Although gross assumptions are involved, these calculated $t_{1/2\ obsd}$ are satisfying because they are the same orders of magnitude as experimentally determined values for in vivo lifetimes of 6-OHDA and 6-ADA, respectively. Using in vivo injection techniques, McCreery et al.[4,5] found electrochemically detectable 6-OHDA had an in vivo lifetime of ca. 30 min and 6-ADA ca. 90 min. This agreement is considered quite satisfactory in view of the fact that the intracyclization is assumed to be the only reaction of the oxidized forms. Similar calculations for compound **3** indicate a $t_{1/2\ obsd}$ of 1.3 hr, a result in agreement with its established neurotoxicity and our hypotheses.

Pursuing this argument for the other 6-ADA derivatives (compounds **5–9**) suggests that all of them would be considerably less effective neurotoxins. They are oxidized within 10–15 mV as easily as 6-ADA; yet, the lifetimes of their oxidation products are extremely short. This is in accord with experimental results—none of the compounds when injected intracerebrally into mouse brain caused any long-term norepinephrine depletion.[9] However, this does not validate the above hypothesis. For obvious structural reasons, it is almost certain that these compounds are not taken up effectively by catecholamine neurons. Hence, there is no effective way of testing the arguments for these 6-ADA derivatives. Similarly, compound **10**, the side-chain quaternary compound, oxidized readily yet cannot intracyclize. It should be an effective compound by the arguments above. Obviously, however, it is not taken up by catecholamine neurons.

It is interesting, in this light, to compare the behavior of the so-called 5-hydroxydopamine, compound **11**. Its quinone undergoes very rapid chemical reaction ($t_{1/2} \sim$ 20 msec) and, at first glance, might be considered a poor candidate for uptake. However, it is considerably more difficult to oxidize than either 6-OHDA or 6-ADA since it can only form an *o*-quinone. Thus, it remains a very effective molecule for uptake and is widely used as a catecholamine neuronal "marker". However, even when it accumulates intraneuronally, it is not neurotoxic because it is too difficult to oxidize.

Experimental Section

Compounds **1** and **11** (Table I) were reagent grade, commercially obtained compounds (Regis). Compound **4** was prepared locally as previously described.[10] The syntheses of compounds **5**, **8**, **9**, and **10** are described in a paper in this journal.[7] Compounds **2** and **3** were prepared by Reid,[11] and compounds **6** and **7** were prepared by Nerland and Smissman.[12]

Conventional electrochemical techniques were used to measure the oxidation potentials and the rates of reaction of the generated quinones. Oxidation potentials (and qualitative rate information) were obtained by cyclic voltammetry (a voltage scanning technique) at scan rates of 2 V/min up to 1000 V/min. In addition to yielding information about the redox properties of the quinone–hydroquinone pair, cyclic voltammetry detects the presence of electroactive products of chemical reactions of the oxidized species. The reported oxidation potentials were measured with a Hg electrode vs. a saturated calomel electrode (SCE). A further description of cyclic voltammetry and other electrochemical techniques and their application to molecules of neuropharmacological interest is available.[13]

To measure the rate of reaction of quinone, the hydroquinone was oxidized at a constant potential and the current–time decays were observed to follow an inverse $\sqrt{t}$ behavior which indicates that any chemical reactions of quinone generate a reducible species. At a later time, the electrode was switched to a potential sufficient to reduce the quinone previously electrogenerated. The measured current at this potential corresponds to the amount of quinone which has not been consumed by a chemical reaction. From a knowledge of the potential switch time (which can vary from 50 msec to 20 sec) and the amont of quinone consumed, one can calculate the reaction rate of the quinone. Further details of this technique are available.[9] Rates were measured at a Hg electrode and a carbon paste electrode with identical results.

Since many of the compounds in Table I are easily air-oxidized at physiological pH, all solutions were deoxygenated with a vigorous stream of argon. Under these conditions the hydroquinone forms were stable for about 30 min at millimolar concentrations.

