ration of the solvent gave an oil that was distilled: bp 120–122° (20 mm); 75% yield; nmr (CCl_4) δ 0.93 (d, 3 H, 4-CH_3, $J \cong 7.0$ Hz), 1.34–2.68 (m, 8 H, cyclopentane protons), 2.23 [s, 6 H, $N(CH_3)_2$], and 3.95 ppm (s, 4 H, ethylenedioxy). *Anal.* ($C_{11}H_{21}NO_2$) C, H, N.

B. A solution of **9** (1.0 g) in ethanol (10 ml) was added to 10 ml of a 30% solution of $NH(CH_3)_2$ in H_2O. The solution was heated at 100° for 4 hr in a sealed tube. After the evaporation of the ethanol, the solution was extracted with chloroform to yield 0.5 g of an oil that was distilled to give **4**.

4-Methyl-3-oxo-1-(*N,N*-dimethylaminomethyl)cyclopentane (5). A solution of **4** (1.1 g) in 2 *N* HCl (5 ml) was left at room temperature overnight. Evaporation of the solvent under reduced pressure gave 0.7 g of hydrochloride as a white solid that was crystallized from ethanol: mp 180–182°. This solid was dissolved in H_2O (2 ml), and the solution was alkalinized with 2 *N* NaOH and extracted with chloroform to give a light oil that was distilled under reduced pressure: bp 92–94° (12 mm); ir (neat) 1740 cm^{-1} (CO); nmr (CCl_4) δ 1.06 (d, 3 H, 4-CH_3, $J \cong 7.0$ Hz), 1.67–2.84 (m, 8 H, cyclopentane and 1-CH_2 protons), and 2.26 ppm [s, 6 H, $N(CH_3)_2$]. *Anal.* ($C_9H_{17}NO$) C, H, N.

4-Methyl-3-oxo-1-trimethylammoniomethylcyclopentane Iodide (1). A. An excess of CH_3I (5 ml) was added to a solution of **5** (2.3 g) in ether (100 ml). After standing at room temperature overnight a white solid was obtained that crystallized from anhydrous ethanol into white needles: mp 223–226°; 95% yield; ir (Nujol) 1740 cm^{-1} (CO); nmr (D_2O, 100 MHz) δ 1.06 (d, 3 H, 4-CH_3, $J \cong 6.5$ Hz), 2.00–3.05 (m, 6 H, cyclopentane protons), 3.18 [s, 9 H, $^+N(CH_3)_3$], and 3.53 ppm (d, 2 H, 1-CH_2–). *Anal.* ($C_{10}H_{20}INO$) C, H, N.

B. A solution of **12** (2.0 g) in 10 ml of 21% trimethylamine in benzene was left at room temperature for 48 hr. **1** was obtained as a white solid in 75% yield after recrystallization from anhydrous ethanol.

4-Methyl-3,3-ethylenedioxy-1-carbomethoxy- (6) and -1-carboethoxycyclopentane (7). These were obtained using the same procedure described for **3** from the corresponding esters of 4-methyl-3-oxocyclopentane-1-carboxylic acid. The methyl ester **6** distilled at 70–72° (0.1 mm): 72% yield; ir (neat) 1740 cm^{-1} (CO); nmr (CCl_4) δ 0.90–0.93 (d, 3 H, 4-CH_3, trans and cis forms, $J \cong 6.5$ Hz), 1.34–2.50 (m, 5 H, 2-, 4-, and 5-cyclopentane protons), 2.50–3.17 (m, 1 H, 1-H), 3.60 (s, 3 H, $-OCH_3$), and 3.84 ppm (s, 4 H, ethylenedioxy). *Anal.* ($C_{10}H_{16}O_4$) C, H. The ethyl ester **7** distilled at 83–85° (0.5 mm): 70% yield; ir (neat) 1735 cm^{-1} (CO); nmr (CCl_4) δ 0.88–0.92 (d, 3 H, 4-CH_3, trans and cis forms, $J \cong 7.0$ Hz), 1.25 (t, 3 H, CH_3), 1.70–3.30 (m, 6 H, cyclopentane protons), 3.85 (s, 4 H, ethylenedioxy), and 4.05 ppm (q, 2 H, OCH_2–). *Anal.* ($C_{11}H_{18}O_4$) C, H.

