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Synthesis and Biological Activity of Some Carbocyclic Analogs of Muscarine

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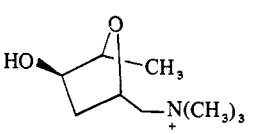
 Received June 26, 1972

Optimum muscarinic potency has heretofore been assumed to require the presence in the drug of an oxygen atom more or less analogous to the ether oxygen of muscarine. This paper describes the synthesis of several carbocyclic muscarine analogs which lack this atom and yet retain very appreciable muscarinic potency. One, (±)-*trans*-1-hydroxy-*cis*-2-methyl-4-trimethylammoniomethylcyclopentane iodide (**3**), obtained *via* a stereospecific photochemical pathway, was shown to be a direct muscarinic agonist and to possess about five to ten times the potency of (±)-muscarine and acetylcholine. These results indicate a need to consider further muscarinic drug-receptor theory.

The various proposals put forward regarding the nature of the muscarinic receptor generally agree that, for maximum and selective muscarinic activity, an agonist must have a quaternary nitrogen, an ether oxygen, and an additional oxygen, all separated by critical spatial distances.[1-4] Even though it has been demonstrated that the quaternary nitrogen is essential in muscarine (**1**),[1] and that decreased activity is noted when the hydroxyl group is removed,[5] no one has heretofore replaced the ether oxygen with an isosteric unit



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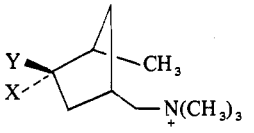
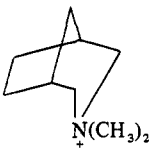


2, X = Y = H
3, X = H; Y = OH

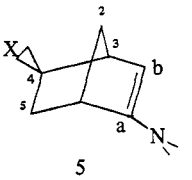


4

whose electronic properties differ radically from those of the ether oxygen, which has nevertheless been assumed necessary for optimum receptor interaction.[3]

This paper describes the syntheses and biological activity of compounds **2** and **3** which are carbocyclic analogs corresponding to deshydroxymuscarine and muscarine, respectively. Compound **4**, obtained fortuitously in one of the synthesis schemes, can be viewed as a conformationally biased analog of **2** and is therefore an interesting additional analog of deshydroxymuscarine. The cyclopentane ring was selected because it is isosteric with the tetrahydrofuran ring of muscarine (**1**), but the cyclopentane methylene cannot have the same electronic contribution toward receptor interaction postulated for oxygen in the tetrahydrofuran ring of muscarine.

Chemistry. A stereospecific synthesis was envisioned for compounds **2** and **3** from an appropriate norbornyl derivative, such as **5**. This would yield the desired stereochemical relationship among the 1, 3, and 4 substituents by cleavage



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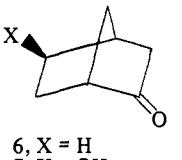
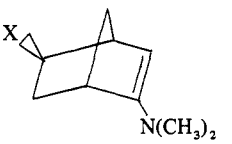


6, X = H
7, X = OH
8, X = OAc
9, X = OTHP
10, X = OCH-$(CH_3)OC_2H_5$



11, X = H
12, X = OAc
13, X = OTHP
14, X = OCH-$(CH_3)OC_2H_5$

of the a-b bond. Synthetic approaches toward the desired compound began with norcamphor (**6**) and *exo*-5-hydroxybicyclo[2.2.1]heptan-2-one (**7**).[6,7]

Treatment of **6** with trisdimethylaminoborane as described for hindered ketones[8] produced the dimethylenamine **11**. This enamine could not be obtained by conventional methods, probably because of the strain produced in the bicyclic system by the introduction of the enamine double bond. The acetate **8**, an intermediate in the synthesis of **7**, afforded enamine **12**. The low yields obtained probably resulted from aminolysis of the ester. Dimethylacetamide, the expected aminolysis product, was also isolated. However, the THF adduct **9** and the ethyl vinyl ether adduct **10** produced good yields of the corresponding enamines **13** and **14**, respectively. From the yields of **13** and **14** and their subsequent reactions, **14** proved to be the more useful derivative.