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Stereochemical Studies of Adrenergic Drugs. Diastereomeric 2-Amino-1-phenylcyclobutanols†

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The synthesis of the *cis*- and *trans*-2-amino-1-phenylcyclobutanols **2** and **3** is described. The results of the potentiation of the action of (−)-norepinephrine by these two compounds are discussed.

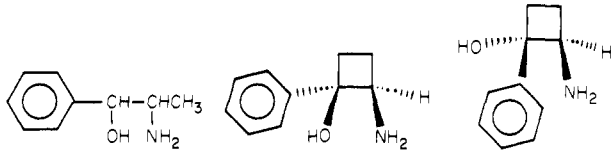
The mechanism by which catecholamines, as well as other phenethanolamines, interact with various segments of the adrenergic nervous system has been of great interest in recent years.[1-3]

Almost all of the phenethanolamine derivatives studied thus far have been conformationally flexible molecules. An

† This paper is dedicated to Edward E. Smissman.

intriguing search is that of the spacial relationships of the important functional groups in drugs producing a variety of adrenergic pharamcological responses. An approach at attempting to delineate what the conformational requirements for the interaction of adrenergic drugs with various receptors has been to synthesize rigid and semirigid molecules in which the relative position of the various functional groups is in a fixed or restricted position. Some of the initial work in preparing conformationally rigid analogs of phenethanolamines has been carried out by Smissman and coworkers,[4-6] Nelson and Miller,[7] Miller et al.,[8] and Grunewald et al.[9]

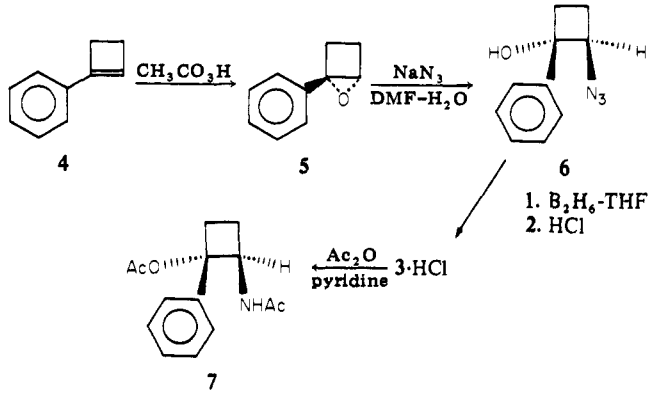
A major criticism of the early work in this area was the hydrocarbon bulk added to the molecule in order to form conformationally rigid systems. Because of the low biological activity of these molecules, the added hydrocarbon skeleton must, in some manner, be either preventing the drug from getting to the adrenergic receptors or not allowing for a favorable interaction at the adrenergic receptor. We have initiated a study of conformationally restricted phenethanolamine derivatives in which a minimum number of atoms have been added or deleted from the parent molecule.[8] This report includes the synthesis and biological actions of *cis*- and *trans*-2-amino-1-phenylcyclobutanols **2** and **3**, respectively, which can be considered conformationally restricted analogs of norephedrine **1**. The intent of this work is to gain further insight into the interaction of phenethanolamines with adrenergic receptors and also to contribute to the chemistry of substituted cyclobutanes.



1 2 3

Chemistry. The synthesis of **3**, outlined in Scheme I, was initiated by the treatment of phenylcyclobutene (**4**)[10] with peracetic acid according to the procedure of Korach and coworkers.[11] The resulting epoxide **5** tended to be rearranged upon standing and thus without further purification was treated immediately with NaN_3 in H_2O and DMF to give the *trans*-azido alcohol **6**. The azide **6** was reduced using either $LiAlH_4$[12] or B_2H_6,[13] with B_2H_6 giving better yields under the conditions employed. The *trans*-amino alcohol **3** was treated with acetic anhydride to give the *N,O*-diacetyl derivative **7**.[7]

