mole of hydrogen. Prolonged heating of the *cis*-ketone **3** with piperidine afforded the epimerized *trans*-ketone **5** and some

SCHEME II



(6) The conversion of *cis*-alcohol of configuration A to the B configuration with TFA was followed by nmr over a period of 2 hr and the results are consistent with the following reasonable equilibrium.



(7) Jones reagent consists of 26.72 g of chromic acid and 23 ml of sulfuric acid diluted to 100 ml with water: K. Bowden, I. M. Heilbron, E. R. H Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

1-cyclohexen-1-yl *p*-methoxyphenyl ketone, the elimination product. Treatment of the *cis*-ketone with a stronger base (sodium methoxide) gave largely the elimination product. Besides the mode of formation and stability, the assignment of the *cis* and *trans* stereochemistry to the ketones is also supported by nmr analysis. The *cis*-ketone **3** showed in deuteriochloroform a sharp peak at 233 cps with a somewhat broad

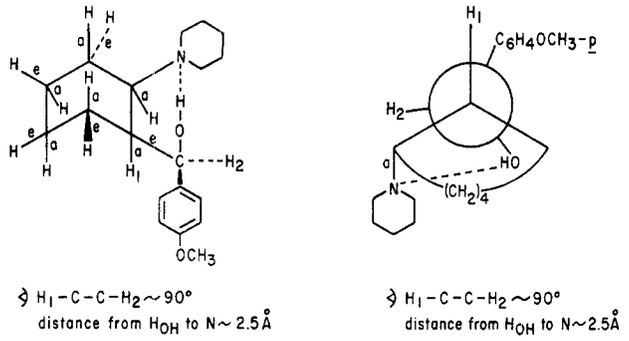


Figure 1.—Conformations of isomer **4A**.

base; the area corresponded to four hydrogens which included the methoxyl and the hydrogen α to the carbonyl. The *trans*-ketone **5** showed in deuteriochloroform a sharp peak at 232 cps corresponding to three hydrogens of the methoxyl and a multiplet centered at 210 cps (hydrogen of intensity one corresponding to the hydrogen α to the carbonyl) in which three doublets were visible. This spectrum is most consistent with the ketone of *trans* configuration, the Dreiding model of which indicates that the axial hydrogen α to the carbonyl is subject to two *trans* diaxial interactions with adjacent hydrogens (dihedral angle 180°) and one axial–equatorial interaction (dihedral angle 60°).[8]

Catalytic reduction of the *cis*-ketone in ethanol in the presence of platinum oxide afforded 89% of alcohol **4A**; sodium borohydride reduction gave 72 and 14% and lithium aluminum hydride gave 67 and 23% of alcohols **4A** and **4B**, respectively.

The *trans*-ketone **5** was hydrogenated in ethanol in the presence of platinum oxide to give *trans*-alcohol **4C** in 91% yield. When $LiAlH_4$ was used, a mixture of alcohols **4C** and **4D** resulted in 59 and 19% yield, respectively. Alcohols **4C** and **4D** were oxidized by Jones reagent[7] to the same *trans* ketone 5 which demonstrated that these two alcohols differed only in their configuration at the benzylic carbon and possessed the *trans* stereochemistry in the cyclohexane ring. On 20-min treatment with trifluoroacetic acid, **4C** afforded a 13% yield of alcohol **4D** and 54% of alcohol **4C** was recovered; after 17 hr the yields of alcohol **4D** and **4C** were 6 and 43%, respectively.[9] If equilibrium conditions were achieved during the epimerization experiment, it follows that the carbonium ion intermediate leads to alcohol **4C** and **4D** of which **4C** is thermodynamically preferred. Dreiding models (see analysis in Table I) support this view since **4D** shows more interference than **4C** with respect to steric compression of the *p*-methoxyphenyl group and the axial hydrogen of the cyclohexane ring.

Configuration of the Side-Chain Asymmetric Center Relative to the Other Two Asymmetric Centers.—Two approaches are presented for the elucidation of the configuration of the side chain asymmetric relative to the other two: namely, conformational analysis of the four racemates based on nmr data and the corresponding analysis of a rigid molecule.

With three asymmetric centers in compound **4**, four racemates are possible which possess configurations **A, B, C,** and **D**. All four racemates are in hand. The conformational analysis of this system is presented in Table I along with experimental data. Isomer **4B** (*cis*) and isomers **4C** and **4D** (*trans*) do not present any special problem and have been assigned conformations β, γ, and δ, respectively, on the basis of infrared and nmr measurements. Only configuration **A** remains for the second *cis* isomer. The nmr spectrum of compound **4A** can be rationalized in terms of configuration **A** as follows. Isomer **A** exhibits proton H_c as a singlet. A doublet would be predicted on the basis of conformation α' and a small doublet (2.5 cps) on the basis of conformation α. This last possibility can be excluded because of very severe steric interference of the *p*-methoxyphenyl group and the cyclohexane hydrogens. The observed singlet points to a dihedral angle of about 90° for the H_c–C–C–H_b system. This angle can be realized with Dreiding or Courtauld models in two ways with the assumption that the molecule is conformationally homogeneous by virtue of hydrogen bonding between the hydroxyl and the amino functions. The first involves a structure which has one of the conformations with cyclohexane in the boat form. The most attractive one is pictured in Figure 1 in which the hydrogen bond to nitrogen is ~2.5 Å. The second points to a structure corresponding to conformation α' in which cyclohexane is in the chair form, piperidine is axial, and the hydrogen bond to N is lengthened to ~2.5 Å in order to accommodate the angle of 90° for H_1–C–C–H_2, thus relieving the steric interaction between the *p*-methoxyphenyl group and two hydrogens on the cyclohexane ring (see Figure 1). We prefer the latter possibility for alcohol **4A** based on the higher energy requirements of the boat form.[10] The inherently high energy of configuration **A** is experimentally supported by its essentially complete conversion to compound **4B** with TFA.

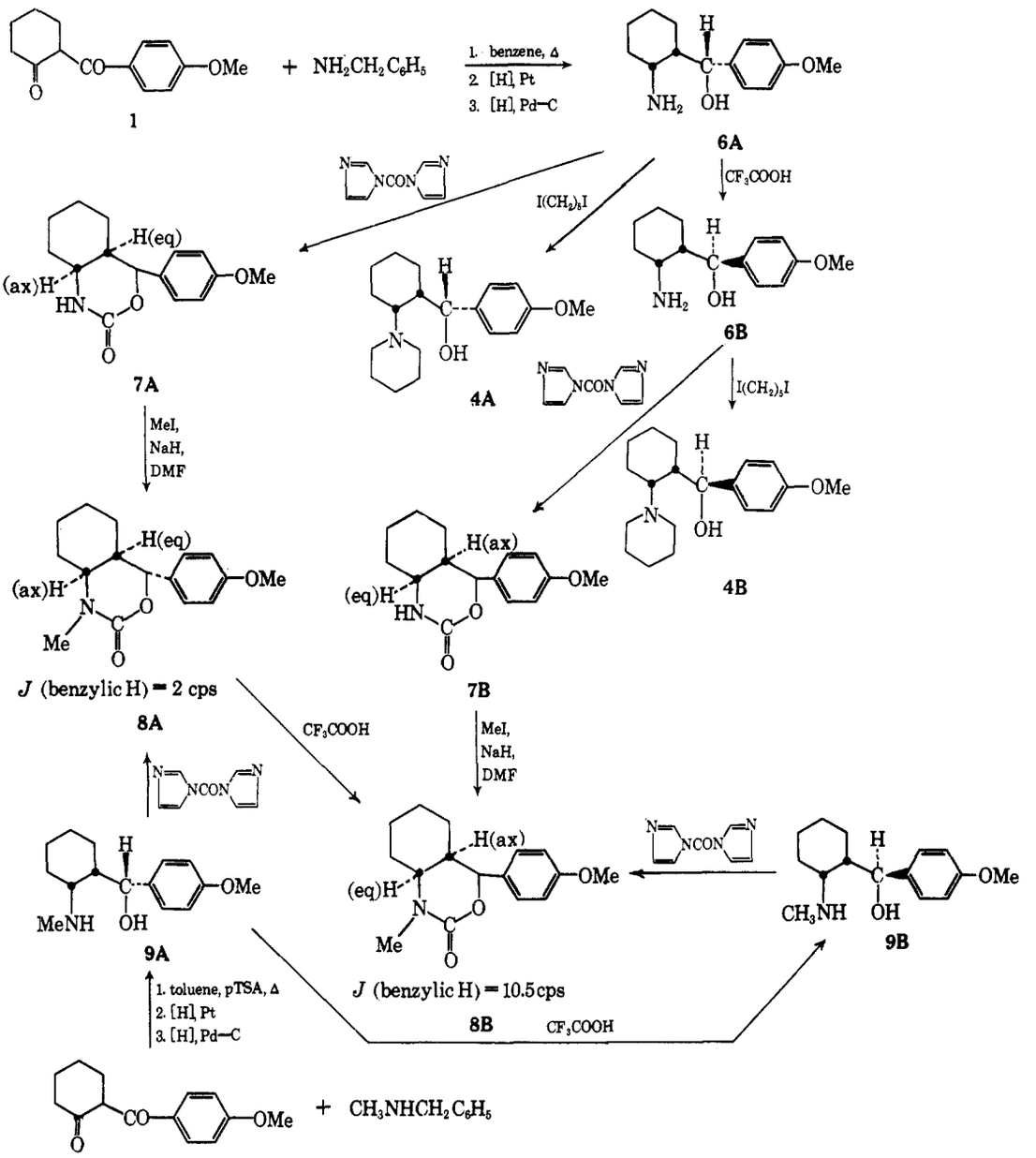
The hypothesis that compounds **4A** and **4B** are held in a rigid configuration by intramolecular hydrogen bonding was tested by generating the model compounds **8A** and **8B** in which a covalent bond was substituted for a hydrogen bond. In compounds **8A** and **8B** an octahydro-2H-3,1-benzoxazin-2-one ring system was used for this purpose. The configurations of compounds **4A** and **8A** and of compounds **4B** and **8B** were established by chemical transformations (see below). The nmr of **8A** exhibited a doublet (which corresponds to the hydrogen on the benzylic carbon) with a very small splitting constant (J = 2 cps) and possesses a configuration analogous to compound **4** of configuration **A** (see Table II). This near singlet again points to a dihedral angle for H_c–C–C–H_b (see formula in Table II) that approaches 90°. Dreiding models in which the cyclohexane ring is *either* chair or boat provide a dihedral angle estimated to be about 60° and point to conformation α' for compound **8A**. The alternative conformation α shows severe steric interference between the *p*-

(8) See ref 15 and 16 in M. Stiles, R. R. Winkler, Y. Chang, and L. Traynor, *J. Am. Chem. Soc.*, **86**, 3337 (1964), and ref 7–15 in C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, **31**, 1000 (1966).

(9) The transformation of alcohol **4C** to **4D** with TFA was followed by nmr over a period of 5 hr. After 8 min a doublet at 281–291 cps and a quartet from 356 to 367 cps was observed. The spectrum remained essentially constant over the 5-hr period. Further work would be required to ascertain the nature of the species responsible for these two absorptions. The doublet may be due to the proton on the carbon bearing the positive charge in the open-chain carbonium ion species or to the proton on the benzylic carbon in the four-membered ring cyclic intermediate[6] produced by attack of the nitrogen atom on the benzylic carbon. The quartet may be due to a styrene-type elimination product.

(10) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 206.

SCHEME III[11]



methoxyphenyl group and cyclohexane hydrogens. This evaluation is consistent with the small splitting constant observed and supports the explanation for the singlet for H_c in compound **4A**. Further support for the assignment of conformation α' rather than α to compound **8A** stems from the comparison of the values for chemical shift of H_a (see formula in Table II) in the nmr spectra of **8A** and **8B**. In isomer **8A**, H_a is buried in the sharp aromatic methoxyl band at 229 cps, while in isomer **8B**, which has been assigned unequivocally conformation β, H_a is a quintuplet centered at 196 cps with J = 5 cps. Conformation α would be expected to show a chemical shift for H_a similar to conformation β (see Table II) and this is not the case. Compound **8B** exhibits a doublet with J = 10.5 cps for H_c, a value identical with that for compound **4B**, and this fact points to conformation β for **8B** (see Table II). This identity establishes further support for the rigid conformation (owing to hydrogen bonding) for compounds **4A** and **4B**.

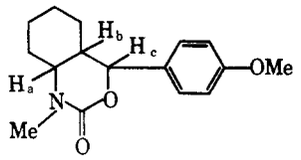
Synthesis of model compounds **8A** and **8B** and correlation with alcohols **4A** and **4B** was accomplished as outlined in Scheme III. The stereochemical equivalence of **6A** and **4A** on one hand, and of **6B** and **4B** on the other was first established. The primary amino alcohol **6A** was converted to compound **4A** with 1,5-diiodopentane in the presence of base.[12] Treatment of **6A** with trifluoroacetic acid afforded primary amino alcohol **6B** which gave compound **4B** on treatment with 1,5-diiodopentane and base. Compound **8A** was prepared in two ways. Treatment of **6A** with N,N′-carbonyldiimidazole gave octahydrobenzoxazinone **7A**, which was converted to the N-methyloctahydrobenzoxazinone **8A** (J = 2 cps for the benzylic hydrogen) on treatment with sodium hydride and methyl iodide in dimethylformamide. The same compound **8A** resulted when the

(11) See footnote *a*, Table II.

(12) F. N. Hayes, L. C. King, and D. E. Peterson, *J. Am. Chem. Soc.*, **78**, 2527 (1956).