The instability of these dimethylenamines made it impossible to effect their characterization by standard spectrometric and microanalytical methods. Characterization was carried out by obtaining the mass spectra of the major peak obtained when **11** and **14** were subjected to analytical gas chromatography, and the gas chromatographic effluent passed directly into the mass spectrometer. The spectra obtained were consistent with the structures assigned **11** and

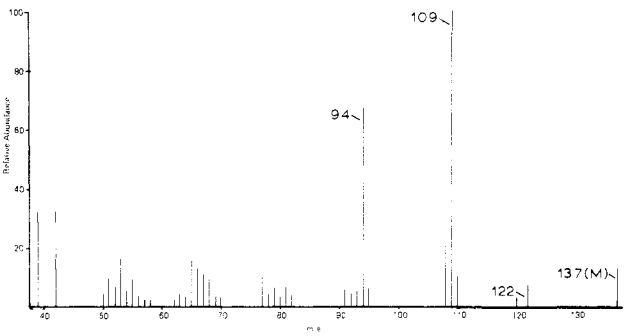


Figure 1. Mass spectrum of 2-dimethylaminobicyclo[2.2.1]hept-2-ene (11). Peaks of abundance ratio less than 2% have been omitted.

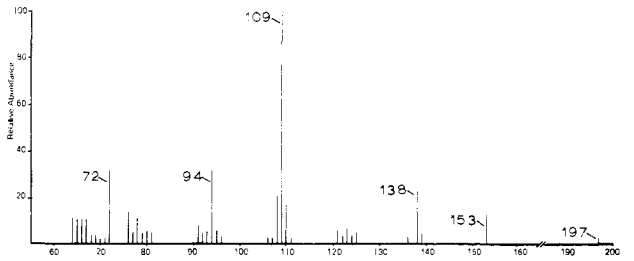
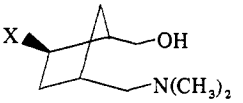


Figure 2. Mass spectrum of 2-dimethylamino-5-(1-ethoxyethoxy)-bicyclo[2.2.1]hept-2-ene (14). Peaks of abundance ratio less than 2% have been omitted.

14 (see line graphs Figures 1 and 2 and fragmentation patterns Schemes I and II).

In order to obtain the desired *cis*-1,3-substituted cyclopentane, cleavage of the enamine double bond was undertaken. Cleavage of the sensitive enamines **11** and **14** could be effected only by ozonolysis, and no advantage accrued using ozone in N_2 over ozone in O_2. Attempts to cleave the double bond by use of the method described by Lemieux and von Rudloff[9] failed because hydrolysis of enamines to the starting ketones occurred even at a pH above 7. Likewise, use of sodium dichromate and glacial AcOH in benzene failed even when anhydrous reagents were used.[10] By modification of a method used for steroidal enamines,[11] ozonolysis of enamines **11** and **14** and subsequent treatment of the ozonolysis mixture with $LiAlH_4$ produced amino alcohols **15** and **16**, respectively. Use of diborane in THF instead of $LiAlH_4$ gave lower yields of **15** from **11**.