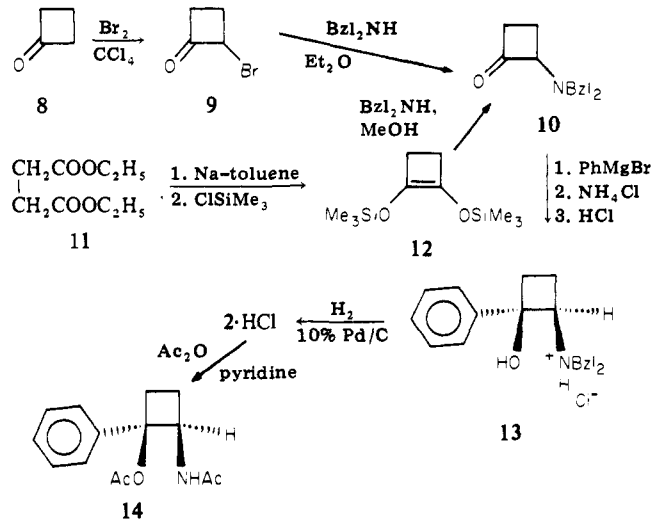
Scheme I



4 5 6 7

The NMR spectrum of **7** was consistent with the functional groups being present as assigned. In $CDCl_3$ the amide proton of **7** absorbed as a broad doublet at δ 5.30 ($J_{NH,CH}$ = 8.0 Hz) while the methine proton absorbed as a broad quartet at δ 4.80, which appeared as a triplet at δ 4.80 (J_{CH,CH_2} = 8.5 Hz) after deuterium exchange of the amide proton. The known trans opening of the epoxides with sodium azide[14] and the NMR data of **7** in contrast to that obtained from **14** led to the functional group and stereochemical assignments of **3**.

Scheme II



8 9 10 11 12 13 14

The synthesis of the *cis*-amino alcohol **2** was dependent upon the preparation of the α-amino ketone **10** shown in Scheme II. We investigated two methods of preparing **10**. The first involved a series of reactions analogous to those used by Burger and Ong.[15] Bromination of cyclobutanone was carried out with bromine in CCl_4 to give the desired α-bromo ketone **9**.[16] The α-bromo ketone was then allowed to react with dibenzylamine in ether to give **10**. A less expensive and more convenient route to **10** was through the acyloin condensation of diethyl succinate to give **12** using the conditions of Rühlmann et al.[17] and Bloomfield.[18] Treatment of **12** with dibenzylamine in methanol at 20° gave **10**. The amino ketone **10** was then treated with phenylmagnesium bromide to give the *cis*-amino alcohol **13**. Removal of the benzyl groups was carried out via hydrogenolysis using 10% Pd/C as a catalyst. The amino alcohol **2** was then treated with acetic anhydride and pyridine to give the *N,O*-diacetyl derivative **14**.[7]

The NMR spectrum was consistent with a cis disposition of groups in **14**. The amide proton of **14** absorbed as a broad doublet at δ 6.60 ($J_{NH,CH}$ = 8.0 Hz) which was farther downfield than the amide proton of **7** (δ 5.30). In **7** the amide proton is cis to the phenyl ring and one would expect it to absorb upfield in comparison to the amide proton of **14**, since this shielding property of a phenyl ring has been observed on groups cis to such a phenyl substituent in other four-membered ring systems.[8,19-21] The methine proton in **14** absorbed as a quartet at δ 4.60, which appeared as a triplet δ 4.60 (J_{CH,CH_2} = 8.5 Hz) after deuterium exchange of the amide proton. Again it is consistent that the methine proton in **14** absorbs at a higher field than that of **7** since it is cis to the phenyl ring in **14**. This work indicates that the Grignard addition to the tertiary amino ketone **10** went in a stereospecific manner and indicates the phenylmagnesium Grignard reagent attacked the carbonyl group from the least hindered side. This is analogous to the bulky hydride reductions of cyclic tertiary amino ketones to give *cis*-amino alcohols.[22]