4-Methyl-3,3-ethylenedioxy-1-hydroxymethylcyclopentane (8). To a suspension of $LiAlH_4$ (0.036 mol) in dry ether (50 ml), a solution of **6** or **7** (0.03 mol) in dry ether (50 ml) was added dropwise for about 45 min. The suspension was then refluxed for 4 hr and worked up as described for **4** to give an oil that was distilled under reduced pressure: bp 128–130° (10 mm); 70% yield; ir (neat) 3400 cm^{-1} (OH, broad); nmr (CCl_4) δ 0.92 (d, 3 H, 4-CH_3, $J \cong 6.5$ Hz), 1.34–2.40 (m, 6 H, cyclopentane protons), 3.40 (d, 2 H, 1-CH_2), and 3.84 ppm (s, 4 H, ethylenedioxy). *Anal.* ($C_9H_{16}O_3$) C, H.

4-Methyl-3,3-ethylenedioxy-1-cyclopentylmethyl *p*-Toluenesulfonate (9). *p*-Toluenesulfonyl chloride (0.011 mol) was added portionwise to a solution of **8** (0.01 mol) in pyridine (4 ml). After standing 24 hr at room temperature the solution was poured into cold 2 *N* HCl (25 ml) and immediately extracted with ether. The ether was washed (saturated $NaHCO_3$ solution) and dried (Na_2SO_4). Evaporation of the solvent gave an oil that was almost pure and suitable for the following reaction: 70% yield; nmr (CCl_4) δ 0.90 (d, 3 H, 4-CH_3, $J \cong 6.5$ Hz), 1.34–2.56 (m, 6 H, cyclopentane protons), 2.56 (s, 3 H, CH_3-Ar), 4.03 (s, 4 H, ethylenedioxy), 4.11 (d, 2 H, 1-CH_2), and 7.90 ppm (m, 4 H, aromatics). *Anal.* ($C_{16}H_{22}O_5S$) C, H, S.

4-Methyl-3-oxo-1-hydroxymethylcyclopentane (10). 4-Methyl-3,3-ethylenedioxy-1-hydroxymethylcyclopentane (**8**, 12.0 g) in 1:1 H_2SO_4 (50 ml) was left at room temperature for 48 hr; then the solution was poured into ground ice, extracted with chloroform, washed (saturated $NaHCO_3$ solution), and dried (Na_2SO_4). Evaporation of the solvent gave an oil that was distilled under reduced pressure: bp 124–126° (10 mm); 75% yield; ir (neat) 3420 (OH), 1740 cm^{-1} (CO); nmr (CCl_4) δ 1.06 (d, 3 H, 4-CH_3, $J \cong 7.0$ Hz), 1.34–2.84 (m, 6 H, cyclopentane protons), 3.56 (d, 2 H, 1-CH_2), and 4.18 ppm (s, 1 H, OH). *Anal.* ($C_7H_{12}O_2$) C, H.

4-Methyl-3-oxo-1-cyclopentylmethyl *p*-Toluenesulfonate (11). This was synthesized as described for **9**. The product is nearly pure and suitable for the reaction which follows: 90% yield; ir (neat) 1740 cm^{-1} (CO); nmr (CCl_4) δ 0.95 and 0.98 (d, 3 H, trans and cis forms, $J \cong 6.5$ Hz), 1.5–2.70 (m, 6 H, cyclopentane protons), 2.43 (s, 3 H, CH_3-Ar), 4.02 and 4.05 (d, 2 H, trans and cis forms, $J' \cong 6.5$ Hz), and 7.60 ppm (m, 4 H, aromatics). *Anal.* ($C_{14}H_{18}O_4S$) C, H, S.

4-Methyl-3-oxo-1-iodomethylcyclopentane (12). A solution of **11** (2.0 g) and NaI (3.0 g) in acetone (10 ml) was refluxed for 1 hr. The white precipitate was filtered and washed with acetone. The solution evaporated under reduced pressure gave 1.8 g of an oil that was purified by column chromatography (Kieselgel 60; solvent system EtOAc–cyclohexane 3:7): tlc (silica gel) R_f 0.46; ir (neat) 1740 cm^{-1} (CO); nmr (CCl_4) δ 1.10 (d, 3 H, 4-CH_3, $J \cong 6.5$ Hz), 1.68–3.17 (m, 6 H, cyclopentane protons), and 3.60 ppm (d, 2 H, 1-CH_2, $J' \cong 6.5$ Hz). *Anal.* ($C_7H_{11}IO$) C, H.