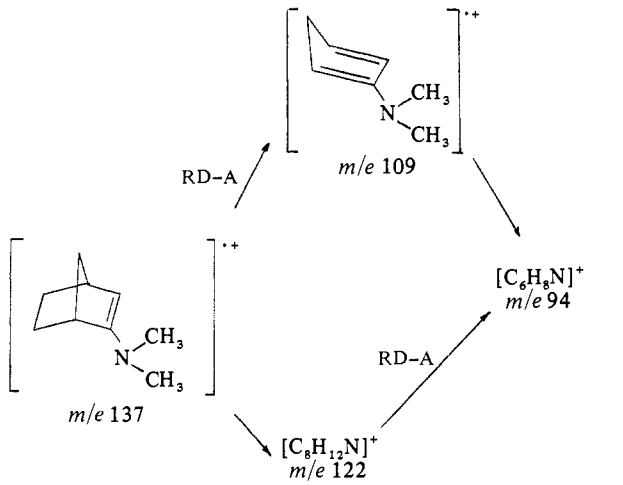


15, X = H
16, X = $OCH(CH_3)OC_2H_5$

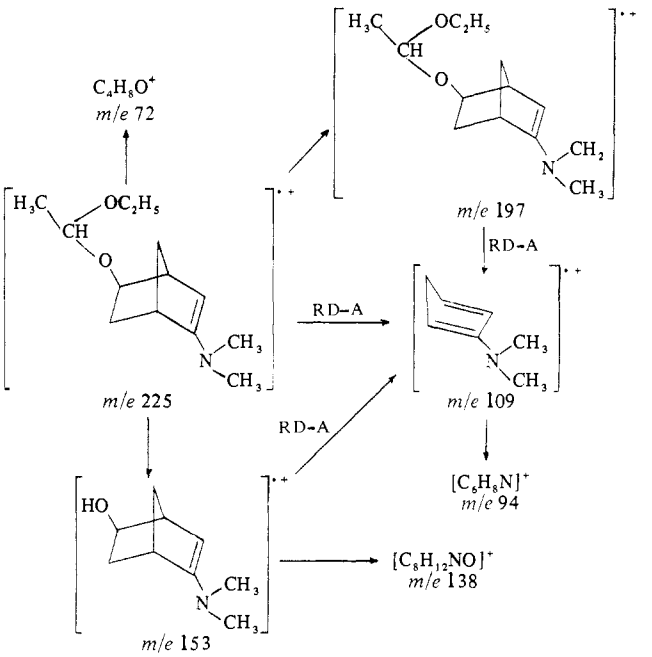
Removal of the hydroxyl group from **15** and **16** would afford **2** and **3**, respectively. This might be accomplished by converting the hydroxyl group into a moiety, such as a sulfonate ester or halide, potentially susceptible to hydrogenolysis. However, such approaches from **15** led only to the bicyclic quaternary compound **4**, which apparently resulted from intramolecular nucleophilic attack by the amine nitrogen upon the displaceable group.[12]

Amides **17** and **18** also appear to afford facile entry into the desired series of compounds. Reduction of the ozonide obtained from **11** with $NaBH_4$ afforded **17** in fair yield, but several variations of this procedure[13-15] failed to produce **18**,

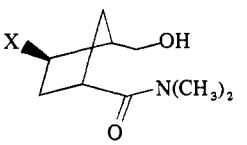
Scheme I. Proposed Fragmentation Pattern of 2-Dimethylaminobicyclo[2.2.1]hept-2-ene (11). RD-A = Reverse Diels–Alder Reaction



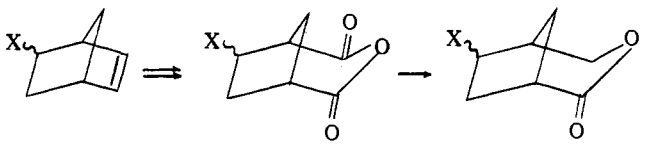
Scheme II. Proposed Fragmentation Pattern of 2-Dimethylamino-5-(1-ethoxyethoxy)bicyclo[2.2.1]hept-2-ene (14). RD-A = Reverse Diels–Alder Reaction



a potentially useful precursor of **3**. Improved yields of **17** were obtained starting from bicyclo[2.2.1]heptene. Cleavage of this olefin with $KMnO_4$[16] or O_3[17] afforded the corresponding diacid, which was converted to anhydride **19**,[18] thus assuring cis stereochemistry. Lactone **22** was obtained using $LiAlH_4$ at −55°[14] and in lesser yields by other methods.[16,19] From **22**, amide **17** was easily obtained.[20] Conversion of **17** to the corresponding bromide **23** was



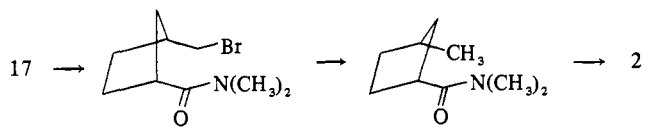
17, X = H
18, X = $OCH(CH_3)OC_2H_5$



19, X = H
20, X = OH
21, X = OAc

22, X = H

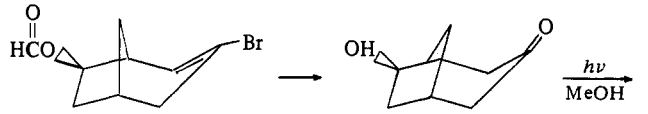
effected with PBr_3, from which the bromine atom was effectively removed with Ph_3SnH[21,22] to yield the methyl amide **24**. Reduction of **24** with $LiAlH_4$ yielded the corresponding amine,[23] which was easily quaternized to **2**. The



23 24

amine was also obtained from **17** by treatment of the corresponding sulfonate esters[24] with $LiAlH_4$, but yields in both steps were poor.