TABLE II

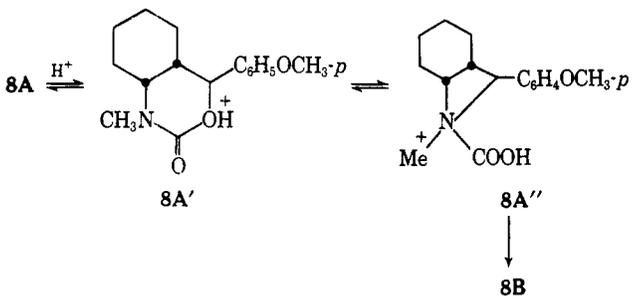
CONFORMATIONS[a] OF *cis* **8A** AND *cis* **8B**



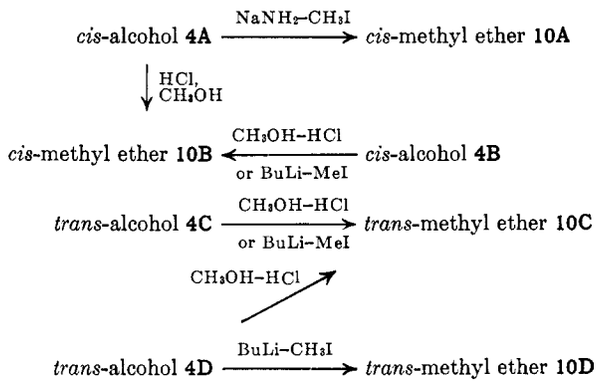
Configuration	Conformational designation	H_a[c]	H_b[c]	H_c[c]	C_6H_4OMe-*p*	Steric interference of C_6H_4OMe-*p*	H_b–C–C–H_c deg	Predicted splitting[b] H_b–C–C–H_c	Obsd splitting
cis **A**	α	*e*	*a*	*e*	*a*	Yes	~60	2–7 cps	
	α'	*a*	*e*	*a*	*e*	No	~60	2–7 cps	2 cps, isomer **A**
cis **B**	β	*e*	*a*	*a*	*e*	No	~180	5–13.5 cps	10.5 cps, isomer **B**
	β'	*a*	*e*	*e*	*a*	No	~60	3–4 cps	

[a] The hydrogens are defined with reference to the heterocyclic ring, assuming a chair (a boat conformation does not alter the arguments). [b] These are values for cyclohexane quoted from R. H. Bible, "Interpretation of nmr Spectra An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 37. [c] *e* = equatorial; *a* = axial.

SCHEME IV



SCHEME V
METHYL ETHERS



N-methyl compound **9A**, obtained in three steps starting from 2-(*p*-methoxybenzoyl)-cyclohexanone and N-methylbenzylamine, was subjected to reaction with N,N'-carbonyldiimidazole. Compound **8B** was synthesized three ways. First, **8B** (J = 10.5 cps for the benzylic hydrogen) was obtained on treatment of **8A** with trifluoroacetic acid. Second, it was produced *via* the sequence **6B** → **7B** → **8B**. Finally, the third route involved **9A** → **9B** → **8B**.

An interesting sidelight to the stereochemistry and synthesis in this octahydrobenzoxazinone system is the seemingly anomalous behavior of compound **8A** which isomerizes to **8B** with TFA without decarboxylation. Compound **7A** under the same conditions gives **6B**, the decarboxylation and isomerization product, and a mixture of N-trifluoroacetyl derivatives of **6A** and **6B**. One possible explanation for the above difference is that in the case of **8A**, ring closure of the intermediate formed is faster than decarboxylation, which is not so in the case of the –NH containing carbamate **7A**.[13] Another possible explanation (see Scheme IV) is that the protonated species **8A'** is in equilibrium with **8A''** which undergoes intramolecular ring opening to give the product **8B**. Greater ease of formation of the four-membered ring intermediate and greater stability of the product in the case of **8A** due to the N-methyl group would be expected in the case of **8A** compared with **7A**.

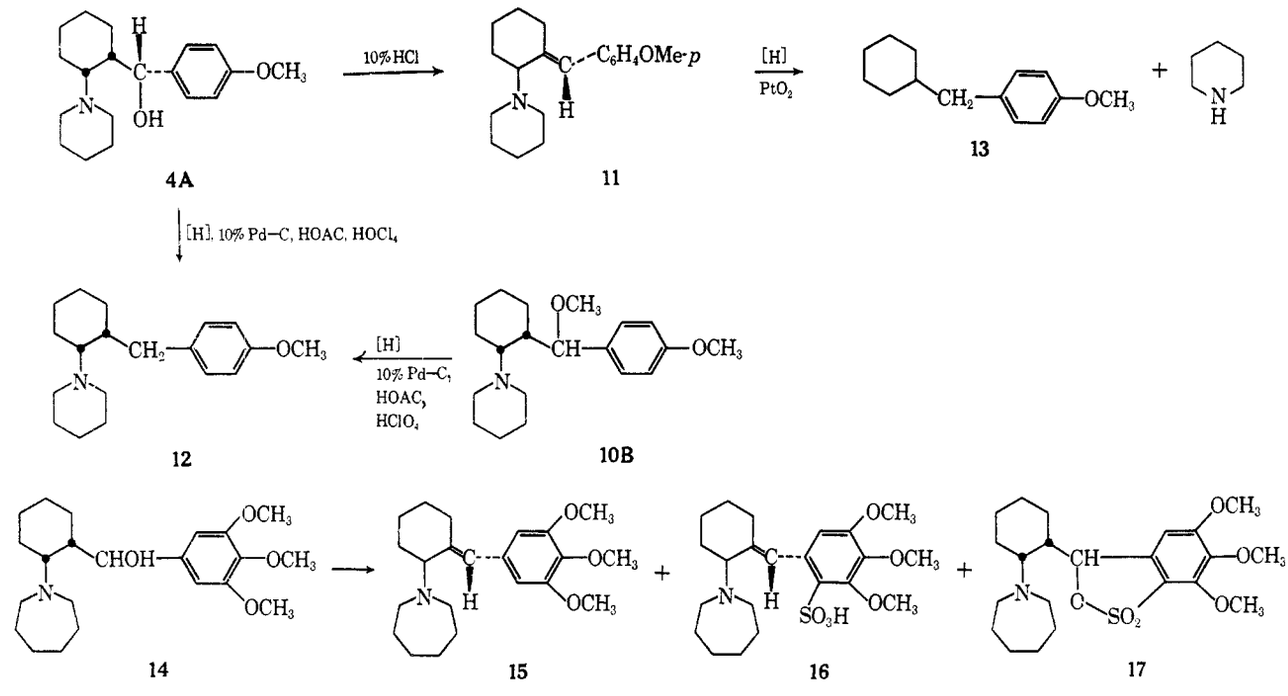
Conformational Analysis of Methyl Ethers.—The relative stabilities of the diastereoisomers of this study were further examined by synthesis of the methyl ethers of alcohols **4A**, **4B**, **4C**, and **4D** and also by interconversions in this series (see Scheme V). Each alcohol gave the corresponding methyl ether without epimerization by the Williamson ether synthesis. As expected, hydrogen chloride catalyzed etherification of the four alcohols proceded by a solvolytic mechanism which, in principle, could lead through the carbonium ion to either of two diastereoisomers. Only two ether products were ever detected among the products of this reaction; alcohols **4A** and **4B** gave methyl ether **10B** and alcohols **4C** and **4D** afforded methyl ether **10C**. Had olefin intervened as an intermediate in formation of ether, more isomers would be expected. A control experiment demonstrated that olefin does not give ether under conditions of the experiment.

Furthermore, analysis of the coupling constants of the benzylic hydrogen in methyl ethers makes it possible to assign conformations to these compounds. Methyl ether **10B** shows J = 9 cps which is almost identical with the coupling constant in the corresponding N-methylbenzoxazine **8B** (J = 10) and *cis*-alcohol **4B** (J = 10 cps). One can, therefore, assign to methyl ether **10B** the sterically most stable staggered conformation as shown in the Newman projection (Figure 2). The sterically most preferred of the four possible partially eclipsed conformations is shown for methyl ether **10C** and the most likely staggered conformation is shown for methyl ether **10D**.

Only methyl ether **10A** remains to be evaluated. It showed J = 5.5 cps for the benzylic hydrogen which suggests a dihedral angle of ~40 or ~125°. The four most probable conformations (out of possible eight) for **10A** are shown in Figure 3, all possessing cyclohexane in

(13) M. L. Bender and R. B. Homer, *J. Org. Chem.*, **30**, 3975 (1965); I. Christenson, *Acta Chem. Scand.*, **18**, 904 (1964). We wish to thank Professor F. M. Menger of Emory University for bringing this reference to our attention.

SCHEME VI



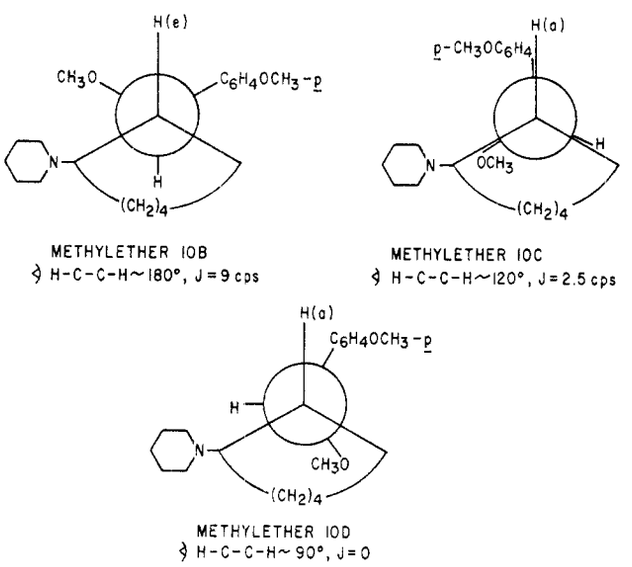


Figure 2.—Conformations of methyl ethers **10B**, **10C**, and **10D**.

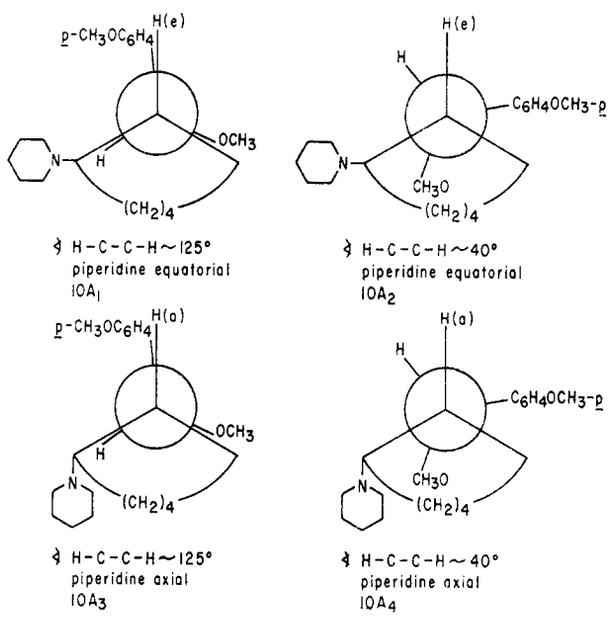


Figure 3.—Conformations of methyl ether **10A**.

the chair form. The other four conformations all show severe steric interactions for the *p*-methoxyphenyl group. Projections **10A**$_1$ and **10A**$_2$ represent conformations in which piperidine is equatorial and **10A**$_3$ and **10A**$_4$ represent conformations in which piperidine is axial. Dreiding models show that **10A**$_3$ and **10A**$_4$ exhibit less steric interaction between piperidine and the *p*-methoxyphenyl ring than **10A**$_1$ and **10A**$_2$. Therefore, methyl ether **10A** is best represented as an equilibrium mixture of conformers **10A**$_3$ and **10A**$_4$.

Miscellaneous Reactions.—Several transformations of the amino alcohols deserve comment (see Scheme VI). Brief treatment of *cis*-alcohol **4A** with 10% hydrochloric acid afforded the styrene **11**, the most likely structure of which is shown and is based on steric considerations. Attempted preparation of the benzyl compound **12** by hydrogenation of **11** hydrochloride in ethanol in the presence of platinum oxide resulted in hydrogenolysis to *p*-(cyclohexylmethyl)anisole (**13**) and piperidine.[14] The desired compound **12** was prepared by hydrogenation of alcohol **4A** (or preferably ether **10B**) in acetic acid solution in presence of 10% palladium on carbon and perchloric acid.

Treatment of the trimethoxy *cis*-alcohol **14** with concentrated sulfuric acid afforded three products. The styrene compound **15** showed the expected λ_{max} 261 mμ (ϵ 12,800), one vinyl proton at 394 cps, and two aromatic protons at 388 cps. The second compound is

(14) For other cases of hydrogenolysis of allylic amines, see R. K. Hill, T. M. Chan, and J. A. Joule, *Tetetrahedron*, **21**, 147 (1965); J. P. Dickinson, J. Harley-Mason, and J. H. New, *J. Chem. Soc.*, 1858 (1964); A. A. Santili, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964); T. Nakano, T. H. Yang, and S. Terao, *Tetrahedron*, **19**, 609 (1963), and *J. Org. Chem.*, **28**, 2619 (1963); S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, and Y. Tamura, *Tetrahedron*, **19**, 2085 (1963).

assigned structure **16** as it showed 252 mμ (sh) (ε 9250) and two singlets at 400 and 427.5 cps which correspond to one aromatic and one vinylic proton, respectively. The third compound showed no extended conjugation in the ultraviolet, one proton of type HCO– at 263.5 cps, and one aromatic proton at 392 cps; it is therefore assigned structure **17**.