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Further Studies on Carbocyclic Analogs of Muscarine. Oxidation of Desethermuscarine to Desethermuscarone†

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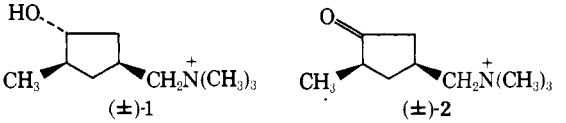
Earlier we reported[1,2] on the stereospecific synthesis of the carbocyclic analog of muscarine which we term desethermuscarine [(±)-**1**]. The unusually high activity found for (±)-**1** suggests that the role of the ether oxygen is not as critically important as has been assumed previously.[3] However, more critical tests of this postulate would be the relative behavior of other desether analogs in the muscarine series, the relative activity of the individual enantiomers of (±)-**1**, and other structural modifications between the two sets of compounds. We wish to report our chemical and biological results on the first variation in the series, namely the oxidation product of (±)-**1**.



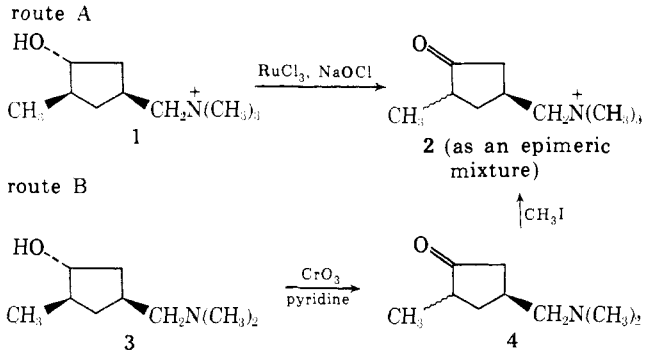
(±)-1 (±)-2

†Paper 2. For paper 1, see ref 1. A preliminary report on the muscarine and muscarone analogs was presented; see ref 2.

‡NDEA Fellow, 1970–1973.

Chemistry. In order to minimize the possibility of epimerization of the C-2 methyl group of **2** during the oxidation, mild conditions at nearly neutral pH were investigated. The method selected employed ruthenium tetroxide generated *in situ* by the reaction of ruthenium trichloride and sodium hypochlorite.[4] The oxidation product of (±)-**1** (route A, Scheme I) obtained from these conditions displayed the characteristic spectral changes for the desired product (±)-**2** (*e.g.*, loss of the hydroxy peak at 2.92 μ and appearance of the cyclopentanone carbonyl at 5.73 μ). The nmr spectrum of the oxidation product showed a doublet for the C-2 methyl group, indicating that no epimerization had occurred or that both C-2 methyl epimers had similar chemical shift and coupling constant values. An indication that the latter might be the case was the inability to reduce the melting point range (210–215°) after repeated recrystallizations. However, tlc, ir, nmr, and elemental analysis were all indicative of a single, homogeneous product. The coincidence of the chemical shifts for the two isomers was readily shown by the addition of a trace of D_2O–NaOD to the nmr sample. The new spectrum showed a singlet at δ 1.05. The salt isolated from this exchange experiment had the same melting point range. The most reasonable interpretation of this result is that a mixture of the two isomers (*cis*-3-methyl and *trans*-3-methyl) is generated by the exchange with base and, furthermore, that the two methyl groups have nearly identical chemical shifts. However, the less likely possibility of a single cis isomer from this reaction sequence still remains.

Scheme I. Routes to Desethermuscarone Epimers (±)-2



A second route to (±)-**2** was also investigated (route B, Scheme I). The dimethylamine analog **3** from the stereospecific synthesis of (±)-**1** was oxidized with Jones reagent to the ketone **4** giving a *ca.* 1:1 mixture of the two epimeric ketones as shown by nmr analysis (overlapping doublets at δ 1.1 and 1.2 for the C-2 methyls). This mixture was subsequently allowed to react with methyl iodide to give the same mixture of desethermuscarone epimers as obtained in the ruthenium tetroxide oxidation as shown by melting point, mixture melting point, nmr (only one doublet observed for both C-2 methyls), and ir analysis. Attempts to separate the epimeric amines by chromatography or recrystallization were unsuccessful. A recent report[5] on the extremely facile racemization of (2*R*)-2-methylcyclopentanone even under neutral conditions (methanol solution) suggested that further attempts at amine isomer separation would be unsuccessful also. Attempts to find conditions for separation of the epimeric ammonium iodides by recrystallization, column chromatography, and tlc were not successful in our hands. Furthermore, since the muscarinic and nicotinic activity of the corresponding muscarone epimers are both significantly higher than muscarine and since both epimers have approximately the same activity indicating a loss of stereospecificity for agonist action,[6] significant results could be obtained from the epimeric mixture of desethermuscarone. Therefore, the epimeric mixture was submitted for biological testing.