Unfortunately, it was impossible to obtain anhydrides **20** and **21**, either by methods used for **19** or by treating the thallium carboxylates with $SOCl_2$,[25] so that **3** was not accessible by this route. In another effort to eliminate the troublesome intramolecular reaction observed in attempts to remove the hydroxyl group from **15** and **16**, these compounds were first quaternized and the quaternary compounds characterized as tetraphenylboron salts.[26] Although this made it possible to functionalize the hydroxyl group as a sulfonate ester or iodide,[27,28] it was impossible to effect hydrogenolysis of these groups under a variety of conditions.[29,30]



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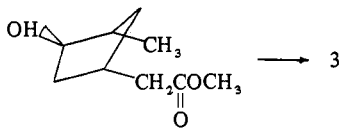

27

The desired muscarine analog **3** was finally obtained by a novel photochemical route starting from bromoformate **25**.[31] This, upon treatment with 50% aqueous sulfuric acid, yielded the bicyclic hydroxy ketone **26**, which in turn afforded, upon irridation in MeOH, a mixture of hydroxy ester **27** and the positional isomer resulting from ring opening in the other direction.† These were separated by silica gel column chromatography and characterized by their nmr behavior upon addition of europium shift reagents. Ester **27**, upon sequential treatment with hydrazine hydrate, $NaNO_2$, HCl, and MeI-NaOH, afforded the desired muscarine analog **3**.

Biology. Compounds listed in Table I were tested in whole guinea pig ileum preparations obtained from male American Standard Guinea Pigs, Small Stock. Four preparations were used at each dose level. The preparations were immersed in Tyrode solution at 37°. Acetylcholine and DL-muscarine were used as standards. Since all compounds gave full contraction, all had unit intrinsic activity, and typical cumulative dose-response curves were obtained in each case. The results indicate that the bicyclic quaternary compound **4** possesses about $^1/_{10}$ the activity of acetylcholine, whereas the desoxy compound **2** is tenfold less active. Significantly, the racemic cyclopentane muscarine analog **3** is about five to ten times more active than acetylcholine and muscarine. The inhibitor data also show the observed ileum contraction to have resulted from a muscarinic effect, since atropine, but not hexamethonium, strongly interfered with the effect.

Table I. Muscarinic Agonist Potency in Guinea Pig Ileum

Compound	Antagonist	Equipotent concn, m*M*	Rel activity
Acetylcholine		5×10^{-6}	1.0
DL-Muscarine[a]		5×10^{-6}	1.0
DL-2		5×10^{-4}	0.01
DL-3		5×10^{-7}[b]	5–10
4		5×10^{-5}	0.1
Acetylcholine	Atropine, 3×10^{-6} *M*	5×10^{-4}	
DL-Muscarine	Atropine, 3×10^{-6} *M*	5×10^{-4}	
DL-3	Atropine, 3×10^{-6} *M*	5×10^{-3}	
Acetylcholine	Hexamethonium, 3×10^{-3} *M*	5×10^{-6}	
DL-Muscarine	Hexamethonium, 3×10^{-3} *M*	5×10^{-7}	
DL-3	Hexamethonium, 3×10^{-3} *M*	5×10^{-7}	

[a] Generously supplied by Professor C. H. Eugster. [b] At this concentration, slightly submaximal contractions were obtained.

The very high potency of **3**, together with data indicating appreciable potencies for other compounds in this study and in the literature, indicates a need critically to reexamine muscarinic drug-receptor interaction theories.

All current theories of muscarinic drug-receptor interactions postulate an electron-rich center analogous to the ester oxygen of acetylcholine as a primary site of interaction. Since **3** lacks such a center and is at least as active as DL-muscarine, such hypotheses seem open to serious question, and it becomes vital to determine whether **3** behaves analogously to muscarine in other respects, notably with respect to the isomer potency ratio. Also, it would be most interesting to have biological data for the ketone corresponding to **3**. Studies along these lines are in progress in these laboratories.

Experimental Section

Melting points were determined on a calibrated Thomas-Hoover Unimelt and were corrected. Infrared spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers and were as expected. Mass spectra were recorded on a Finnegan 1015 mass spectrometer in combination with separation on a directly attached Varian Aerograph 1700 gas chromatograph using a 6 ft × $^1/_8$ in. stainless steel column packed with 5% Apiezon L on DMCS treated 80–100 mesh H. P. Chromosorb G at 85 cc/min flow rate of He with a column temperature of 100° for 11 and 170° for 14. Nuclear magnetic resonance spectra were recorded on Varian A-60 and A-60A spectrometers using tetramethylsilane and 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standards and were as expected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on F & M Model 185 carbon hydrogen nitrogen analyzer, University of Kansas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within 0.4% of the theoretical values.