Experimental Section[15-20,21a]

2-(*p*-Methoxybenzoyl)cyclohexanone (1).—A solution of *p*-anisoyl chloride (167 g, 0.98 mole) in 480 ml of chloroform was added during 1.5 hr to a solution of distilled 1-cyclohexen-1-ylpyrrolidine[21b] (371.7 g, 2.46 moles) in 1260 ml of chloroform and the temperature was maintained at 5–10° by ice cooling. After stirring overnight at room temperature, the mixture was decomposed by addition of 1800 ml of 10% aqueous hydrochloric acid over about 20 min and stirred for 2 hr. The organic layer was separated and the aqueous layer was extracted with two 250-ml portions of chloroform. The combined extracts were washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated. A solution of the resulting brown oil in 1 l. of ethanol was added to a solution of 344 g of cupric acetate monohydrate in 5200 ml of water preheated to 65°. The mixture was stirred for 0.5 hr, cooled to room temperature; and filtered, the precipitate was washed with water and then ether. It was dissolved in 800 ml of chloroform and added to a solution of 300 ml of concentrated hydrochloric acid in 1100 ml of water. The mixture was stirred for 1 hr. The organic layer was separated and the aqueous layer was extracted once with chloroform. The combined extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated. The resulting solid was crystallized from 7 l. of methanol to give 136.5 g of **1** as a mixture of keto and enol forms, mp 115–128°. The second crop amounted to 26 g: mp 116–127°; yield, 71%.

A sample was recrystallized for analysis from methanol: mp 117–122°;[22] ultraviolet, λ_{max} 219 mμ (ε 10,900), 279 (16,450); infrared, =CH 3010 cm^{-1}, C=O 1704, 1668, 1660, C=C 1602, 1575, 1512, CO 1316, 1287, 1250, 1170, 1125; aromatic, 914, 857, 810, 779.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.30; H, 7.05.

(15) Melting points were taken in Pyrex capillaries and are corrected. Ultraviolet spectra (recorded in millimicrons) were determined in 95% ethanol (unless otherwise specified) using a Cary spectrophotometer, Model 14. Infrared spectra (recorded in cm^{-1}) were determined in Nujol using a Perkin-Elmer spectrophotometer, Model 21. Nuclear magnetic resonance (nmr) spectra were run on a Varian high resolution 60-Mc instrument; measurements are expressed in cycles per second downfield from tetramethylsilane used as an internal standard and deuteriochloroform was used as a solvent unless otherwise specified. Florisil is a synthetic magnesia–silica gel adsorbent manufactured by the Floridin Co., Warren, Pa. Skellysolve B is a saturated hydrocarbon fraction, bp 60–70°, available from Skelly Oil Co., Kansas City, Mo. Silica gel, 0.05–0.20 mm, for chromatography, E. Merck AG Distribution, Brinkmann Instruments, Inc., Great Neck, L. I., N. Y. Thin layer chromatography (tlc) on silica gel, Florisil, and neutral alumina (Woelm) were used extensively throughout the experimentation.

(16) Vapor phase chromatography (vpc) was run isothermally using F & M Model 720 (thermal conductivity unit) with a 6 ft × 0.25 in. o.d. (stainless steel tube) column packed with (a) XE-60 or (b) QF-1-0065 both on Gas Chrom Z (60–80 mesh) or (c) Apiezon-L on Gas Chrom Z (80–100 mesh). (d) Vpc was run isothermally using F & M Model 400 (flame ionization unit) with a 4 ft × 0.25 in o.d. (glass tube) column packed with SE-40 on Gas Chrom Z (60–80 mesh).

(17) Helium flow rate: (a) 45 ml/mm; (b) 54 ml/mm; (c) 60 ml/mm; (d) 65 ml/mm; (e) 70 ml/mm; (f) 95 ml/mm.

(18) Injection port temperature: (a) 280°; (b) 290°; (c) 300°; (d) 305°; (e) 310°.

(19) Detector temperature: (a) 230°; (b) 235°; (c) 240°; (d) 245°; (e) 250°; (f) 255°; (g) 260°; (h) 265°.

(20) Column temperature: (a) 195°; (b) 200°; (c) 210°; (d) 215°.

(21) (a) The authors are indebted to Dr. W. A. Struck and his associates for microanalyses, to Mrs. B. Zimmer for ultraviolet spectra, to Mr. P. A. Meulman and Miss L. M. Pschigoda for infrared spectra, to Messr. J. F. Zieserl, Jr., and F. A. MacKellar for nmr spectra, to Mr. G. E. Bronson for vpc analyses, and to Mr. L. G. Laurian for laboratory assistance. (b) See ref 2, p 98.

(22) This compound was prepared previously by a different procedure by C. R. Hauser, F. W. Swamer, and B. I. Ringler, *J. Am. Chem. Soc.*, **70**, 4023 (1948), and by B. O. Linn and C. R. Hauser, *ibid.*, **78**, 6066 (1956).

***cis*-2-(Piperidino)-α-(*p*-methoxyphenyl)cyclohexanemethanol (4A).**—A mixture of **1** (23.2 g, 0.1 mole), piperidine (25.5 g, 0.3 mole), 800 ml of toluene, and 0.67 g of *p*-toluenesulfonic acid was refluxed for 25 hr using an azeotropic separator (1.7 ml of water was collected). The mixture was evaporated to dryness; the residue was dissolved in 300 ml of ethanol and hydrogenated in the presence of 1 g of platinum oxide and an initial pressure of 51 psi. Hydrogen (2 moles) was absorbed in 2.5 hr. The mixture was filtered through Filtercel and evaporated to dryness, and the residue was dissolved in 250 ml of ether. Crystallization ensued and the resulting solid was filtered and washed with ether: yield, 1 g; mp 152–168°. Crystallization from methanol–ether afforded the *p*-toluenesulfonic acid salt of the desired alcohol **4A** as clusters of colorless needles: mp 182–183°; ultraviolet, λ_{max} 223 mμ (21,800), 256 sh (705), 262 sh (980), 268 sh (1360), 275 (1530), 282 (1280); infrared, OH 3320 cm^{-1}, =CH 3010, $\geq \overset{+}{N}H$ 2760, C=C 1615, 1590, 1515, CO–CN 1245, 1160, 1115, 1050, 1005; aromatic, 680.

Anal. Calcd for $C_{26}H_{37}NO_5S$: C, 65.66; H, 7.84; N, 2.95; S, 6.74. Found: C, 65.27; H, 7.88; N, 2.89; S, 6.86.

The above ethereal filtrate was stirred with 200 ml of 10% aqueous acetic acid for 0.5 hr. The aqueous layer was separated and extracted once with ether ("neutral ether layer"). The aqueous layer was cooled, basified, and extracted with four 75-ml portions of methylene chloride. The extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 22.5 g of oil. Crystallization from petroleum ether (bp 30–60°) afforded 21.4 g (71% yield; 92.4% pure by vpc;[16a,17d,18c,19a,20d] retention time 11.1 min) of **4A**: mp 78–80° raised to 81–83° on recrystallization; ultraviolet, λ_{max} 225 mμ (11,500), 275 (1500), 283 (1300); infrared, OH 3100 cm^{-1}, *t*-amine 2800, 2760, C=C 1605, 1585, 1505, 1485, CO–CN 1235, 1160, 1125, 1095, 1045, 1025; aromatic, 830, 815, 805. The infrared spectrum in CS_2 solution was run in various dilutions and revealed only intramolecular bonded OH at 3160; nmr, benzylic H singlet at 304 cps (area 1), OCH_3 singlet at 228.5 (area 3).[23]

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.17; H, 9.88; N, 4.47.

A sample of **4A** was treated in ether with ethereal hydrogen chloride. The resulting solid was washed well with ether. It was crystallized from methanol–ether and melted at 235–236°: ultraviolet, λ_{max} 226 mμ (12,100), 276 (1600), 283 (1350); infrared, OH 3200 cm^{-1} (s), $\geq \overset{+}{N}H$ 2640, 2540, C=C 1610, 1585, 1510; CO–CN 1245, 1200, 1170, 1130, 1040, 1025, 100; aromatic, 750.

Anal. Calcd for $C_{19}H_{29}NO_2 \cdot HCl$: C, 67.14; H, 8.90; Cl, 10.43; N, 4.12. Found: C, 67.20; H, 8.98; Cl, 10.72; N, 4.12.

The hydrochloride could also be crystallized from water or methylene chloride. The hydrochloride (0.4 g) was recovered unchanged in quantitative yield after refluxing overnight in 50 ml of methanol. A sample of **4A** was converted to the *p*-toluenesulfonic acid salt which was identical with the material obtained above.

The "neutral ether layer" (obtained from a run three times the size of the present one) was washed separately with two 50-ml portions of 5% sodium hydroxide, water, and saturated salt solution, dried (Na_2SO_4), and evaporated to give 18 g of an oil. It was dissolved in 50 ml of methylene chloride and chromatographed on 540 g of Florisil. Elution with seven 250-ml portions 6% acetone–Skellysolve B gave 1.34 g of solid melting in the range 56–82°. Two crystallizations from Skellysolve B gave 0.25 g of product which is likely α-(*p*-methoxyphenyl)-cyclohexanemethanol:[24] mp 81.5–82.5° raised to 82–83° on further recrystallization: ultraviolet, λ_{max} 225 mμ (11,000), 275 (1670), 281.5 (1420); infrared, OH 3440 cm^{-1} (s), C=C 1640, 1610, 1595, 1580, 1510, CO 1250, 1170, 1100, 1075, 1030, 1000; aromatic, 820; nmr (in $CDCl_3$ + D_2O), benzylic H doublet

(23) The following nmr results were obtained for the benzylic hydrogen in other solvents: dimethylformamide-d_6, doublet centered at 297.5 cps (J = 2 cps), which collapsed to broad singlet on addition of D_2O; dimethyl sulfoxide-d_7, doublet centered at 303 cps (J = 2 cps) which somewhat collapsed on addition of D_2O; acetone-d_6, broad singlet at 304 cps unaffected on addition of D_2O; CD_3OD, a multiplet centered at 302 cps, $W_{1/2}$ = 2 cps. *Cf.* reference quoted in ref 17 by C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, **31**, 1000 (1966), and their pertinent comment concerning small differences in J values.

(24) E. M. Arnett and G. B. Klingensmith, *J. Am. Chem. Soc.*, **87**, 1023 (1965).

centered at 257.5 cps (area 1), J = 7 cps, OCH_3 singlet at 227.5 cps (area 3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.55; H, 9.31.

Elution with further 250 ml gave 86 mg which was discarded. Elution with four 250-ml portions of 12% acetone–Skellysolve B gave 0.394 g of oily product which was discarded. Further elution with five 250-ml portions gave 11.7 g of solid fractions melting in the range 96–100°. Crystallization from ether–Skellysolve B afforded 6.6 g of product which is likely 2-hydroxy-α-(*p*-methoxyphenyl)cyclohexanemethanol: mp 100–102° unchanged on recrystallization; ultraviolet, λ_{max} 225 mμ (11,000), 275 (1550), 282 (1320); infrared, OH 3260 cm^{-1} (s), impurity at 1750, 1720, C=C 1610, 1585, 1510, CO 1245, 1175, 1090, 1040; aromatic, 870, 815; nmr, benzylic H at 293.5 cps (area 1), cyclohexane H on carbon bearing hydroxyl at 246.5 cps (area 1), OCH_3 singlet at 227 cps (area 3), two OH at 214 and 177 cps (exchanged with D_2O).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.91; H, 8.67.

***cis-p*-Methoxyphenyl-2-Piperidinocyclohexyl Ketone (3).**—The reaction of 1 (139 g, 0.6 mole) with piperidine was run as above and the subsequent hydrogenation was stopped after the absorption of 1 mole of hydrogen. The mixture was filtered through Filtercel and the solution was evaporated to dryness. The resulting deep yellow oil was dissolved in 1200 ml of ether and crystallization was allowed to proceed for 15 min. The precipitate was filtered and washed with ether: yield, 5.3 g; mp 125–127°. This was likely a *p*-toluenesulfonic acid salt, but attempted purification by crystallization from methanol–ether was not successful. The ethereal filtrate was stirred with 1 l. of 10% aqueous hydrochloric acid for 45 min. The acidic layer was separated, filtered, and basified with 20% aqueous sodium hydroxide. The resulting oil (which solidified after a short time) was extracted with five 200-ml portions of methylene chloride. The combined organic solution was washed with water, then with saturated salt solution, dried (Na_2SO_4), and evaporated. The crude product (116 g) was crystallized from 300 ml of petroleum ether to give 75 g (42%) of colorless needles, mp 86–88°, in two crops. The analytical sample melted at 86.5–88° (from the same solvent). Ultraviolet spectra were found at λ_{max} 217, mμ (11,850), 273 (15,800), 278 (15,500); infrared bands were found for *t*-amine 2860, 2760, C=O 1665, C=C 1600, 1580, 1515, CO–CN 1250, 1225, 1170, 1110 and 1030; aromatic, 840.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 76.19; H, 9.19; N, 4.88.

***trans-p*-Methoxyphenyl 2-Piperidinocyclohexyl Ketone (5).**—A solution of the *cis*-ketone **3** (68.3 g, 0.227 mole) in 683 ml of piperidine was refluxed for 68 hr. It was evaporated to dryness and the residue (55 g of oil) was dissolved in 500 ml of ether and extracted with four 100-ml portions of 10% aqueous acetic acid. The acid extract was cooled in ice, basified with 20% aqueous sodium hydroxide, and extracted with four 150-ml portions of methylene chloride. The organic solution was washed with saturated salt solution, dried (Na_2SO_4), and evaporated to give 22 g of colorless solid. It was crystallized from 150 ml of petroleum ether: yield, 12.05 g; mp 100–101°. The second crop amounted to 3.5 g: mp 99–100° (23%); ultraviolet, λ_{max} 216 mμ (12,900), 271 (15,350); infrared, *t*-amine 2800, 2740 cm^{-1}, C=O impurity 1725 w, C=O 1665, C=C 1600, 1575, 1510, CO–CN 1250, 1215, 1170, 1110, 1030; aromatic, 850, 835, 825, 815, 810.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.28; H, 8.66; N, 4.62.