Table I. Comparative Biological Activity of Muscarine, Desethermuscarine (±-**1**), Muscarone, and Desethermuscarone (±-**2**)

Compound	Relative activity[a] Muscarinic[b]	Nicotinic[c]
DL-Muscarine	1.0	0.02[f]
DL-**1**	0.1–0.5[d]	0.012
DL-Muscarone	7.7[e]	2.0[f]
DL-*allo*-Muscarone	3.5[e]	5.0[f]
DL-**2** (as a mixture)	1.0	1.2

[a]Equipotent activity relative to acetylchlorine (ACh = 1.0). [b]Guinea pig ileum unless noted otherwise. [c]Chicken biventor muscle unless noted otherwise. [d]Further tests have shown that our initial preliminary report[1] of an activity of 5–10 was too high (see text). [e]Rabbit ileum, ref 6. [f]Frog rectus, ref 3, pp 253–254.

Biology. The compounds listed in Table I were tested according to the procedures used previously (see Experimental Section and ref 1 and 2). The muscarinic activity of (±)-**1** has also been rechecked several times and a revised value included for comparison. As can be seen from these results, the muscarinic activity of the ketone is significantly higher than the alcohol in the desether series. In the muscarine–muscarone series the ketone is reported to show about an eightfold increase in activity over the racemic alcohol.[6]

Nicotinic activity was also investigated for (±)-**2** using the chicken biventor cervicis preparation (see Experimental Section and ref 7). Under these conditions, the epimeric mixture of (±)-**2** was significantly more active than the alcohol, indicating a very prominent change in nicotinic activity with oxidation to the ketone.

The results on (±)-**2** further substantiate our suggestion that the desethermuscarine is behaving in a similar manner to the muscarine series. These results coupled with our earlier findings indicate that the role of the ether oxygen is not one of primary binding though it must be exerting some secondary influence, the nature of which remains uncertain at this time. One possible role could involve increased hydrophilic bonding at the membrane surface allowing enantiomer recognition at the receptor site. Further investigations are in progress on this and on other structure-activity correlations of the two series of compounds.

Experimental Section

Melting points were obtained on a hot-stage apparatus and are uncorrected. The following spectrometers were used: nmr, Varian A-60 or T-60; ir, Beckman 1R8 or 1R33; mass, Varian Mat CH-5. Microanalyses were performed on an F&M Model 185 carbon hydrogen nitrogen analyzer, University of Kansas. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements are within ±0.4% of the theoretical values.

Chromic Acid Oxidation of Tertiary Amine 3. To 50 mg (0.32 mmol) of amine in 1 ml of water was added 2 equiv of Jones reagent and the solution agitated for 30 min at room temperature. The solution was then neutralized with sodium bicarbonate, saturated with sodium chloride, and extracted with ether (10 × 10 ml). The combined extracts were dried ($MgSO_4$) and the ether was removed *in vacuo* to afford 30 mg (60%) of the ketoamine 4: ir ($CDCl_3$) 3.34, 3.38, 3.45, 3.50, 3.56, 5.73, 6.85, and 8.62 μ; nmr ($CDCl_3$–TMS) δ 2.8–1.5 (m, 14 H), 1.2 (d, 1.5 H, J = 7 Hz, CH_3CH), and 1.1 (d, 1.5 H, J = 7 Hz, CH_3CH). The signals at δ 1.1 and 1.2 indicate that epimerization of the methyl group α to the

ketone had occurred. This was analyzed as the methiodide salt (*vide infra*).

[(3-Methyl-4-oxocyclopentyl)methyl]trimethylammonium Iodide (2). To a solution of 30 mg (0.19 mmol) of the ketoamine mixture in 1 ml of ether was added 100 mg (0.77 mmol) of methyl iodide. The solution was allowed to sit overnight for complete precipitation of the iodide salt. The ether was then decanted and the iodide washed with additional ether to afford 48 mg (87%) of the keto iodide **2**: mp 210–215°; ir (KBr) 3.29, 3.36, 3.39, 3.46, 5.73, 6.71, 6.85, 8.58, 8.73, 9.09, 10.31, and 11.11 μ; nmr (D_2O–external TMS) δ 3.55 (d, 2 H, J = 6 Hz, CH_2N^+), 3.15 (s, 9 H, $^+N(CH_3)_3$), 3.1–2.3 (m, 6 H), and 1.05 (d, 3 H, J = 6 Hz, CH_3CH). Tlc analysis on Silicar plates using 25% acetone–75% methanol (R_f 0.55) and 66% 1-butanol–34% acetic acid (R_f 0.20) as well as other combinations showed only one spot. *Anal.* C, H, N.