2-Dimethylaminobicyclo[2.2.1]hept-2-ene (**11**). Ketone **6** (22 g, 0.20 mol), dry K_2CO_3 (5 g), $(Me_2N)_3B$ (31.5 g, 0.22 mol), and Me_2NH (35 ml, freshly condensed) were added to a 100-ml glass-lined steel autoclave. The autoclave was heated at 95–105° for 108–120 hr, cooled, and allowed to stand for an additional 12–24

†R. S. Givens and D. Rademacher, unpublished work, University of Kansas, Lawrence, Kan., Oct 1971.

hr. After cooling in ice, the autoclave was opened and excess Me_2NH removed with a steam of dry N_2 and finally on a rotary evaporator. The residue was distilled, the fraction collected at 89–100° (50 mm) was redistilled, and 11 was collected at 89–95° (50 mm) (17 g, 62%): ir (neat) 3080, 2950, 2860, 2800, 1610, 1450, 1370 1100 cm^{-1}; nmr (C_6H_6) δ 4.15 (d, 1 H), 2.65 (m, 2 H), 2.35 (s, 6 H), 0.9–1.6 (m, 6 H). The structure of 11 was confirmed by mass spectral analysis of the material eluted as the major peak on analytical vpc (line graph Figure 1, fragmentation pattern Scheme I).

5-(1-Ethoxyethoxy)bicyclo[2.2.1]heptan-2-one (10). Ketone 7[6,7] (25.2 g, 0.2 mol) was dissolved in ethyl vinyl ether (21.6 g, 0.3 mol). Concentrated HCl (7 drops) was added and the reaction mixture stirred for 24 hr, after which time powdered NaOH (100 mg) was added and stirring continued for 2 hr. The excess ethyl vinyl ether was removed on a rotary evaporator, the residue was distilled, and 10 was collected at 82–85° (0.6–0.8 mm) (36.3 g, 92%): ir (neat) 2960, 2920, 2860, 1740, 1199, 1050 cm^{-1}; nmr ($CDCl_3$) δ 4.70 (m, 1 H), 3.9 (m, 1 H), 3.5 (m, 2 H), 2.5 (m, 2 H), 1.82 (d, 2 H), 1.72 (m, 4 H), 1.0–1.4 (m, 6 H).

Anal. C, H.

2-Dimethylamino-5-(1-ethoxyethoxy)bicyclo[2.2.1]hept-2-ene (14). This enamine was prepared and characterized by the procedure described for 11, carried out on 10 (19.8 g, 0.1 mol) at 50–60° for 24 hr. Distillation yielded 14 at 88–92° (0.5–1.5 mm) (19.5 g, 86%): ir (neat) 3080, 2960, 2860, 2920, 2860, 2790, 1610, 1520, 1370, 1340 cm^{-1}; nmr (neat) δ 4.45 (m, 1 H), 3.91 (m, 1 H), 3.3 (m, 3 H), 2.65 (m, 2 H), 2.35 (s, 6 H), 0.8–1.6 (m, 10 H); mass spectral analysis (line graph Figure 2, fragmentation pattern Scheme II).

cis-3-Hydroxymethyl-1-(*N,N*-dimethylaminomethyl)cyclopentane (15). Enamine 11 (8.5 g, 0.062 mol) was dissolved in dry THF (50 ml). With N_2 bubbling through, the reaction mixture was cooled to −78°. Dry (bubbled through concentrated H_2SO_4) O_2–O_3 (*ca.* 1 mmol of O_3 per min) was bubbled through the cold reaction mixture until O_3 was evident in the exhaust (*ca.* 60–75 min). Excess O_2–O_3 was removed (N_2); then the clear reaction mixture was added dropwise over 20–25 min to a mechanically stirred $LiAlH_4$–Et_2O solution [$LiAlH_4$ (5 g) in dry Et_2O (150 ml) was refluxed for 1 hr and allowed to stand 30 min, after which time the supernatant was poured into the reaction flask]. The reaction mixture was refluxed (6 hr) and cooled, H_2O (3.6 ml) in THF (15 ml) was added dropwise over 15 min, and stirring was continued for an additional 12 hr at room temperature. Next 25% Na_2CO_3 (15 ml) was added and stirring continued for 30 min. The resulting white precipitate was removed by filtration and digested on a steam bath with THF (50 ml) and 25% Na_2CO_3 (15 ml). The precipitate was again removed by filtration and discarded while the combined filtrates were reduced in volume on a rotary evaporator until H_2O began distilling. The residue was extracted with Et_2O (5 × 15 ml) and the extract was dried (Na_2SO_4) and concentrated on a rotary evaporator and then dried *in vacuo* to yield 15 (5.5 g, 56%) sufficiently pure for use in the subsequent reaction.