The original ether layer was washed with 5% aqueous sodium hydroxide, then with saturated salt solution, dried (Na_2SO_4), and evaporated to give 32 g of yellow oil: vpc,[16a,17c,18c,19a,20d] one peak (retention time 2.1 min identical with that of 1-cyclohexen-1-yl *p*-methoxyphenyl ketone obtained below). The neutral oil was combined with the residue from crystallization (total 35.6 g) and was refluxed in piperidine (356 ml) for 60 hr. The resulting suspension was filtered and the crystalline material was washed with ether: yield, 4.5 g; mp 244–245°. This was proven to be piperidine hydrochloride (by infrared comparison and mixed melting point with authentic sample). The filtrate was worked up as before to give 20 g of neutral material and a total of 14.4 g of the *trans*-ketone, which was obtained in three crops melting in the range 100–103°. The neutral fraction and the residue from the last basic filtrate were combined (25 g) and refluxed for 68 hr with 250 ml of piperidine. No precipitate appeared during the reaction. Work-up as above afforded 8 g of neutral fraction and 9.3 g of the *trans*-ketone, mp 103–104°. The total yield of the *trans*-ketone from these three passes was 58%. The neutral fraction (8 g) was shown to be 99.1% pure by vpc[16a,17d,18c,19a,20d] (retention time 2 min). Distillation from an oil-jacketed flask afforded 6.1 g of 1-cyclohexen-1-yl *p*-methoxyphenyl ketone[25] as a yellow oil boiling at 145–155°, which later solidified: ultraviolet, λ_{max} 226 mμ (11,000), 253 sh (8600), 278 sh (12,100), 283 (12,200); infrared, C=O 1640 cm^{-1}, C=C 1600, 1575, 1510, CO 1255, 1175, 1035; aromatic, 840; nmr, vinyl H quintuplet centered at 389 cps, J = 2 cps, OCH_3 singlet at 230 cps.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.99; H, 7.57.

Catalytic Reduction of *cis*-Ketone 3 to 4A.—A solution of *cis*-ketone **3** (3.01 g, 0.01 mole) in 100 ml of ethanol was subjected to hydrogenation in the presence of platinum oxide (0.3 g) at initial pressure of 53 psi of hydrogen. Hydrogen (1 mole) was absorbed in 25 hr. The mixture was filtered and the filtrate was evaporated to dryness. The resulting oil (3.1 g) showed four peaks in vpc;[16a,17d,18c,19a,20d] the **4A** peak corresponded to 89% (retention time 10.2 min). The oil (2.9 g) was chromatographed on 150 g of Florisil. Elution with four 150-ml portions of 6% acetone–Skellysolve B gave 0.126 g which was discarded. Elution with eight 150-ml portions of 12% acetone–Skellysolve B gave 2.294 g of solid melting at 81–82°. Elution with four 150-ml portions of 25% acetone–Skellysolve B gave 0.309 g of solid melting at 81–82°. Crystallization of the combined solid from petroleum ether afforded 2.2 g, mp 81–82°, in the first crop and 0.2 g, mp 81.5–82.5°, in the second crop. Mixture melting point with an authentic sample of alcohol **4A** showed no depression.

Reduction of *cis*-Ketone 3 with Sodium Borohydride to 4A and 4B.—*cis*-Ketone **3** (3.01 g, 0.01 mole) was added to an ice-cooled solution of sodium borohydride (3 g) in 100 ml of ethanol and the mixture was stirred at room temperature for 16 hr. It was evaporated to dryness *in vacuo* at 40°, 100 ml of water was added, and the mixture was stirred for 30 min. The resulting oil was extracted three times with ether. The extract was washed with water (discarded water) and then with four 25-ml portions of 10% aqueous acetic acid. The acidic extract was washed once with ether (discarded ether) and was then cooled in ice and basified with 15% sodium hydroxide solution. The mixture was extracted three times with ether and the extract was washed with water, then with saturated salt solution, dried (Na_2SO_4), and evaporated to give 3.0 g of oil. It showed no residual carbonyl absorption in the infrared spectra. Vpc[16a,17e,18b,19a,20d] showed four components: alcohol **4A** peak corresponded to 76.87% (retention time 9.5 min) and alcohol **4B** to 13.84% (retention time 13.0 min). The mixture was crystallized from 50 ml of petroleum ether to give 1.8 g of alcohol **4A** (by mixture melting point), mp 78–80°. The filtrate was evaporated to dryness and the residue was chromatographed on 60 g of Florisil. Elution with two 150-ml portions of 6% acetone–Skellysolve B, four 150-ml portions of 12% acetone–Skellysolve B, and three 150-ml portions of 20% acetone–Skellysolve B gave 0.576 g of alcohol **4A**, which afforded 0.45 g, mp 80–81°, after recrystallization from petroleum ether. Elution with four 150-ml portions of 50% acetone–Skellysolve B and two 250-ml portions of acetone gave 0.316 g of crude alcohol 4B, which on crystallization from ether melted at 135–136° (0.1 g) and did not depress the melting point of an authentic sample. The total yield of alcohol **4A** was 74.5% and of alcohol **4B** was 3.3%.

Reduction of *cis*-Ketone 3 with Lithium Aluminum Hydride to 4A and 4B.—A solution of *cis*-ketone **3** (0.9 g, 3 mmoles) in 25 ml of ether was added dropwise during 5 min to a solution of lithium aluminum hydride in 100 ml of ether and the mixture was stirred for 22 hr. It was then decomposed in succession with 1 ml of water, 1 ml of 15% sodium hydroxide, and 3 ml of water. The suspension was stirred for 2 hr; it was filtered; and the solid was washed with ether. The filtrate was extracted with three 30-ml portions of 10% acetic acid and the combined acetic extracts were back-washed once with ether. The acidic extract was basified with 15% sodium hydroxide and extracted three times with ether. The ether extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 0.77 g of colorless oil. Infrared showed no residual carbonyl absorption. Vpc[16a,17e,18b,19a,20d] showed four peaks: alcohol **4A** peak corresponded to 63.76% (retention time 9.5 min) and alcohol

(25) W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.*, **81**, 967 (1959).

4B to 29.57% (retention time 13.6 min). The crude oil was chromatographed on 35 g of Florisil. Elution with four 150-ml portions of 6% acetone–Skellysolve B gave 0.607 g (67%) of alcohol **4A**, mp 80–81° (no depression on mixed melting point with authentic sample). Further elution with four 150-ml portions of 12% acetone–Skellysolve B gave 0.209 g (23%) of alcohol **4B**, mp 134–135° (no depression on mixture melting point with authentic sample).

Catalytic Reduction of *trans*-Ketone 5 to 4C.—A solution of *trans*-ketone **5** (3.01 g, 0.01 mole) in 100 ml of ethanol was hydrogenated in the presence of 0.5 g of platinum oxide at initial pressure of 53 psi of hydrogen. After 138 min, the mixture was filtered through Filtercel and the filtrate evaporated to give 3.0 g of solid, mp 141–145°. Vpc (run as below) indicated 98.9% purity. Crystallization from methanol in the cold afforded 2.5 g of colorless needles, mp 148–149°, unchanged on recrystallization. The second crop amounted to 0.25 g: mp 145–146°; yield of alcohol **4C**, 91%; ultraviolet, λ_{max} 225 mμ (12,150), 275 (1500), 281 (1300); infrared, OH 3070 cm^{-1} (bonded), C=C 1610, 1585, 1515; CO–CN 1250, 1175, 1065, 1035, aromatic, 860, 835, 825. The infrared spectrum in CS_2 solution was run in various dilutions and revealed only intramolecular bonded OH at 3060; vpc,[16a,17c,18c,19a,20d] 98.74% purity (retention time 12.8 min); nmr, benzylic H doublet centered at 265.5 cps, J = 9 cps (area 1), OCH_3 singlet at 228 (area 3).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.18; H, 9.81; N, 4.82.

Reduction of *trans*-Ketone 5 with Lithium Aluminum Hydride to 4C and 4D.—A solution of the *trans*-ketone **5** (23.9 g, 0.0795 mole) in 575 ml of ether was added to a solution of 24 g of lithium aluminum hydride in 2400 ml of ether over a 30-min period. The mixture was stirred overnight. It was then decomposed in succession with 24 ml of water, 24 ml of 15% sodium hydroxide, and 72 ml of water. The mixture was filtered and the cake was washed with ether. The filtrate was evaporated to dryness to give 22.5 g of a colorless oily solid. Crystallization from 75 ml of methanol gave 13.4 g of alcohol **4C**, mp 145–146°. The filtrate was evaporated to dryness. The residue was dissolved in 50 ml of methylene chloride and chromatographed on 460 g of Florisil. Elution with 3% acetone–Skellysolve B (750 ml) gave 81 mg (discarded). Elution with 19 250-ml portions of 6% acetone–Skellysolve B gave 5.31 g of solid fractions melting with range 80–82°. Further elution with four 250-ml portions of 15% acetone–Skellysolve B gave 0.535 g of solid, mp 80–81°. Recrystallization of the combined material from petroleum ether afforded 4.6 g of alcohol **4D**, mp 81–82°. Further elution with four 250-ml portions of 25% acetone–Skellysolve B gave 0.884 g, mp 135–142° (not worked up). Elution with four 250-ml portions of 50% acetone–Skellysolve B followed by acetone (5750 ml) gave 2.836 g, which was crystallized from methanol to give 0.9 g of alcohol **4C**, mp 146–147.5°. Alcohols **4C** and **4D** were identified by comparison with authentic samples (mixture melting point, infrared spectra). The total yield of **4C** was 59% and of **4D** was 19%.

Treatments with Trifluoroacetic Acid. A. Epimerization of 4A to 4B with Trifluoroacetic Acid.—Trifluoroacetic acid (200 ml) was added to 30.3 g (0.1 mole) of **4A** cooled in ice. The mixture was then stirred at room temperature for 20 min. The resulting green solution was cooled in ice; ice (*ca.* 150 g) was added followed by 500 ml of water and then 500 ml of 20% sodium hydroxide. The mixture was stirred for 15 min and then extracted with five 200-ml portions of methylene chloride. The organic extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to dryness to give 28 g of a colorless solid. It was dissolved in 1 l. of ether and the solution was concentrated to about 200 ml when crystallization commenced: yield, 16.4 g of needles; mp 133–134°; vpc[16a,17c,18b,19a,20d] indicated 97.1% purity (retention time 14.2 min). The second crop (4.7 g, mp 130–131°) and the third crop (2.1 g, mp 129–130°) were combined and recrystallized from ether to give 5.1 g melting at 130–131°. The total yield of **4B** was 71.5% (21.5 g). The analytical sample melted at 134.5–135.5° (from ether): ultraviolet, λ_{max} 225 mμ (13,000), 266 sh (1140), 274 (1500), 281 (1300); infrared, bonded OH 3100 cm^{-1}, *t*-amine 2750, 2670, 2620, C=C 1645 (vw), 1610, 1585, 1515, 1495, CO–CN 1250, 1175, 1105; aromatic, 830, 810. The infrared spectrum in CS_2 solution was run in various dilutions and revealed only intramolecular bonded OH at 3100. Nmr analysis showed a benzylic H doublet centered at 304 cps, J = 10 cps (area 1), and a OCH_3 singlet at 228 cps (area 3).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 74.96; H, 9.62; N, 4.55.

In another run, run exactly the same way as above but on a 0.01-mole scale, direct crystallization yielded only 41% of **4B**. The rest of the material was chromatographed on Florisil (50:1). Elution with 6% acetone–Skellysolve B afforded 8.1% yield of **11** (isolated as hydrochloride). Elution with 12% acetone–Skellysolve B gave 6% yield of **4A** (isolated as hydrochloride). Elution with 20% acetone–Skellysolve B, 50% acetone–Skellysolve B, and acetone gave additional 8% yield of **4B**.

B. Epimerization of 4C to 4D with Trifluoroacetic Acid.—A solution of *trans*-alcohol **4C** (0.60 g, 1.98 mmoles) in 4 ml of trifluoroacetic acid was stirred for 20 min. It was cooled in ice, 10 ml of water was added, followed by 10 ml of 20% sodium hydroxide. The mixture was extracted twice with methylene chloride. The extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 0.6 g of colorless solid, mp 129–140°. Crystallization from methanol afforded 0.325 g (54%) of recovered starting material, mp 145–147° (identified by mixture melting point). The filtrate was evaporated to dryness and the residue was chromatographed on 15 g of Florisil. Elution with 400 ml of 6% acetone–Skellysolve B gave a product which on crystallization from petroleum ether afforded 77 mg (12.8%) of **4D**: mp 81–82°; ultraviolet, 226 mμ (11,100), 276 (1650), 282 (1450); infrared, OH 3220 cm^{-1} (bonded), C=C 1610, 1585, 1510, CO–CN 1245, 1175, 1040; aromatic, 840, 15. The infrared spectrum in CS_2 solution was run in various dilutions and revealed only intramolecular bonded OH at 3210. Nmr analysis showed a benzylic H (br) could easily be doublet centered at 278.5 cps, $J \sim 2$–3 cps (area 1), OCH_3 singlet at 229 cps (area 3).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.19; H, 9.63; N, 4.55.