Ruthenium Tetroxide Oxidation of the Trimethylammonium Salt 1. To 175 mg (0.585 mmol) of the iodide salt **1** in 0.5 ml of water was added 90 mg (0.6 mmol) of AgCl and the mixture was stirred for 45 min. The AgCl was replaced by the yellow AgI which was removed by filtration and washed with water until the filtrate amounted to 1.0–1.5 ml. To this was added 0.3 ml of 2% $RuCl_3$ followed by 0.84 ml of a 1.42 *N* NaOCl solution (household bleach) in portions while observing the black-yellow-black color change after each addition as the oxidation proceeded. After addition was complete a small amount of 2-propanol was added to ensure complete formation of RuO_2 precipitate. The RuO_2 was then removed by filtration and the water removed *in vacuo* to give the keto chloride product and sodium chloride. The keto chloride was dissolved in acetone and an acetone solution of 88 mg (0.59 mmol) of NaI was added to afford the keto ammonium iodide **2** which was recrystallized from acetone–hexane giving 136 mg (0.46 mmol, 79%) of the iodide salt; the melting point, ir, nmr, and tlc results were identical with those previously given (*vide supra*). This route was chosen for synthesis of material used in subsequent biological studies because of the better overall yield and less number of steps.

Animal Tissue Tests. A. Guinea Pig Ileum. The tissue tests consisted of *in vitro* studies on whole guinea pig ileum preparations obtained from male American Standard guinea pigs, small stock. Four preparations immersed in Tyrode solution at 37° were used at each dose level. All compounds tested gave nearly full contraction indicating unit intrinsic activity. Typical dose–response curves were obtained with the concentration at peak half-height being used for relative biological activity. The results are given in Table I. All tests were conducted on racemic material.

B. Chicken Biventor Muscle. The method employed for nicotinic activity of ±-**2** is fully detailed in ref 7.

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Synthesis and Central Nervous System Activity of 1,2,3,4-Tetrahydro-1-amino-4-phenylnaphthalenes

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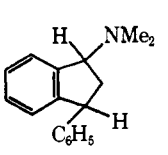
The reported analgetic activity of 1-dimethylamino-3-phenylindan (**1**)[1,†] prompted the synthesis, from 4-cyano-4,4-diphenylbutyric acid,[3] of the compounds described in Table I. The reductive decyanation of this acid with sodium and ethanol gave 4,4-diphenylbutyric acid which was cyclized to 3,4-dihydro-4-phenyl-1(2*H*)-naphthalenone.[4]



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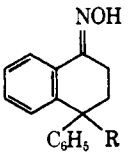
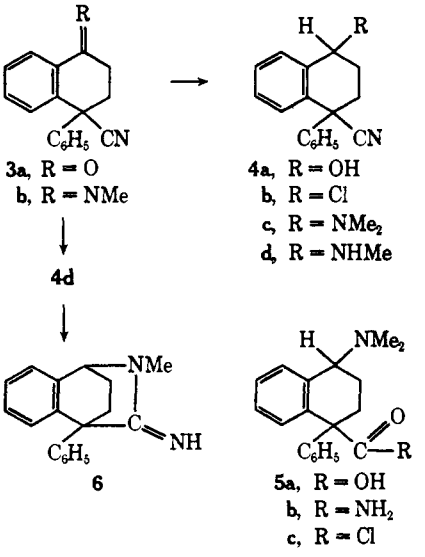


2a, R = H
b, R = CN

The oxime **2a** of this ketone, reduced with Raney nickel, gave compounds **13** and **14** (Table I) and these amines were converted to compounds **15–18** and **22–25** by known procedures. This scheme failed with the cyanooxime **2b.** Its reduction by a Zn–AcOH procedure[5] gave a complex mixture containing 50–60% of the isomeric cyanoamines from which only **27** was isolated in low yield. The reduction of **2b** with Raney nickel in $(AcO)_2O$ gave a mixture of the acetaminonitriles **28** and **29** which was not easily separated. Since the acetyl group of neither isomer could be hydrolyzed by either acid or base without converting the cyano group to an amide, this approach was replaced by that shown in Scheme I.

Scheme I



3a, R = O
b, R = NMe

4d

6

4a, R = OH
b, R = Cl
c, R = NMe_2
d, R = NHMe

5a, R = OH
b, R = NH_2
c, R = Cl

In Scheme I the $NaBH_4$ reduction of **3a**‡ gave a mixture of the cis and trans cyano alcohols **4a**, which with $SOCl_2$ yielded a similar mixture of the cyano chlorides **4b**. The separation of the **4b** isomers was not attempted since the difference in their rate of reaction with Me_2NH in PhMe enabled the preparation of the pure *cis*- and *trans*-aminonitriles **4c**. Their subsequent conversion to the cor-

† See also ref 2 for a brief review of the literature on this compound.
‡ Compound subsequently described; see ref 6.