Biological Results and Discussion. The norephedrine analogs **2** and **3** were examined for their ability to potentiate the action of (−)-norepinephrine. The dense

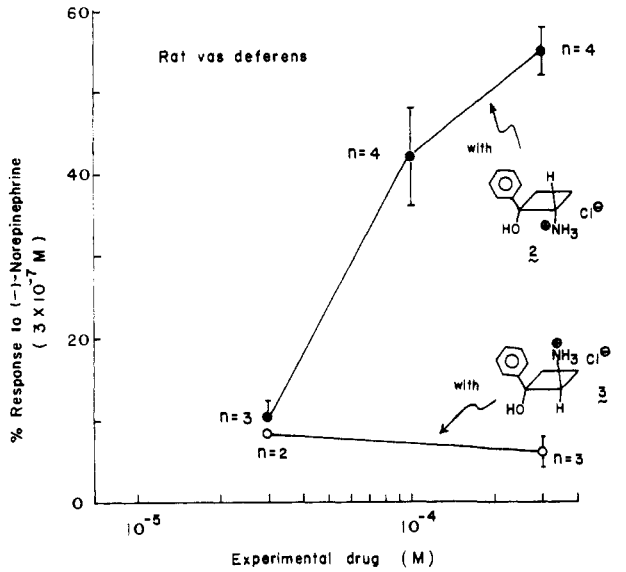


Figure 1. Responses to (−)-norepinephrine (NE, 3×10^{-7} *M*) in the presence of various concentrations of **2**·HCl and **3**·HCl. The tissues were obtained from reserpine-treated rats (5 mg/kg ip, 16–22 hr). (−)-Norepinephrine, 3×10^{-7} *M*, without any drug produced a mean ($n = 6$) contraction of 10 ± 2%. On every tissue the maximal effects of (±)-methoxamine were considered 100%.

adrenergically innervated rat vas deferens provides a good system for the study of the potentiation of the effects of (−)-norepinephrine by various drugs. The potentiation of the response of (−)-norepinephrine by drugs provides an indirect method for the study of the drug's ability to inhibit uptake of norepinephrine.[7,23]

The mean contraction of the reserpine-pretreated tissue to low concentrations of (−)-norepinephrine was 10 ± 2% ($n = 6$) of the maximal tissue contraction elicited by (±)-methoxamine. In the presence of either low (3×10^{-5} *M*) or high (3×10^{-4} *M*) concentrations of **3**, the response to (−)-norepinephrine was not affected. On the other hand, **2** in a concentration dependent fashion potentiated the responses of (−)-norepinephrine. Results of this potentiation of (−)-norepinephrine are illustrated for **2** and **3** in Figure 1. Neither **2** nor **3** produced any intrinsic effects on the tissue alone during the incubation periods.

Since these experimental drugs are analogs of norephedrine (**1**), the potentiation by (−)-**1** was also examined. The drug is mixed acting; hence, as expected it produced some intrinsic effects at 1×10^{-5} and 3×10^{-5} *M*. The intrinsic effects of (−)-**1** could complicate the potentiation experiments. When the concentration of (−)-**1** was lowered to 3×10^{-6} *M*, there was less than 5% intrinsic effect produced; however, the response of the tissue to (−)-norepinephrine in the presence of this concentration of (−)-**1** was increased to 66 ± 8% ($n = 3$) of the maximal. The response to (−)-norepinephrine in the presence of a 3×10^{-4} *M* concentration of **2** was 55 ± 3% ($n = 4$) of the maximal. Approximately equal potentiation of (−)-norepinephrine by the drugs **2** and (−)-**1** at different concentrations indicates that **2** has approximately 1/100th the potency of (−)-norephedrine.