When the above reaction was repeated with 0.283 g (0.935 mmole) of alcohol **4C** and 4 ml of trifluoroacetic acid for 17 hr, 0.107 g of starting material was recovered by direct crystallization. Chromatography afforded 15 mg of starting material (total recovery, 43%) and 18 mg (6.4%) of alcohol **4D**.

C. Treatment of 11 with Trifluoroacetic Acid.—Trifluoroacetic acid (20 ml) was added to 0.01 mole of **11** while cooling in ice and stirring. The deep green solution was stirred at room temperature for 20 min. It was then cooled in ice, 50 g of ice followed by 50 ml of water and 50 ml of 20% sodium hydroxide were added, and the mixture was extracted with three 25-ml portions of methylene chloride. The extract was washed with salt solution, dried ($MgSO_4$), and evaporated to give 2.5 g of a yellow oil. Chromatography on 125 g of Florisil gave a total of 76% recovered **11** as a hydrochloride. It was identified by mixture melting point and comparison of ultraviolet and nmr spectra with those of the authentic sample.

Chromic Acid Oxidations. A. Oxidation of *cis*-Alcohol 4A.—Jones reagent[7] (1.87 ml, 5 mmoles) was added to a solution of **4A** (1.5 g, 5 mmoles) in 25 ml of acetone during 5 min. The mixture was evaporated at 30° *in vacuo* and 25 ml of water was added. The mixture was cooled in ice and was basified with 10 ml of 10% sodium hydroxide. It was extracted three times with methylene chloride. The organic extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 1.5 g of yellow oil. It crystallized on standing (mp 75–80°) and was recrystallized from ether–petroleum ether to give 1 g of ketone **3**, mp 81–83°. It was identical with an authentic sample as determined by mixture melting point and comparison of ultraviolet and infrared spectra.

B. Oxidation of *cis*-Alcohol 4B.—A solution of **4B** (1.5 g, 5 mmoles) in 50 ml of acetone was treated with Jones reagent[7] as described above. The crude product (1.5 g) crystallized and melted at 79–82°. Recrystallization from ether–petroleum ether afforded 1.1 g melting at 81–83°. This compound was identical with ketone **3** as determined by mixture melting point and comparison of ultraviolet and infrared spectra.

C. Oxidation of *trans*-Alcohol 4C.—A solution of **4C** (1.5 g, 5 mmoles) in 50 ml of acetone was treated with Jones reagent[7] as described above. The crude product (1 g) melted at 94–96°. It was dissolved in 75 ml of petroleum ether, the solution was filtered to separate some insoluble material, concentrated to *ca.* 10 ml, and allowed to crystallize: yield, 0.8 g; mp 97–98°. This compound was identical with *trans*-ketone **5** (as determined by mixture melting point and comparison of ultraviolet and infrared spectra).

D. Oxidation of *trans*-Alcohol D.—A solution of **4D** (0.56 g, 1.7 mmoles) in 25 ml of acetone was treated with Jones reagent[7] as described above. The crude product (0.25 g) melted at 104–105° and was identical with *trans*-ketone **5** as determined by mixture melting point and comparison of ultraviolet and infrared spectra.

Synthesis of *cis*-2-Amino-α-(*p*-methoxyphenyl)cyclohexanemethanol (6A). A. *cis*-2-(Benzylamino)-α-(*p*-methoxyphenyl)-cyclohexanemethanol.—A solution of **1** (23.0 g, 0.099 mole) and benzylamine (11.0 g, 0.103 mole) in 150 ml of benzene was heated at reflux for 1.5 hr using a Dean–Stark trap (collected 2.2 ml of water). The solvent was concentrated *in vacuo;* the residue was dissolved in 150 ml of absolute alcohol and hydrogenated in the presence of 1.5 g of platinum oxide for 18 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in 200 ml of 10% acetic acid and 300 ml of ether and the mixture was stirred for 1–1.5 hr. The acid layer was separated and basified with 20% sodium hydroxide solution. The oil which separated was extracted with methylene chloride and the organic extract was washed with water, saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation left 22.8 g of an oil which gave a hydrochloride with ethereal hydrogen chloride. The hydrochloride was crystallized from ethanol–ether: yield, 18.35 g (51%); mp 210–211°. The crop 2 yield was 0.60 g, mp 217.5–218°. The analytical sample melted at 217–218°.

Anal. Calcd for $C_{21}H_{27}NO_2 \cdot HCl$: C, 69.69; H, 7.80; Cl, 9.80; N, 3.87. Found: C, 69.69; H, 8.12; Cl, 9.80; N, 3.74.

A sample of the hydrochloride was converted to the free base: mp 86.5–87.5° (from Skellysolve B); ultraviolet, λ_{max} 225 mμ (12,700), 253 sh (475), 259 sh (732), 264 sh (1050), 268 sh (1250), 275 (1550), 282 (1350); infrared, NH–OH 3310, 3260, 3300 cm^{-1} (br), C=C 1610, 1580, 1510, 1490, CO–CN 1245, 1165, 1090, 1030; aromatic, 840, 830, 820, 755, 745, 720, 695; nmr, benzylic, –CHO singlet at 297.5 cps, OCH_3 singlet at 226.5 cps.

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.68; H, 8.32; N, 4.33.

B. Hydrogenolysis to 6A.—A suspension of the above benzylamino compound (20.0 g, 0.0615 mole) in 1 l. of absolute alcohol was hydrogenated in the presence of 3.0 g of 10% palladium on carbon for 32 hr at 30 psi. The catalyst was removed by filtration and the filtrate evaporated. The residue was dissolved in ether. The solution was dried and evaporated and the product crystallized from Skellysolve B: yield, 11.1 g (77%); mp 86.5–88.5° unchanged on recrystallization; ultraviolet, λ_{max} 224 mμ (11,700), 275 (1550), 282 (1300); infrared, NH–OH 3360, 3310 cm^{-1} (both sharp), ~2900 br, C=O–NH def 1610, 1585, 1510, 1485, CO–CN 1245, 1165, 1040, 1095, 1085, 1030; aromatic, 835, 820, 810; nmr, benzylic H singlet at 296 cps (area 1), OCH_3 singlet at 227 cps (area 3).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.10; H, 9.00; N, 5.88.

Compound **6A** was also prepared in 67% yield without isolation of the benzylamino intermediate.

Conversion of 6A to 4A with 1,5-Diiodopentane.—A mixture of **6A** (1.10 g, 4.67 mmoles), 1,5-diiodopentane (1.6 g, 4.94 mmoles), and 7.0 g of anhydrous potassium carbonate in 75 ml of methyl ethyl ketone was stirred at reflux for 16.5 hr. The solvent was evaporated *in vacuo* and the residue was dissolved in methylene chloride–water. The organic layer was separated, washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated. A solution of the resulting oil was chromatographed on 100 g of silica gel. Elution with 500 ml of methylene chloride gave fractions which were discarded. Elution with 1 l. of 2.5% an 1 l. of 5% methanol in methylene chloride gave a gum (0.66 g) which had the same tlc (silica gel) mobility as **4A**. $Vpc^{16d,17f,18a,19b,20d}$ indicated 96.5% of **4A** (retention time 7.3 min) and no **4B**. The gum was dissolved in pentane, seeded with **4A**, and allowed to crystallize at −2°: crop 1, 148 mg, mp 81.5–83.5°; crop 2, 275 mg, mp 80–82°; crop 3, 70 mg, mp 78.5–81.5°. Mixture melting point with **4A** showed no depression and the infrared spectra were identical. A hydrochloride was prepared from mother liquors of crop 3 and its was crystallized from isopropyl alcohol–ether: yield, 28 mg; mp 217.5–221°. Mixture melting point with **4A** hydrochloride showed no depression. The total yield of **4A** was 37%. When this reaction was run with **6A**, 1,5-dibromopentane, and potassium carbonate in dimethylformamide for 16 hr at 95°, the yield of **4A** was 8% (isolated as the hydrochloride).

Conversion of 6A to 6B with Trifluoroacetic Acid.—Compound **6A** (2.35 g, 0.01 mole) was added in one portion to 20 ml of trifluoroacetic acid at 0–10°, the ice bath was removed, and the greenish solution was stirred for 40 min. The solution was then cooled in an ice bath and 20 g of ice, 50 ml of water, and 50 ml of 20% sodium hydroxide solution were added and the mixture was stirred for 45 min. It was extracted with methylene chloride, the organic extract was washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 2.45 g of gum. $Vpc^{16b,17b,18d,19g,20b}$ showed six components and indicated the presence of 42.77% of **6B** (retention time 3 min).

The oxalate was prepared in ether and the salt was suspended in 200 ml of methyl ethyl ketone and warmed on the steam bath for *ca.* 5 min. The suspension was filtered and the white solid (1.5 g, mp 173–173.5°) crystallized from methanol–ether or ethanol–ether: yield, 1.42 g (44%); mp 178–179°. The oxalate (1.3 g) was converted to the free base in methanol with excess sodium methoxide. The solution was diluted with water and extracted several time with methylene chloride. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 1.03 g of oil. Trituration with pentane gave a solid, mp 79–81°, which on crystallization from Skellysolve B afforded 0.43 g of **6B**, mp 84–85°; second crop, 0.27 g, mp 82–83.5°. Mixture melting point with **6A** showed a depression. The analytical sample melted at 86–87° (from Skellysolve B): ultraviolet, λ_{max} 225 mμ (11,600), 274 (1550), 281 (1300); infrared, NH–OH 3360, 3340, 3300, 3280, 3100, cm^{-1} (br, strong), C=C–NH def 1605, 1580, 1505, CO–CN 1240, 1165, 1080, 1030; aromatic, 825; nmr, benzylic H doublet centered at 285.5 cps, J = 4.5 cps (area 1), OCH_3 singlet at 228 cps (area 3); $vpc^{16b,17b,18c,19e,20b}$ indicated 99.4% purity (retention time 3.2 min).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.90; H, 8.93; N, 5.89.

Conversion of 6B to 4B with 1,5-Diiodopentane.—A mixture of **6B** (1.1 g, 4.67 mmoles), 1,5-diiodopentane (1.6 g, 4.84 mmoles), and 7.0 g of anhydrous potassium carbonate in 75 ml of methyl ethyl ketone was stirred at reflux for 23 hr. The solvent was evaporated *in vacuo* and the residue was dissolved in ether–water. The ether layer was separated and extracted with 10% hydrochloric acid. The acid extract was basified, the mixture was extracted with methylene chloride, and the organic extract was washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 1.17 g of an oil. $Vpc^{16d,17f,18a,19b,20d}$ showed 44.5% of **4B** (retention time 9.2 min) and 54.2% of **6B** (retention time 2.3 min). A solution of this oil in methylene chloride was chromatographed on 100 g of silica gel. Elution with 500 ml of CH_2Cl_2 gave fractions which were discarded. Elution with 1 l. of 5% methanol in methylene chloride gave 0.5 g (36%) of crude **4B** as solid, mp 128–135°. Crystallization from Skellysolve B afforded 0.362 g (26%) of **4B** in three crops, melting in the range 133.5–138°. Mixture melting point with authentic **4B** showed no depression and the infrared spectra were identical.

Elution with 1.5 l. of 10% methanol in methylene chloride gave fractions which were discarded. Elution with 3 l. of methanol afforded 0.33 g of a gum which crystallized from Skellysolve B: yield, 0.15 g (14% of **6B**); mp 81.5–84.5°. Mixture melting point with authentic **6B** showed no depression and the infrared spectra were identical.

***cis*-α-(*p*-Methoxyphenyl)-2-(methylamino)cyclohexanemethanol (9A).**—A solution of 58 g (0.25 mole) of **1**, 91 g (0.75 mole) of N-methylbenzylamine, and 1.6 g of *p*-toluenesulfonic acid monohydrate in 2 l. of toluene was heated at reflux for 20 hr, using a Dean–Stark trap (collected 4.0 ml of water). The solvent was concentrated *in vacuo;* the residue was dissolved in 400 ml of ethanol and hydrogenated in the presence of 2.5 g of platinum oxide at 30 psi for 18 hr. The catalyst was filtered off and the yellow filtrate was hydrogenated in the presence of 4.0 g of 10% palladium on carbon for 20 hr. The catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the residue taken up in 600 ml of ether and 500 ml of 10% acetic acid. The mixture was stirred for 1 hr, the acetic acid layer was separated and basified with 20% sodium hydroxide solution, and the oil which separated was extracted with methylene chloride. The organic layer was washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was recrystallized from ether–pentane: crop 1, 26.6 g, mp 88–91°; crop 2, 5.25 g, mp 84–88°. The yield of **9A** was 51%. The analytical sample was prepared from Skellysolve B: mp 88–90°; $vpc^{16b,17b,18e,19a,20a}$ showed one peak (retention time 4 min); ultraviolet, λ_{max} 225 mμ (11,250), 276 (1550), 282 (1350); infrared, NH 3270 cm^{-1}, OH ~2900 br, C=C 1610, 1580, 1510, 1485,

CO–CN 1240, 1165, 1095, 1030; aromatic, 835; nmr, benzylic H singlet at 299.5 cps (area 1), OCH_3 singlet at 227.5 cps (area 3), NCH_3 singlet at 147.5 cps (area 3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.17; H, 9.55; N, 5.55.