For analysis, a fraction was distilled and 15 was collected at 68–74° (0.05–0.1 mm): ir (neat) 3330, 2980, 2860, 2780, 1450, 1150, 1110, 880, 835 cm^{-1}; nmr ($CDCl_3$) δ 3.5 (d, 2 H), 3.15 (s, 1 H), 2.2 (s, 8 H), 1.7–2.1 (m, 2 H), 0.9–1.6 (m, 6 H).

Anal. C; H: calcd, 12.18; found, 11.77.

cis-3-Hydroxymethyl-*trans*-4-(1-ethoxyethoxy)-1-(*N,N*-dimethylaminomethyl)cyclopentane (16). This compound was prepared by the procedure described for 15 carried out on enamine 14 (6.3 g, 0.028 mol). The concentrated dried extract was 16 (5.5 g, 80%) which was sufficiently pure to use in subsequent reactions.

For analysis, a fraction was distilled and 16 was collected at 118–128° (0.5–1.0 mm): ir (neat) 3400, 2960, 2920, 2860, 2760, 1450, 1370, 1330, 1120, 1080, 1050 cm^{-1}; nmr ($CDCl_3$) δ 4.7 (d, 1 H), 3.55 (m, 6 H), 2.4 (m, 2 H), 2.2 (s, 6 H), 1.4–2.1 (m, 6 H), 1.0–1.4 (m, 6 H).

Anal. C, H, N.

N,N-Dimethyl-3-azoniabicyclo[3.2.1]octane Bromide (4, Br) [Attempted Synthesis of *cis*-3-Bromomethyl-1-(*N,N*-dimethylaminomethyl)cyclopentane]. Amino alcohol 15 (5.1 g, 0.033 mol) was placed in a flask with dry $CHCl_3$ (5 ml) and, while stirring (N_2), cooled to 0°. PBr_3 (3.3 g, 0.012 mol) in dry $CHCl_3$ (2 ml) was added dropwise over 30 min; stirring was continued for 30 min at 0°, then at room temperature for 1 hr, and at 65–70° for 18 hr. After cooling, $CHCl_3$ (50 ml) and 48% HBr (5 ml) were added, and the reaction mixture was stirred for 30 min. The layers were separated and the $CHCl_3$ layer was washed with saturated NaBr (2 × 5 ml); then the combined H_2O layers were extracted with $CHCl_3$ (20 ml), neutralized ($NaHCO_3$), made basic (pH >10) (20% NaOH), and then extracted with Et_2O (5 × 20 ml). The Et_2O extract was dried (Na_2SO_4) and concentrated to yield a white solid (400 mg) which was recrystallized from EtOH–EtOAc to yield 4 (100 mg, 10%), a white powder which decomposed without melting: nmr δ 3.55 (d, 4 H), 3.3 (s, 3 H), 3.1 (s, 3 H), 2.85 (m, 2 H), 1.6–2.0 (m, 6 H).

Anal. C, H, N.

cis-3-Hydroxymethyl-1-(*N,N*-dimethylcarboxamido)cyclopentane (17). Method A. Into a 500-ml round-bottom flask was placed $LiAlH_4$ (2.2 g, 0.058 mol) and dry THF (200 ml). This was refluxed while stirring under N_2 for 1 hr and then cooled to −55 ± 5°, and anhydride 19[18] (14 g, 0.1 mol) in dry THF (150 ml) was added dropwise (45 min). Stirring was continued (90 min) while the reaction mixture warmed to 0°; then it was stirred at 0° (20 min). The reaction mixture was cooled to −15° and 6 *N* HCl (40 ml) was added dropwise (10 min) while stirring, after which time it was allowed to stir at room temperature (4 hr). The two layers were separated and the H_2O layer was extracted (Et_2O, 4 × 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to yield a viscous oil.

The oil was dissolved in dry C_6H_6 (100 ml) and the resulting mixture refluxed under a Dean-Stark trap for 3 hr to remove H_2O. C_6H_6 was removed on a rotary evaporator until the volume of the residue was 30 ml; then this was placed in a 100-ml glass-lined steel autoclave along with Me_2NH (50 ml, freshly condensed) and Me_2NH·HCl (25 mg) and heated at 160–170° (72 hr). After cooling in ice, the autoclave was opened and excess solvent removed. The residue was distilled and 17 was collected at 133–137° (0.5 mm) (12 g, 70% based on 19): ir (neat) 3400, 2940, 2850, 2780, 1650, 1630, 1400, 1130, 1040 cm^{-1}; nmr ($CDCl_3$) δ 4.5 (s, 1 H), 3.5 (d, 2 H), 3.1 (s, 3 H), 2.9 (s, 3 H), 1.5–2.5 (m, 8 H).