This work appears to be in agreement with previous studies on the inhibition of (−)-norepinephrine uptake by conformationally restricted phenethylamine analogs.[8,24] It was shown with the *cis*- and *trans*-2-phenylcyclopropylamines that the trans compound was considerably more effective in inhibiting the uptake of (−)-norepinephrine in both peripheral[8] and central nervous system tissues.[24] In the more effective norephedrine analog, **2**, there is a trans relationship between the phenyl ring and the amino function; thus this would appear to lend some credence to the thought that compounds may bind and inhibit the amine uptake pump in an anticlinal or antiperiplanar conformation.[8,25,26] The details of the studies related to the inhibition of uptake of tritium labeled (−)-norepinephrine by these substances will be reported elsewhere.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 257 infrared spectrophotometer and a Varian A-60A nuclear magnetic resonance spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

trans-**2-Azido-1-phenylcyclobutanol (6).** To an ice-cooled mixture of 1-phenylcyclobutene (**4**,[10] 0.06 mol) and 16 g of anhydrous sodium carbonate (0.14 mol) in 50 ml of CH_2Cl_2 was added 13 g of 40% peracetic acid (0.07 mol) in acetic acid (a trace of sodium acetate was added to the peracetic acid to neutralize any sulfuric acid present). The reaction mixture was then allowed to come to room temperature and stirred for an additional 1 hr at room temperature. The reaction mixture was then filtered and the sodium carbonate was washed with several portions of CH_2Cl_2. The CH_2Cl_2 layers were combined and washed with 5% sodium bicarbonate and water, dried (Na_2SO_4), and evaporated to give a light yellow liquid **5** (8.7 g, 97%): NMR ($CDCl_3$) δ 7.58 (s, 5 H, aromatic), 4.07 (m, 1 H, CH), and 1.7–2.6 (m, 4 H, CH_2CH_2). Upon standing at room temperature this material underwent rearrangement to a mixture of 1-phenylcyclopropanecarboxaldehyde[27] and 2-phenylcyclobutenone.[15]

The crude epoxide **5** (12.1 g, 0.083 mol) and sodium azide (40 g, 0.06 mol) in 100 ml of H_2O were added to 800 ml of DMF. The reaction mixture was stirred for 7 hr at 80–90°. The dark brown solution was cooled with the aid of an ice bath and then extracted with three 200-ml portions of ether. The ether layers were combined and washed with a saturated NaCl solution and dried (Mg_2SO_4), and the solvent was evaporated to yield 11.6 g of light brown oil. Column chromatography using silica gel with 30% ether in *n*-pentane afforded 4.8 g of **6** (52%). A portion was recrystallized from *n*-pentane–ether to give a white solid: mp 64–65°. Anal. ($C_{10}H_{11}N_3O$) C, H, N.

trans-**2-Amino-1-phenylcyclobutanol (3).** The azide **6** was added to 250 ml of B_2H_6 (1 *M* in THF). The mixture was stirred at 50° for 48 hr. Alcohol saturated with HCl was added until no further reaction occurred. The solvent was removed and the remaining white residue was taken up in water and the pH was adjusted to 9 with 2 *N* NaOH. The basic solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated to give 2.6 g of an oil (76%) which crystallized from benzene–hexane as a white solid, **3**: mp 88.5–90°.

A small amount of the oil was converted to the HCl salt of **3** which crystallized from MeOH–Et_2O as a white solid, mp 223–224° dec. Anal. ($C_{10}H_{14}NOCl$) C, H, N.

trans-**2-Acetamido-1-phenyl-1-acetoxycyclobutane (7).** To a solution of 10 ml of pyridine and 10 ml of acetic anhydride was added 300 mg of the HCl salt of **3**. The solution was kept at room temperature overnight and then evaporated to an oil, to which was treated 10 ml of 3% HCl for 30 min. The mixture was then taken up in $CHCl_3$ and washed with 10% aqueous HCl, a saturated solution of $NaHCO_3$, and H_2O. The $CHCl_3$ layer was then dried (Na_2SO_4) and evaporated to yield a solid residue that was recrystallized from $CHCl_3$–Et_2O to yield 292 mg of solid: mp 159.5–161°; NMR ($CDCl_3$) δ 1.65 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3), 2.2–3.0 (m, 4 H, CH_2CH_2), 4.80 (q, 1 H, CH, $J_{CH,CH_2} = 8.5$ Hz), 5.30 (br d, NH, $J_{NH,CH} = 8$ Hz), and 7.34 (s, 5 H, aromatic); exchange NH with D_2O, δ 4.80 (t, 1 H, CH). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