Conversion of 9A to 9B with Trifluoroacetic Acid.—Compound **9A** (10 g, 0.040 mole) was added to 80 ml of trifluoroacetic acid at 0–10°, the ice bath was removed, and the mixture stirred at 10–25° for 45 min. The mixture was cooled in an ice bath; 60 g of ice, 200 ml of water, and 200 ml of 20% sodium hydroxide solution were added; and the mixture was stirred for 45 min. The mixture was extracted with methylene chloride and the organic extract washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 9.45 g of gum. Vpc[16b,17b,18c,19f,20b] showed four components and indicated 14.2% of **9A** (retention time 2.6 min) and 77.3% of **9B** (retention time 3.2 min). The gum was dissolved in 100 ml of pentane and seeded with a sample of **9B**: crop 1, 6.0 g, mp 90.5–94°; crop 2, 1.16 g, mp 90–92°; yield, 71.6%. The analytical sample melted at 92–93° (from ether–Skellysolve B) and depressed the melting point of **9A** (mmp <75°). Vpc[16b,17b,18d,19f,20a] indicated 99.1% purity (retention time 4.5 min); the ultraviolet spectrum showed λ_{max} 225 mμ (11,200); 275 (1550), 282 (1300); infrared, NH–OH 3300, 3070, 2800, 2740, 2710, 2660 cm^{-1}, C=C 1605, 1580, 1505, 1480, CO–CN 1235, 1170, 1110, 1090, 1085, 1035; aromatic, 840, 810; nmr, benzylic H doublet centered at 292 cps, J = 5.5 cps (area 1), OCH_3 singlet at 228 cps (area 3), NCH_3 singlet at 145 cps (area 3). The crystal seed of **9B** was obtained by converting a sample of the gum to the oxalate salt, mp 227–228° (methanol–ether), and then releasing the free base, mp 92–94°.

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.61; H, 9.45; N, 5.89.

Conversion of 9A to Octahydro-4-(*p*-methoxyphenyl)-1-methyl-2H-3,1-benzoxazin-2-one (8A) with N,N′-Carbonyldiimidazole.—A solution of **9A** (2.5 g, 0.01 mole) and 3.5 g of N,N′-carbonyldiimidazole in 25 ml of dry tetrahydrofuran (purified by passage over neutral alumina) was kept at room temperature for 15 min. The mixture was evaporated *in vacuo* and the residue was diluted with cold water and extracted with methylene chloride. The organic extract was washed with 10% hydrochloric acid, water, saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation gave 2.70 g (98%) of **8A** as a white solid, mp 120–122°. A sample was crystallized from benzene–Skellysolve B: mp 121–122°; ultraviolet, λ_{max} 223 mμ (11,950), 274 (1350), 281 (1250); infrared, C=O 1685 cm^{-1} C=C 1645, 1610, 1580, 1510, CO–CN 1305, 1250, 1220, 1170, 1110, 1080, 1035; aromatic, 850, 810, 755; nmr, benzylic H doublet centered at 319.5 cps, J = 2 cps (area 1), OCH_3 and HCN singlet at 229.5 (area 4), NCH_3 singlet at 182 cps (area 3).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.04; H, 7.68; N, 5.27.

A polymorph of **8A** was also obtained, mp 139–141° (from benzene–Skellysolve B). The nmr spectrum was identical with that of **8A** above.

Conversion of 9B to 8B with N,N′-Carbonyldiimidazole.—The reaction was carried out as described in the case of the conversion of **9A** to **8A**. From 1.25 g (0.005 mole) of **9B** and 1.8 g of N,N′-carbonyldiimidazole in 25 ml of dry tetrahydrofuran, 1.45 g (quantitative yield) of **8B** was obtained, mp 186–187°. The sample for analysis was crystallized from benzene–Skellysolve B: mp 187–188°; ultraviolet, λ_{max} 226 mμ (13,250); 274 (1450), 281 (1250); infrared, C=O 1680, 1670 cm^{-1}, C=C 1610, 1585, 1510, CO 1245, 1140, 1055, 1025; aromatic, 845, 815; nmr, benzylic H doublet centered at 320 cps, J = 10.5 cps (area 1), OCH_3 singlet at 229 cps (area 3), HCN quintuplet centered at 196 cps, J = 5 cps (area 1), NCH_3 singlet at 181.5 cps (area 3).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.78; H, 7.82; N, 5.03.

Epimerization of 8A to 8B. A. With Trifluoroacetic acid.—Trifluoroacetic acid (5 ml) was added to 1.03 g of **8A**. After 15 min, the greenish solution was poured into 300 ml of cold 5% sodium carbonate solution and the product was extracted with chloroform. The organic extract was washed with water, saturated sodium chloride solution, dried ($MgSO_4$), and evaporated *in vacuo* to give 1.3 g of solid, mp 175–185° Trituration with boiling ether left 0.945 g of **8B**, mp 184–187°. The infrared and nmr spectra were identical with those of authentic **8B**. The second crop was obtained by concentration of ether: yield, 0.04 g, (96%); mp 186–187°. The third crop amounted to 0.036 g (3.5%), mp 135–137°, and was identical with **8A** (polymorph mp 139–140°) as shown by mixture melting point determination and comparison of infrared spectra. When the above reaction was run for 16 hr, a 90% yield of **8B** was obtained.

B. With Formic Acid.—A solution of 0.50 g of **8A** in 5.0 ml of 98% formic acid was heated on the steam bath for 15 min (a transient bluegreen color was observed). The solution was poured into 150 ml of ice water and the mixture was extracted with methylene chloride. The organic extract was washed with water, 10% sodium carbonate solution, dried ($MgSO_4$), and evaporated. The residue was triturated with Skellysolve B: yield, 0.26 g; mp 175–184°. Crystallization from benzene–Skellysolve B afforded 0.22 g (44%) of **8B**, mp 185–187°. The infrared spectrum was identical with that of the authentic sample.

Conversion of 6A to Octahydro-4-(*p*-methoxyphenyl)-2H-3,1-benzoxazin-2-one (7A) with N,N′-Carbonyldiimidazole.—This reaction was carried out as described in the case of the conversion of **9A** to **8A**. From 2.35 g of **6A** and 3.5 g of N,N′-carbonyldiimidazole in tetrahydrofuran, 2.6 g (quantitative yield) of **7A** resulted, mp 235–240° dec. Crystallization from ethanol gave colorless plates: 1.65 g (63%); mp 245.5–247°, unchanged on recrystallization; ultraviolet, λ_{max} 226 mμ (12,450), 268 sh (1200), 274 (1600), 282 (1400); infrared, NH 3220, 3180, and 3100 cm^{-1}, C=O 1700, C=C 1610, 1580, 1510, CO–CN 1250, 1175, 1130, 1080, 1055, 1025; aromatic, 840; nmr (DMF-d_7 at 120°), benzylic H doublet centered at 324 cps, J = 2 cps, OCH_3 singlet at 227.5 cps.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.71; H, 7.16; N, 5.38.

Methylation of 7A to 8A.—A mixture of **8A** (0.52 g, 2 mmoles) and 0.12 g of 53.3% sodium hydride mineral oil dispersion in 35 ml of dry dimethylformamide was stirred at room temperature for 35 min. A solution of 0.45 g (3.2 mmoles) of methyl iodide in 5 ml of dimethylformamide was added over 2 min, the mixture stirred for 2.5 hr, and the resulting yellow solution poured in 350 ml of water. The mixture was extracted several times with ether, the ether layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give a gum. Trituration with pentane gave 0.515 g (93.5%) of a yellow solid, mp 140–141°, unchanged on crystallization from benzene–Skellysolve B. Mixture melting point with **8A** (polymorph mp 140°) showed no depression and the infrared and nmr spectra were identical.

Conversion of 6B to 7B with N,N′-Carbonyldiimidazole.—The reaction was carried out as described in the case of the conversion of **9A** to **8A**. From 2.35 g (0.010 mole) of **6B** and 3.5 g of N,N′-carbonyldiimidazole in 25 ml of tetrahydrofuran, 2.14 g (82%) of **7B** was obtained: mp 152–155°, raised to 156–157° on recrystallization from benzene–Skellysolve B; ultraviolet, λ_{max} 226 mμ (12,650), 268 sh, 274 (1550), 281 (1300); infrared, NH 3240, 3190, 3120 cm^{-1}, C=O 1705, C=C 1605, 1580, 1510, CO–CN 1245, 1115, 1030; aromatic, 825; nmr, benzylic H doublet centered at 316 cps, J = 5.5 cps (area 1), OCH_3 singlet at 228.5 cps (area 3).

Methylation of 7B to 8B.—The reaction was carried out with **7B** (0.52 g, 2 mmoles) as described in the case of the methylation of **7A** to **8A**, except methylene chloride was used for extraction of the dimethylformamide–water layer since **8B** is not very soluble in ether The resulting oil was triturated with ether–pentane to give a colorless solid which was washed with ether and dried: yield of first corp, 0.40 g, (mp 186–187.5°); yield of second crop, 0.070 g (mp 184.5–185.5°). Mixture melting point with authentic **8B** showed no depression and the infrared spectra were identical. The yield was 85.5%.

Reaction of 7A with Trifluoroacetic Acid.—A solution of 1.0 g of **7A** in 5 ml of trifluoroacetic acid was allowed to stand for 15 min. During this time evolution of gas (probably CO_2) was observed. The green solution was poured into 300 ml of cold 5% sodium carbonate solution, the mixture was extracted with ether, and the ether layer extracted with five 50 ml portions of 10% acetic acid. The acid extract was basified with 20% sodium hydroxide solution and extracted with methylene chloride. The organic layer was washed with water, saturated sodium chloride solution, dried ($MgSO_4$) and evaporated to give 0.198 g of gum. It was crystallized from pentane: yield, 0.095 g; mp 79–82.5°. Recrystallization from Skellysolve B gave 0.061 g, mp 83–84°. Mixture melting point with **6B** showed no depression, whereas mixture melting point with **6A** was 62–70°.

The above ether layer was washed with 5% sodium hydroxide solution, water, saturated sodium chloride solution, dried

($MgSO_4$), and evaporated to give 0.767 g of gum. This material is probably a mixture of the N-trifluoroacetyl derivatives of **6A** and **6B**: ultraviolet, λ_{max} 224 mμ (a = 37.59), 269 sh (a = 3.50), 275 (a = 4.43), 282 (a = 3.77); infrared, NH–OH 3440, 3320 cm^{-1}, C=O 1710, C=C–NH def 1610, 1585, 1560, 1540, 1510, CO–CN–CF_3 1245, 1210, 1185–1145, 1030; aromatic, 830.

Anal. Calcd for $C_{16}H_{20}F_3NO_3$: F, 17.2. Found: F, 15.7.

When alcohol **6A** (1 g) was treated with trifluoroacetic acid as described above, the neutral fraction amounted to 0.784 g. The infrared spectrum was essentially identical with that of the neutral fraction above.

Preparation of Methyl Ethers. A. Conversion of 4A to *cis*-1-[2-(*p*,α-Dimethoxybenzyl)cyclohexyl]piperidine (10B) with MeOH–HCl.—A solution of 11.5 g of hydrogen chloride in 115 ml of methanol was added to a solution of alcohol **4A** (7 g, 0.0231 mole) in 115 ml of methanol and the resulting solution was allowed to stand for 18 hr. It was then evaporated at 50°. The oily residue was dissolved in 100 ml of water, basified with 20% sodium hydroxide solution, and extracted with ether (in another experiment the reaction mixture was first basified and then evaporated to give the same result as described below). The ether extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated. The crude product (7 g) was crystallized from 25 ml of ethanol to give 6 g (82%) of **10B**: mp 81–82° raised to 83–84° on recrystallization; ultraviolet, λ_{max} 226 mμ (13,200), 275 (1460), 282 (1210); infrared, *t*-amine 2780, 2740, 2660 cm^{-1}, C=C 1615, 1585, 1515, CO–CN 1250, 1230, 1170, 1155, 1130, 1110, 1080, 1040; nmr, benzylic H doublet centered at 256.5 cps, J = 9 cps (area 1); aromatic, OCH_3 singlet at 227 cps (area 3), benzylic OCH_3 singlet at 188 cps (area 3).

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.70; H, 10.06; N, 4.15.

The hydrochloride was prepared in ether with ethereal hydrogen chloride solution and was crystallized from methylene chloride–ether: mp 209–211° unchanged on recrystallization; ultraviolet, λ_{max} 227 mμ (12,500), 275 (1400), 281 (1200); infrared, =CH/$\geqslant\overset{+}{N}H$ 3040, 2630, 2580, 2500, C=C 1615, 1590, 1515, CO–CN 1245, 1230, 1175, 1125, 1105, 1080, 1030.

Anal. Calcd for $C_{20}H_{31}NO_2 \cdot HCl$: C, 67.87; H, 9.12; Cl, 10.02; N, 3.96. Found: C, 67.41; H, 9.31; Cl, 10.47; N, 3.83.

B. Methylation of 4A to 10A with $NaNH_2$–CH_3I.—A solution of **4A** (3.03 g, 0.01 mole) in 25 ml of ether was added during 10 min to a suspension of freshly prepared sodium amide (0.01 ml) in 100 ml of liquid ammonia. The suspension was then stirred for 1 hr. A solution of methyl iodide (1.42 g, 0.01 mole) was added during 10 min while cooling in a Dry Ice–acetone bath and the resulting solution was stirred for 30 min. The Dry Ice bath was then removed and the solution stirred for 6 hr. It was evaporated and 50 ml of water was added. The product was extracted with three 50-ml portions of methylene chloride. The extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 3 g of oil. A solution of this oil in 25 ml of petroleum ether was allowed to crystallize overnight at 4° to give 1.65 g (mp 76–78°) of starting material as determined by mixture melting point and comparison of ultraviolet and infrared spectra. The filtrate was evaporated to dryness and the residue (1.35 g) was dissolved in 20 ml of Skellysolve B and chromatographed on 54 g of Florisil. Elution with nine 100-ml portions of 3% acetone–Skellysolve B gave 0.653 g of **10A** as an oil, which was converted to the hydrochloride in ether with ethereal hydrogen chloride: yield, 0.6 g (15.5%); mp 196–197°. Crystallization from 2 ml of methanol and 30 ml of ether gave 0.51 g of colorless prisms melting at 196.5–197.5°: ultraviolet, λ_{max} 227 mμ (11,400), 274 (1380), 281 (1200); infrared, OH of methanol 3360 cm^{-1}, $\geqslant\overset{+}{N}H$ 2670 2570, 2540, C=C 1610, 1585, 1510, CO–CN 1245, 1175, 1095, 1075, 1030; aromatic, 830; nmr, benzylic H doublet centered at 309 cps, J = 3 cps (area 1), aromatic OCH_3 singlet at 228 cps (area 3), methanol CH_3 singlet at 208 cps (area 3), benzylic OCH_3 singlet at 194 cps (area 3).