Anal. C, H, N.

cis-3-Hydroxymethyl-1-(*N,N*-dimethylcarboxamido)cyclopentane (17). Method B. Enamine 11 (3.7 g, 0.027 mol) was dissolved in dry THF (45 ml) and, while bubbling dry N_2 through, the reaction mixture was cooled to −78°. Dry (bubbled through concentrated H_2SO_4) O_2–O_3 (*ca.* 1 mmol of O_3 per min) was bubbled through the cold reaction mixture until O_3 was evident in the exhaust (*ca.* 50–70 min). Excess O_2–O_3 was removed (N_2). The reaction mixture was allowed to warm to room temperature, H_2O (25 ml) was added, and the volume reduced on a rotary evaporator until H_2O began distilling. The resulting H_2O solution was added dropwise over 5 min to a solution of $NaBH_4$ (1.0 g, 0.027 mol) in H_2O (25 ml, containing 2 drops 20% NaOH) while stirring. Initially the reaction was exothermic, and stirring was continued for 2.5 hr, after which time the reaction mixture was made acidic (pH <3) with concentrated HCl and heated at 60–70° for 15 min. After cooling, the reaction mixture was made basic (pH >9) with 20% NaOH and saturated with NaCl and then was extracted with $CHCl_3$ (5 × 40 ml). The extract was dried (Na_2SO_4) and concentrated on a rotary evaporator, and the residue was dried *in vacuo* to yield a viscous oil (2.1 g) which was chromatographed on Merck silica gel (42 g) and, after preliminary elution with 50% $CHCl_3$ in C_6H_6, the product 17 was obtained (0.6 g, 14%) on elution with $CHCl_3$. Its spectral properties matched those reported for 17 under method A.

cis-3-Bromomethyl-1-(*N,N*-dimethylcarboxamido)cyclopentane (23). Amido alcohol 17 (4.3 g, 0.025 mol) in dry alcohol-free $CHCl_3$ (filtered through Woelm neutral alumina) (3 ml) was stirred under N_2 and was cooled to 0°, after which time PBr_3 (2,5 g, 0.009 mol) in dry, alcohol-free $CHCl_3$ (5 ml) was added dropwise over 15 min. Stirring was continued for 30 min at 0°, 45 min at room temperature, and 5 hr at 72–77°. After cooling, the reaction mixture was washed with H_2O (3 × 5 ml), dried ($MgSO_4$), and concentrated on a rotary evaporator. The colorless liquid residue was dried *in vacuo* at 40° to yield 26 (4.9 g, 83%): bp 90–95° (0.1 mm); ir (neat) 2950, 2860, 1650, 1500, 1400, 1250, 1130, 960 cm^{-1}; nmr ($CDCl_3$) δ 3.45 (d, 2 H), 3.1 (s, 6 H), 2.9 (s, 6 H), 1.3–2.5 (m, 8 H).

Anal. C, H, N.

cis-3-Methyl-1-(*N,N*-dimethylcarboxamido)cyclopentane (24). Amido bromide 23 (5.6 g, 0.024 mol) in dry C_6H_6 (2 ml) was stirred under N_2 while triphenyltin hydride (8.8 g, 0.025 mol) in dry C_6H_6 (3 ml) was added dropwise over 5–10 min. An exothermic reaction commenced immediately but it subsided within 15–20 min; however, stirring was continued for 6 hr, after which time a voluminous precipitate had formed. This was removed by filtration and was washed with hexane–C_6H_6 (1:1). The filtrate was allowed to stir for an additional 16 hr, and the resulting precipitate was again removed by filtration and washed with hexane–C_6H_6 (1:1). The filtrate was

condensed on a rotary evaporator and the resulting clear yellow oil was distilled to yield 24 at bp 62–65° (0.2–0.4 mm) (2.6 g, 46%): ir (neat) 2940, 2860, 1640, 1480, 1390, 1250, 1130, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.1 (s, 3 H), 2.9 (s, 3 H), 2.9 (s, 3 H), 1.2–2.2 (m, 8 H), 1.0 (d, 3 H).