2-(Dibenzylamino)cyclobutanone (10). Method A. To 950 mg of 2-bromocyclobutanone[16] in 20 ml of anhydrous Et_2O was added 11 g of dibenzylamine (55.76 mmol). The solid material that formed was removed and washed with Et_2O. The Et_2O layer was evaporated and the resultant oil was placed on a silica gel

column and eluted with $CHCl_3$–C_6H_6–MeOH (5:1:1) to give 846 mg of an oil, **10** (53%).

Method B. To a mixture of 17.2 g of sodium (0.748 g-atom) being rapidly stirred in 150 ml of refluxing toluene under N_2 was added dropwise a solution of 32.6 g of diethyl succinate (0.187 mol) and 84.0 g of chlorotrimethylsilane (0.775 mol). After the addition was complete the mixture was stirred for an additional 3 hr. The solution was allowed to cool to room temperature and sodium chloride was then removed by filtration and the filtrate was distilled at 59–61° (2.3 mm) to yield 33.77 g of **12** (78.3%).[17,18]

To 6.9 g of **12** (30 mmol) was added dropwise a solution of 5.92 g of dibenzylamine (30 mmol) in 15 ml of MeOH at 20° under N_2. The reaction mixture was stirred an additional 2 hr after the addition was complete. The MeOH was removed by evaporation and the resulting brown oil (7.9 g) was treated with a saturated solution of HCl in ether and the resulting dibenzylamine hydrochloride solid was separated by fractional crystallization from MeOH–Et_2O. The remaining amino ketone hydrochloride residue was then treated with aqueous 10% NaOH and extracted several times with ether. The ether layers were combined and washed with an aqueous saturated solution of NaCl, dried ($MgSO_4$), and evaporated to a crude oil that was chromatographed on silica gel and eluted with $CHCl_3$–Et_2O (4:1) to give 6.2 g of **10** (78%). A small amount of **10** was further purified by passing it over a silica gel column. The column was eluted with $CHCl_3$ to give a light yellow oil which was taken up in ether. Dry HCl gas was added to the ether solution to give a yellow gummy residue which crystallized after considerable effort from MeOH–Et_2O to give a white solid HCl salt of **10**: mp 80–81°. Anal. ($C_{18}H_{20}NOCl$) C, H, N.

cis-**2-Dibenzylamino-1-phenylcyclobutanol (13).** To a solution of phenylmagnesium bromide, prepared by adding a solution of 2.4 g of bromobenzene (15.2 mmol) in 10 ml of THF to 350 mg of Mg turnings (15.2 mmol) in 20 ml of THF, was added slowly with stirring a solution of 2 g of **10** (7.05 mmol) in 20 ml of THF. The mixture was refluxed with stirring under N_2 for 4 hr and then quenched with aqueous NH_4Cl. The THF layer was separated and the aqueous layer was extracted with ether and the organic layers were combined, washed with aqueous NaCl, dried (Na_2SO_4), and evaporated to give 2.5 g of brown residue. The residue was placed on a silica gel column and eluted with $CHCl_3$ to yield 1.6 g of **13**. A small portion of the solid was recrystallized from MeOH to yield solid **13**: mp 82–83.5°. The free base **13** was converted to a hydrochloride salt yielding a white solid: mp 186–188° dec. Anal. ($C_{24}H_{26}NOCl$) C, H, N.