Anal. Calcd for $C_{20}H_{31}NO_2 \cdot CH_3OH \cdot HCl$: C, 65.34; H, 9.40; Cl, 9.19; N, 3.63. Found: C, 65.50; H, 9.28; Cl, 8.50; N, 4.03.

Conversion of the hydrochloride to the free base in the usual way afforded **10A** as an oil: ultraviolet, λ_{max} 225.5 mμ (11,800), 276 (1570), 282 (1350); infrared, N-alkyl 2800, 2780, 2730 cm^{-1}, C=C 1605, 1580, 1510, CO 1245, 1180, 1100, 1090, 1035; aromatic, 830; nmr, benzylic H doublet centered at 268 cps, J = 5.5 cps (area 1), aromatic OCH_3 singlet at 228 cps (area 3), benzylic OCH_3 singlet at 187.5 cps (area 3); vpc,[16d,17c,18b,19e,20d] 98.51% purity (retention time 5.8 min).

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.59; H, 10.14; N, 4.56.

C. Methylation of 4B to 10B with BuLi–MeI.—A hexane solution of butyllithium (4 ml containing 0.01 mole) was added during 2 min to a solution of **4B** (3.03 g, 0.01 mole) in 30 ml of tetrahydrofuran (purified by passage through Woelm basic alumina, activity I) and the mixture was stirred for 30 min. It was then cooled to −70° (Dry Ice–acetone bath) and a solution of methyl iodide (1.42 g, 0.01 mole) in 10 ml of tetrahydrofuran was added dropwise over a 10-min period. The mixture was stirred at −70° for 1.5 hr and then at room temperature for 19 hr. It was worked up as usual and the crude product (2.7 g) was dissolved in 20 ml of methylene chloride and chromatographed on 135 g of Woelm neutral alumina. Elution with eight 200-ml portions of 5% ether–Skellysolve B gave 1.523 g of solid melting in the range 82–84°. Elution with two 250-ml portions of 25% ether–Skellysolve B two 250-ml portions of 50% ether–Skellysolve B, and two 250-ml portions of 75% ether–Skellysolve B gave a total of 0.204 g. The above fractions were combined and recrystallized from ethanol to give 0.644 g (20%) of methyl ether **10B**: mp 84–85.5°; ultraviolet, λ_{max} 226 mμ (13,200), 275 (1460), 282 (1210); infrared, *t*-amine 2780, 2740, 2660 cm^{-1}, C=C 1615, 1585, 1515, CO–CN 1230, 1230, 1170, 1155, 1130, 1110, 1080, 1040; nmr, benzylic H doublet H doublet centered at 256.5 cps, J = 9 cps (area 1), aromatic OCH_3 singlet at 227 cps (area 3), benzylic OCH_3 singlet at 188 cps (area 3).

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.70; H, 10.06; N, 4.15.

Further elution with 250 ml of methanol gave 1.446 g which was crystallized from methanol–ether overnight at 4°: yield, 0.252 g (0.55%) of **10B** methiodide; mp 219–220°, or 217–218° after recrystallization; ultraviolet, λ_{max} 223 mμ (24,000); 275 (1390), 281 (1280); infrared, no OH, C=C 1610, 1585, 1510, 1490 cm^{-1}, CO–CN 1250, 1235, 1175, 1070, 1030, 1015; aromatic, 850, 825, 815; nmr, benzylic H doublet centered at 272 cps, J = 10 cps, aromatic OCH_3 singlet at 230 cps, NCH_3 singlet at 196.5 cps, benzylic OCH_3 singlet at 183 cps.

Anal. Calcd for $C_{21}H_{34}INO_2$: C, 54.90; H, 7.46; I, 27.63; N, 3.05. Found: C, 55.03; H, 7.68; I, 27.63; N, 3.23.

D. Conversion of 4B to 10B with MeOH–HCl.—A solution of 5 g of hydrogen chloride in 50 ml of methanol was added to a solution of **4B** (3.0 g, 0.01 mole) in 150 ml of methanol. The resulting colorless solution was allowed to stand for 22 hr. It was then cooled in ice and was basified with 50 ml of 20% aqueous sodium hydroxide solution. The suspension was evaporated *in vacuo* to get rid of methanol, 50 ml of water was added, and the solid was filtered and washed with water. The product (3.1 g, mp 70–76°) showed no residual OH in the infrared region (Nujol). It was crystallized from 20 ml of methanol to give 2.27 g melting at 79–81°. The second crop amounted to 0.35 g and melted at 78–80°: yield, 83%. The compound was identical with an authentic sample of **10B** as determined by mixture melting point and comparison of ultraviolet and infrared spectra.

E. Methylation of 4C to 10C with BuLi–MeI.—A hexane solution of butyllithium (5.25 ml containing 0.01 mole; Foote Mineral Co.) was added during 10 min to a solution of **4C** (3.03 g, 0.01 mole) in 40 ml of tetrahydrofuran (purified by passage through Woelm basic alumina, activity I) under nitrogen. The reaction mixture was stirred for 45 min. It was then cooled to −70° and a solution of methyl iodide (1.42 g, 0.01 mole) in 10 ml of purified tetrahydrofuran was added over a 30-min period. The mixture was then stirred overnight at room temperature. It was evaporated to dryness and the residue was dissolved in 50 ml of water and 50 ml of methylene chloride. The aqueous layer was extracted with methylene chloride. The combined extract was washed with saturated salt solution, dried (Na_2SO_4), and evaporated to give 3.2 g of crude product which was chromatographed on 155 g of neutral alumina Woelm (activity I). Elution with six 150-ml portions of 6% ether–Skellysolve B gave 1.642 g of oily product, which was crystallized from 5 ml of methanol: yield, 1.2 g; mp 78–79°. It was identical with *trans*-methyl ether **10C** obtained by the methanol–hydrogen chloride procedure (as shown by comparison of ultraviolet, infrared, and nmr spectra and by mixture melting point). Further elution with two 250-ml portions of 12% ether–Skellysolve B gave 0.149 g of oil which could not be crystallized. Elution with two 250-ml portions of 25% ether–Skellysolve B gave 0.225 g of oil which was crystallized from minimum methanol to give 25 mg

of **10C**, mp 76–77°. Elution with two 250-ml portions of 50% ether–Skellysolve B gave 0.219 g of oil and with two 250-ml portions of ether gave 0.250 g of oil. These fractions could not be crystallized. Elution with 5% methanol–ether (500 ml) gave 1.122 g of product which was crystallized from methanol to give 0.15 g of the starting material, mp 145–146.5°, as shown by mixed melting point.

F. Conversion of 4C to 10C with MeOH–HCl.—A solution of anhydrous hydrogen chloride (1.4 g) in 15 ml of methanol was added to a solution of **4C** (0.8 g, 2.64 mmoles) in 40 ml of methanol. After 17 hr the solution was cooled in ice, basified with 15 ml of 20% sodium hydroxide, and evaporated to get rid of methanol. Water was added and the mixture was extracted twice with methylene chloride. The extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 0.817 g of pale yellow oil. It was dissolved in methylene chloride and chromatographed on 40 g of neutral alumina. Elution with 600 ml of 3% ether–Skellysolve B gave 0.722 g of product which was crystallized from methanol. Two crops of **10C** were collected: yield, 0.372 g (44%); mp 79–80° unchanged on recrystallization; ultraviolet, λ_{max} 225 mμ (11,550), 265 sh (1150), 275 (1550), 282 (1350), infrared *t*-amine 2800 cm^{-1}, C=C 1610, 1580, 1505, CO–CN 1245, 1105, 1095, 1080, 1030; aromatic, 865, 835, 815; nmr, benzylic H doublet centered at 289 cps, J = 2.5 cps (area 1), OCH_3 singlet at 229 cps (area 3), NCH_3 singlet at 194 cps (area 3).

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.80; H, 10.08; N, 4.71.

G. Conversion of 4D to 10D with BuLi–MeI.—A hexane solution of butyllithium (5.25 ml containing 0.01 mole; Foote Mineral Co.) was added during 10 min under nitrogen to a solution of **4D** (3.03 g, 0.01 mole) in 30 ml of purified THF. The mixture was stirred for 40 min. It was then cooled to −70° and a solution of methyl iodide (1.42 g, 0.01 mole) in 10 ml of purified THF was added over a 30-min period. The mixture was stirred overnight at room temperature and worked up as described in the case of **10C**. The crude product (3.2 g) was shown by vpc[16a,17d,18c,19a,20d] to contain a mixture of **10D** (88.72%, retention time 2.3 min) and **4D** (11.28%, retention time 6.5 min). Another impurity was observed in the infrared spectrum at 1675 cm^{-1} (w), perhaps due to a product of a fragmentation process.[26] The product was chromatographed on 100 g of neutral alumina (Woelm), activity I. Elution with five 150-ml portions of 6% ether–Skellysolve B gave 1.145 g of oil: ultraviolet, λ_{max} 228 mμ (12,350), 278 (1550), 284 (1300); infrared, *t*-amine 2780, 2730 cm^{-1}, C=O impurity 1670 (w), C=C 1610, 1585, 1515, CO–CN 1240, 1165, 1105, 1090, 1030; aromatic, 855, 830, 815; nmr, benzylic H singlet at 296.5 cps (area 1), aromatic OCH_3 singlet at 227.5 (area 3), benzylic OCH_3 singlet at 197.5 cps (area 3); vpc (run as above) showed one peak with retention time of 2.5 min.

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.71. Found: C, 75.48; H, 9.93; N, 4.30.

Further elution with varying proportions of ether in Skellysolve B and ether did not give any material. Elution with two 250-ml portions of 5% methanol–ether gave 1.494 g, which was crystallized from petroleum ether to give 0.73 g of recovered **4D**, mp 80–81.5° (identified by mixture melting point).

H. Conversion of 4D to 10C with MeOH–HCl.—A solution of hydrogen chloride (2 g) in 15 ml of methanol was added to a solution of **4D** (0.8 g, 2.64 mmoles) in 40 ml of methanol. The mixture was allowed to stand overnight. The resulting solution was basified with 20% aqueous sodium hydroxide solution. Methanol was evaporated *in vacuo*, 25 ml of water was added, and the product was extracted with three 25-ml portions of methylene chloride. The extract was washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The residue (0.8 g) was dissolved in 3% ether–Skellysolve B and chromatographed on alumina with same solvent mixture. Elution with ten 100-ml portions afforded 0.351 g of an oil (vpc run as below; one peak, retention time 1.5 min) which solidified overnight at −10°. Crystallization from methanol gave **10C**: mp 78–79°; vpc,[16a,17a,18c,19d,20d] one peak (retention time 1.5 min). Nmr, infrared, and ultraviolet spectra were identical with those of the authentic sample. Elution with three 100-ml portions of 1% methanol–ether gave 0.345 g of an oil which solidified *in vacuo*. Nmr showed 80% **10C**, some **4D**, and probably a trace of **4C**.

I. Treatment of 11 with Methanolic Hydrogen Chloride.—A solution of hydrogen chloride (5 g) in 50 ml of methanol was added to a solution of **11** hydrochloride (3.21 g, 0.01 mole) in 150 ml of methanol. The resulting solution was allowed to stand overnight. It was then basified with 15% sodium hydroxide and the methanol was evaporated *in vacuo*. The mixture was extracted with three 25-ml portions of ether. The ether extract was washed with saturated salt solution, dried (Na_2SO_4), and evaporated to give 2 g of a pale yellow oil (94% of **11** by ultraviolet spectrum). The oil was converted to the hydrochloride to give 2.2 g melting at 202–204°. This product was identical with the starting matrial as shown by comparison of the ultraviolet and infrared spectra.

***cis*-1-[2-(*p*-Methoxybenzyl)cyclohexyl]piperidine (12). A. By Hydrogenolysis of 10B.**—A solution of **10B** (2.4 g, 7.6 mmoles) in 50 ml of acetic acid was hydrogenated in the presence of 0.8 g of 10% palladium on carbon and 1.2 g (8.36 mmoles) of 70% aqueous perchloric acid. The initial pressure was 53.5 psi and 1 mole of hydrogen was absorbed during 19.5 hr. The resulting suspension was diluted with 100 ml of water. The mixture was then added to an ice-cooled solution of 40 g of sodium hydroxide in 160 ml of water. Methylene chloride (200 ml) was added, the whole was filtered through Filtercel, and the catalyst was washed with methylene chloride. The layers in the filtrate were separated. The aqueous layer was extracted twice with methylene chloride and the combined organic solution was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 2 g of yellow solid melting at 75–81°. Two crystallizations from methanol (Nuchar) afforded 1.4 g (64%) of colorless rods melting at 84–86°: ultraviolet, λ_{max} 225 mμ (11,990), 278 (1700), 285 (1400); infrared, *t*-amine 2790, 2750 cm^{-1}, C=C 1610, 1580, 1510, CO–CN 1245, 1175, 1110, 1030; aromatic, 840, 820, 800; nmr, OCH_3 singlet at 226.5 cps (area 3), benzylic H doublet centered at 176.5 cps, J = 11 cps (area 2).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.25; H, 10.32; N, 4.95.