Anal. C, H, N.

cis-3-Methyl-1-(trimethylammoniomethyl)cyclopentane Iodide (2). Into a 100-ml, round-bottom flask was added $LiAlH_4$ (0.54 g, 0.014 mol) and dry Et_2O (50 ml); this was refluxed for 45 min. After cooling, a solution of amide 24 (2.2 g, 0.014 mol) in dry THF (20 ml) was added dropwise over 15 min to the stirred reaction mixture and it was refluxed (2 hr). H_2O (0.5 ml) in THF (10 ml) was added dropwise (10–15 min) and the reaction mixture was stirred (20 hr). The resulting precipitate was removed by filtration, digested on a steam bath with THF (25 ml), and filtered, and the digestion was repeated with 20% NaOH (5 ml) in THF (20 ml). The filtrate was made acidic with concentrated HCl (pH <3) and concentrated on a rotary evaporator until H_2O began distilling. The resulting H_2O solution was washed with Et_2O (3 × 10 ml) which was discarded, and the H_2O solution was made basic (pH >10) with solid NaOH, saturated with NaCl, and extracted with Et_2O (7 × 20 ml). The extract was dried ($MgSO_4$) and concentrated on a rotary evaporator to yield a slightly yellow oil [*cis*-3-methyl-1-(dimethylaminomethyl)cyclopentane] (1.3 g, 70%).

This yellow oil and MeI (10 ml, 0.16 mol) were placed in a 10-ml pear-shaped flask and the resulting mixture was allowed to stand for 16 hr. The resulting precipitate was removed by filtration, washed with Et_2O, and dried *in vacuo* at 60° to yield 2 (2.3 g, 57% based on amide 24: mp 193–197°; ir (KBr) 3000, 2940, 2850, 1480, 970, 900 cm^{-1}; nmr (D_2O) δ 3.6 (d, 2 H), 3.15 (s, 9 H), 1.3–2.4 (m, 8 H), 0.95 (d, 3 H).

Anal. C, H, N.

trans-1-Hydroxy-*cis*-2-methyl-4-(trimethylammoniomethyl)-cyclopentane Iodide (3). Ester 27 (100 μl, 0.58 mmol), hydrazine hydrate (44 μl), and absolute EtOH (250 μl) were refluxed 46 hr. The EtOH and excess $(H_2N)_2$ were removed *in vacuo* affording 98 mg of white solid (mp 121–123°; ir 3220, 2890, 1613, 1530, 1430, 1350, 1060, 1000, 935, 690 cm^{-1}) which was used without further purification. This hydrazide (98 mg, 0.58 mmol), 2.8 ml of H_2O, 0.12 ml of concentrated HCl, and 3.5 ml Et_2O were cooled with rapid stirring to 0°. A concentrated H_2O solution of $NaNO_2$ (123 mg) was added all at once. The reaction temperature was maintained below 5° by addition of ice. After 5 min the Et_2O was collected and the H_2O layer washed with Et_2O (3 × 1.5 ml). The water layer was then covered with Et_2O (150 ml) and saturated with $MgSO_4$. The mixture was shaken, the Et_2O decanted, and the water layer again extracted with Et_2O (3 × 100 ml). The water layer was again covered with Et_2O and the water removed using anhydrous $MgSO_4$, which was washed with Et_2O (3 × 100 ml). The combined Et_2O extracts were concentrated *in vacuo* to 200 ml, dried ($MgSO_4$), and concentrated to 5–7 ml. C_6H_6 (20 ml) was added; the mixture was dried with 4A molecular sieves and refluxed for 10 hr. The partially cooled C_6H_6 solution was added to rapidly stirred 20% HCl (20 ml) and stirred for 1 hr. The H_2O layer was collected and the C_6H_6 washed (H_2O). The H_2O was removed *in vacuo* to yield the crude amine HCl, which was then refluxed in 2.8 ml of MeOH with protection from atmospheric CO_2 (NaOH). MeI (0.55 ml, 9 mmol) and NaOH (88 mg, 2.2 mmol) were added portionwise over 3 hr. The MeOH was removed *in vacuo*. The remaining white solid was continuously extracted with $CHCl_3$, which was then concentrated to 30 ml and extracted (H_2O). The H_2O was removed *in vacuo* to yield crude 3, which was then recrystallized from Me_2CO–C_6H_{14} to afford 3 (42.6 mg, 25% from 27): ir 3410, 3010, 2470, 2525, 1610, 1480, 1060, 970, 910 cm^{-1}; nmr δ 3.8 (m, 1 H), 3.4 (d, 3 H), 3.15 (s, 9 H), 1.6–2.3 (m, 6 H), 1.0 (d, 3 H).

Anal. C, H, N.

Acknowledgments. This work was supported by NIH Grant GM 16611 (RSG), by a U. S. Public Health Service Career Development Award 5-K4-GM-16007 (R. W.), and by the University of Kansas General Research Fund. The technical assistance of David R. Allen (NSF Undergraduate Research Participant) is gratefully acknowledged.

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