cis-**2-Amino-1-phenylcyclobutanol (2).** To 100 mg of 10% Pd/C in 2 ml of 95% EtOH, saturated with H_2 at atmospheric pressure for 10 hr, was added 210 mg (0.55 mmol) of the hydrochloride salt of **13** in 6 ml of 95% EtOH. The mixture was stirred for 20 hr in which time 1.14 mmol of H_2 was consumed. The catalyst was removed by filtration and the ethanol filtrate was evaporated to an oil which crystallized from MeOH–Et_2O to give 114 mg of a hygroscopic solid. This solid was dried under vacuum at 80° to yield a white solid HCl salt of **2**, mp 123–124.5°. Anal. ($C_{10}H_{14}NOCl$) C, H, N.

The HCl salt of **2** was converted to the free base by treating the salt with 1 *N* NaOH and extracting the free base into $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to give a solid residue which crystallized from benzene–hexane to give white solid **2**: mp 78–79°.

cis-**2-Acetamido-1-phenyl-1-acetoxycyclobutane (14).** A solution of 90 mg (0.45 mmol) of the HCl salt of **2**, 4 ml of acetic anhydride, and 5 ml of pyridine was stirred at room temperature overnight. The excess pyridine and acetic anhydride were evaporated to give a yellow oil which was treated with 6 ml of 3% HCl for 30 min. The mixture was then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 10% aqueous HCl, a saturated solution of $NaHCO_3$, and a saturated solution of NaCl, dried (Na_2SO_4), and evaporated to give a solid which was recrystallized from petroleum ether (bp 60–110°)–benzene to give 101 mg of **15** (91%): NMR ($CDCl_3$) δ 2.0 (s, 6 H, amide and ester CH_3), 1.80–2.70 (m, 4 H, CH_2CH_2), 4.65 (q, 1 H, CH, J_{CH,CH_2} = 8.5 Hz), 6.60 (br d, 1 H, NH, $J_{NH,CH}$ = 8 Hz), and 7.30 (s, 5 H, aromatic); exchange NH with D_2O, δ 4.65 (t, 1 H, CH).

Pharmacological Testing. Male albino Sprague–Dawley rats weighing 300–375 g were used. To deplete the endogenous catecholamines, rats were injected with 5 mg/kg of reserpine ip, 18–22 hr prior to the experiment. The animals were decapitated and the vas deferens was quickly removed, cleaned of blood vessels and fatty tissue, and mounted in a 10-ml jacketed tissue bath at 37°C ± 0.5 containing modified Krebs solution of the following composition as millimoles: NaCl, 118; KCl, 4.7; $MgCl_2 \cdot 6H_2O$, 0.54; $CaCl_2 \cdot 2H_2O$, 2.5; NaH_2PO_4, 1.0; $NaHCO_3$, 25; glucose, 11. Ethylenediaminetetraacetic acid (EDTA, 10 mg/l.) was added to retard the spontaneous oxidation of (−)-norepinephrine. A mixture of 95% O_2 and 5% CO_2 gas was bubbled through the solution.

The tissue responses were recorded via isotonic myograph on a physiograph (E & M Instrument Co.). The lever exerted 250 mg of tension. The tissue was allowed to equilibrate for 45 min, during which time it was frequently washed. In a series of experiments, a concentration of (−)-norepinephrine which will give a small contraction of the tissue was determined. In another series of experiments the responses to a single dose of (−)-norepinephrine in the presence of the experimental drug (15 min of incubation) were determined. Subsequently, tissues were washed and the maximal effects produced by (±)-methoxamine were obtained. On each tissue the response to (−)-norepinephrine was expressed as the percent of the maxima produced by (±)-methoxamine. The rationale for selecting (±)-methoxamine as a reference drug for the maximal effects was that the drug is mainly direct-acting[28] and the presence or the absence of the potentiating agent does not influence its maximal effects. The experiments were repeated and the results are expressed as mean with SEM.