B. By Hydrogenolysis of 4A.—A solution of 5 g (0.0165 mole) of **4A** was hydrogenated in 110 ml of acetic acid and 2.6 g (0.0182 mole) of 70% perchloric acid in the presence of 1.74 g of 10% palladium on carbon. Hydrogen (1 mole) was absorbed during 24 hr. The mixture was added to ice-cooled solution of 87 g of sodium hydroxide in 350 ml of water. Then 200 ml of methylene chloride was added and the mixture was filtered to separate the catalyst. The aqueous layer was extracted with four 50-ml portions of methylene chloride. The combined extract was washed with saturated salt solution, dried (Na_2SO_4), and evaporated to give 4.7 g of yellow oil. It was crystallized from 10 ml of methanol to give 1.2 g (25%) melting at 86–87°. It was identical with a sample of **12** as shown by mixture melting point and comparison of ultraviolet and infrared spectra.

1-[2-(*p*-Methoxybenzylidene)cyclohexyl]piperidine (11) Hydrochloride.—A mixture of 26.5 g (0.0875 mole) of **4A** and 466 ml of 10% hydrochloric acid was heated on the steam bath for 45 min when a cloudy solution resulted. It was filtered through Filtercel and was allowed to crystallize overnight. The product was filtered and washed with cold water: yield, 18 g (64%); mp 202–204° unchanged on recrystallization from water; ultraviolet, λ_{max} 259 mμ (19,000); infrared, $\overset{+}{>}NH$ 2620, 2540, C=C 1605, 1575, 1505, CO–CN 1245, 1175, 1030; nmr, vinyl H singlet at 396 cps, OCH_3 singlet at 229.5 cps.

Anal. Calcd for $C_{19}H_{27}NO \cdot HCl$: C, 70.90; H, 8.77; Cl, 11.02; N, 4.35. Found: C, 70.86; H, 8.89; Cl, 10.73; N, 4.49.

Treatment of 4C with 10% Aqueous HCl.—A suspension of **4C** (3.03 g, 0.01 mole, mp 145–146°) in 55 ml of 10% aqueous hydrochloric acid was heated on the steam bath for 45 min. The resulting cloudy solution was allowed to stand overnight. It was filtered through Filtercel, cooled, and basified with 15% sodium hydroxide. The product was extracted twice with methylene chloride, the extract was washed with salt solution, dried (Na_2SO_4), and evaporated to give 3.2 g: mp 136–138° (sinters at 128°); vpc,[16a,17b,18c,19c,20d] 85.6% purity (retention time 6 min). Crystallization from methanol gave 2.2 g of recovered **4C**, mp 145–146.5°, identified by comparison of ultraviolet, infrared, and nmr spectra with those of the authentic sample. The filtrate was evaporated to dryness and the residue afforded a further 0.266 g (mp range 140–146°) after chromatography on Florisil.

Hydrogenation of 11 Hydrochloride.—A solution of **11** (1 g, 3.1 mmoles) in 100 ml of ethanol was hydrogenated in the presence of 0.2 g of platinum oxide at initial pressure of 52.5 psi. Hydrogen (2 moles) was absorbed during 50 min (more than 90% during

(26) *Cf.* C. A. Grob, *Bull. Soc. Chim. France*, **27**, 1360 (1960).

the first 25 min). The mixture was filtered and the colorless filtrate was evaporated to dryness. The resulting pink oily solid was recrystallized twice from methanol–ether to give 220 mg (59%) of piperidine hydrochloride melting at 240–242° (sinters at 235°). The ultraviolet, infrared, and nmr spectra were identical with those of the authentic sample.

In another experiment run as above, but using 3.2 g (0.01 mole) of **11** hydrochloride, the crude hydrogenation product was dissolved in 100 ml of ether and 50 ml of water. The aqueous layer was extracted with ether and the combined ether extract was washed with saturated salt solution, dried (Na_2SO_4), and evaporated to give 1.5 g of a yellow oil. Distillation from an oil-jacketed flask at 1.5 mm afforded 1.3 g (64%) of **13**[27] as a colorless oil boiling at 140–150°: ultraviolet, λ_{max} 224 mμ (9370), 278 (1640), 284 (1400); infrared, C=C 1615, 1585, 1510, CO 1245, 1180, 1040; aromatic, 835, 820; nmr, OCH_3 singlet at 226.5 cps, benzylic H doublet centered at 146 cps with J = 5.5 cps; vpc,[16c,17d,18c,19a,20c] 95.6% purity (retention time 20 min).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.44; H, 10.23.

2-(3,4,5-Trimethoxybenzoyl)cyclohexanone was prepared using the procedure described in the case of **1**. The crude product obtained from 2.64 moles of distilled 1-cyclohexen-1-ylpyrrolidine and 1.2 moles of 3,4,5-trimethoxybenzoyl chloride in chloroform (purified by passage through Woelm basic alumina, activity I) did not require purification *via* the copper complex. It crystallized from methanol to give the desired 1,3-diketone in two crops: 210.1 g, mp 139–140°; 29.1 g, mp 138–139.5°; yield, 68%. The analytical sample melted at 141–142° (colorless needles from methanol): ultraviolet, λ_{max} 217 mμ (21,300), 285 (10,000); infrared, C=O 1695, 1675 cm^{-1}, C=C 1595, 1505, CO–CN 1235, 1180, 1165, 1140; aromatic, 750, 680.

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.48; H, 6.84.

2-(Hexahydro-1H-azepin-1-yl)-α-(3,4,5-trimethoxyphenyl)-cyclohexanemethanol (14) Hydrochloride.—The reaction was run using 2-(3,4,5-trimethoxybenzoyl)cyclohexanone (35 g, 0.12 mole) and hexamethyleneimine (35.6 g, 0.36 mole) as described in the case of the synthesis of **4A** from **1** and piperidine. The hydrogenation mixture was filtered through Filtercel and evaporated to dryness. A solution of the residue in 400 ml of ether was stirred with 400 ml of 10% hydrochloric acid for 0.5 hr. The resulting suspension was filtered and the solid was washed with ether to give 18.2 g. It was crystallized from 250 ml of methanol: yield, 16.4 g; mp 244–246° unchanged on further recrystallization; ultraviolet, 228 (sh) mμ (8250), 268 (757), 276 (608); infrared, OH 3180, $\overset{+}{>}NH$ 2580, C=C 1595, 1505, 1485, CO–CN 1240, 1155, 1120, 1055, 1015; aromatic, 735, 710, 670.

Anal. Calcd for $C_{22}H_{35}NO_4 \cdot HCl$: C, 63.83; H, 8.77; Cl, 8.56; N, 3.38. Found: C, 63.95; H, 9.13; Cl, 8.47; N, 3.58.

The aqueous filtrate was separated and extracted with two 50-ml portions ether (discarded). It was then cooled in ice, basified, and extracted with methylene chloride. The extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 3.2 g of oil. The hydrochloride was formed in ether with ethereal hydrogen chloride and was crystallized from methanol: yield, 0.7 g; mp 242–243°. The total yield of **14** hydrochloride was 34%.

Treatment of 14 with Sulfuric Acid.—The free base **14** was released from 31 g (0.07 mole) of the hydrochloride in the usual way. Concentrated sulfuric acid (140 ml) was added all at once with stirring to the resulting oil which was made fluid by warming to *ca.* 30°. The mixture warmed up to 35° and was stirred for 4 hr. It was then added dropwise with stirring and cooling to 700 ml of water so that the temperature did not rise above 15°. Precipitation commenced after about one-third was added. The product was filtered and washed with water: yield of product A, 4.0 g (13%) of **16**; mp 230–232°, sublimes at 227°. The product was soluble in hot water, hot acetic acid, and 10% sodium hydroxide and precipitated with acid.

The filtrate was added to a solution of sodium hydroxide (280 g) in 1120 ml of water with stirring and cooling so that the temperature did not rise above 15°. Methylene chloride was added (*note:* in another run ether was used instead of methylene chloride and was much preferred since no emulsions resulted) and the mixture was stirred until the oil dissolved. Water was added to dissolve the sodium sulfate, the layers were separated, and the aqueous portion was extracted with methylene chloride (emulsion). The organic extract was washed with water and saturated salt solution and filtered through sodium sulfate. The cloudy pale yellow solution was evaporated to dryness and the oily residue was dissolved in 100 ml of ether and allowed to crystallize overnight. The solid was filtered and washed with water to give a colorless product B: yield, 1.1 g (3.6%) of **17**; mp 238–243°, discolors at 195°.

Ethereal hydrogen chloride (70 ml, 1.5 N) was added to the ethereal filtrate and the resulting solid was filtered and washed with ether. It was crystallized from 100 ml of methanol and 800 ml of ether at 4° over the weekend: yield, 19.8 g (72%) of **15** hydrochloride; mp 192–195°, discolors at 180°. Recrystallization from methanol gave material melting at 193–194°: ultraviolet, λ_{max} 216 mμ (31,300), 261 (12,800); infrared, $\overset{+}{>}NH$ 2680, 2510, 2480 cm^{-1}, C=C 1650; aromatic, C=C 1580, 1500; CO–CN 1235, 1150, 1125, 1000; aromatic, 885, 870, 830.

Anal. Calcd for $C_{22}H_{33}NO_3 \cdot HCl$: C, 66.33; H, 8.66; Cl, 8.96; N, 3.54. Found: C, 66.52; H, 8.96; Cl, 8.95; N, 3.44.

The free base **15** was obtained from the hydrochloride in the usual way. Two crystallizations from ether–petroleum ether (with Nuchar) gave colorless needles: mp 80–81.5°; ultraviolet, λ_{max} 217 mμ (33,950); 257 (14,300); infrared, C=C 1650, 1580, 1510, CO 1240, 1130, 1005; aromatic, 895, 875, 845, 815.

Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.55; H, 9.47; N, 3.98.

Product A was crystallized from 1750 ml of methanol to give **16** in three crops which amounted to 3.5 g and melted in the range 237–243°: ultraviolet, λ_{max} 217 mμ (35,600), 252 sh (9250); infrared, OH 3420 (weak, br), *t*-amine 2680, C=C 1635 (w), aromatic C=C 1575, 1555, 1480, sulfate 1335, 1175, 1165, CO–CN 1225, 1145, 1115, 1055, 1040, 1015; aromatic, 875, 865, 840, 830.

Anal. Calcd for $C_{22}H_{33}NO_6S$: C, 60.12; H, 7.57; N, 3.19; S, 7.30. Found: C, 60.07; H, 7.66; N, 3.22; S, 7.66.

Product B (insoluble in 20% sodium hydroxide) was crystallized from 10 ml of methylene chloride and 40 ml of ether to give **17** as colorless needles: mp 238–240°, raised to 240–242° dec, discolors at 200°) on recrystallization; ultraviolet, λ_{max} 213 mμ (44,700), 234 sh (12,800), 275 (1350), 282 (1150); infrared, C=C 1590, 1565, 1495 cm^{-1}, $-SO_2-$CO–CN 1335, 1245, 1205, 1170, 1150, 1110, 1050, 1020; aromatic, 880, 750, 710.

Anal. Calcd for $C_{22}H_{33}NO_6S$: C, 60.12; H, 7.57; N, 3.19; S, 7.30. Found: C, 60.31; H, 7.78; N, 3.24; S, 7.36.

The same three products resulted when **15** was subjected to treatment with sulfuric acid as described above in the case of **14**. The yields obtained by isolation were as follows: 54% of compound **15**; 16% of **16**, and 5.5% of **17**.

Registry No.—**1**, 7402-39-3; **3**, 13724-42-0; **4A**, 13724-45-3, **4A** *p* toluenesulfonic acid salt, 13724-44-2; **4A** hydrochloride, 13724-43-1; **4B**, 13724-46-4; **4C**, 13724-47-5; **4D**, 13724-48-6; **5**, 13724-49-7; **6A**, 13724-50-0; **6A** N-trifluoroacetyl derivative, 13724-51-1; **6B**, 13724-52-2; **6B** N-trifluoroacetyl derivative, 13724-53-3; **7A**, 13724-54-4; **7B**, 13724-55-5; **8A**, 13724-56-6; **8B**, 13724-57-7; **9A**, 13724-58-8; **9B**, 13724-59-9; **9B** oxalate salt, 13724-60-2; **10A**, 13724-61-3; **10A** hydrochloride, 13724-62-4; **10B**, 13724-61-3; **10B** hydrochloride, 13724-64-6; **10B** methiodide, 13724-65-7; **10C**, 13724-66-8; **10D**, 13724-67-9; **11** hydrochloride, 13724-68-0; **12**, 13724-69-1; **13**, 13724-70-4; **14** hydrochloride, 13724-71-5; **15**, 13724-72-6; **15** hydrochloride, 13724-73-7; **16**, 13724-74-8; **17**, 13724-75-9; α-(*p*-methoxyphenyl)cyclohexanemethanol, 835-68-7; 2-hydroxy-α-(*p*-methoxyphenyl)cyclohexanemethanol, 13724-77-1; 1-cyclohexen-1-yl *p*-methoxyphenyl ketone 13724-78-2; *cis*-2-(benzylamino)-α-(*p*-methoxyphenyl)-cyclohexanemethanol, 13724-79-3; *cis*-2-(benzylamino)-α-(*p*-methoxyphenyl)cyclohexanemethanol hydrochloride, 13724-80-6; 2-(3,4,5-trimethoxybenzoyl)cyclohexanone, 13724-81-7.

(27) J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 366 (1963).