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7-Aza Analogs of the Analgetic Agent Azabicyclane. Synthesis and Pharmacologic Analysis†

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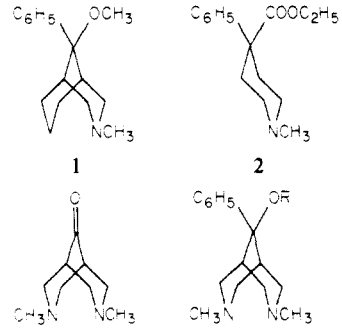
Three 3,7-diazabicyclo[3.3.1]nonane derivatives (4) with a structural similarity to the analgetic agent azabicyclane (1) were prepared. The amino alcohol **4a** was found to prefer a conformation wherein the six-membered ring to which the hydroxyl group is syn is in the boat form. These three compounds had increased basicity in comparison with 1 due to various forces stabilizing their monocationic states. Compounds **4a–c** did not show analgetic activity at the dose levels tested.

The analgetic agent azabicyclane (1) has been reported to be six to eight times as potent as meperidine (2),[1] and related compounds have also been reported to have high analgetic activity and low toxicity.[2] The influence on analgetic activity of an *N*-methyl group, in place of the 7-methylene group, in analogs of 1 was of interest. These compounds (4) feature the two nitrogen atoms in close proximity, and it was anticipated that this would result in increased basicity in relation to 1, due to an increased stability of the monoprotonated state as a result of intramolecular hydrogen bonding.[3] It was thought that the increase in basicity could conceivably result in an increased affinity of the monoprotonated forms of one or more of these compounds at the anionic site of the analgetic receptor, resulting in improved potency and duration of action.

Chemistry. Addition of a solution of amino ketone **3**[4] in ether to excess ethereal phenyllithium, followed by aqueous work-up, furnished the amino alcohol **4a**. Alternatively, treatment of the initially formed anion with propionyl chloride[5] gave amino ester **4b**. Attempted synthesis of this ester by treatment of **4a** with propionyl chloride or propionic anhydride in pyridine at elevated temperatures failed, probably due to the restricted nature of the hydroxyl group in this compound. The methyl ether **4c** was prepared in low yield by treatment of the anion with iodomethane. The low yield of this latter reaction was due to the formation of significant amounts of quaternized products, which demonstrates the similarity of nucleophilic character of the oxide anion and the two closely positioned amine functions.

Compounds **4b,c** were not readily amenable to a conformational analysis of their fused six-membered rings. It is reasonable to assume that these ring systems adopt double chair conformations in analogy with the preferred conformation of the bicyclic diamine **5**.[6]



1 2 3

4a, R = H
b, R = COC_2H_5
c, R = CH_3

In contrast, compound **4a** was shown by infrared spectrometry to exhibit a strong preference for the chair–boat conformer, with the ring to which the hydroxyl group is syn taking the boat conformation.[7] In the infrared spectrum of **4a** there is a broad, strong band centered at 3230 cm^{-1} due to associated O–H stretch which results from transannular O–H···N bonding; weak absorbance at 3640 cm^{-1} is due to unassociated O–H stretch. Absorbance positions and intensities were invariant with concentration. Examples of compounds displaying 1,4 O–H···X bonding are somewhat rare owing to unfavorable energy differences usually existing between boat and chair conformers; however, a number of examples in mono- and bicyclic systems have been reported.[8] A measure of strength of the intramolecular hydrogen bond in **4a** is obtained from a consideration of the difference, $\Delta\nu$, between the positions of free and associated OH stretch.[9] The usual magnitude of $\Delta\nu$ is 200–250 cm^{-1}; however, in this instance $\Delta\nu$ is 410 cm^{-1} which suggests that the transannular O–H···N hydrogen bond approaches the strength of intermolecular hydrogen bonding observed in neat or concentrated samples of amino alcohols.[10]

Compounds **4a–c** were found to be strong bases with pK_{a_2}* values as high as 11.73. In contrast, the C-7 analog

† This paper is dedicated to the memory of Professor Edward E. Smissman.

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