other N-substituted compounds (9–13 and 15–19) were prepared as follows. Ethyl 3-phenylpyrrolidine-3-carboxylate (6) or ethyl 3-phenylnipecotate (7) was dissolved in EtOH (*ca.* ten times the weight of the free amine) and $NaHCO_3$ or Na_2CO_3 (a weight equal to that of the free amine) was added. The appropriate alkyl halide (10% molar excess) was added dropwise to the warm (*ca.* 50°) reaction mixture. The stirred mixture was refluxed and the progress of the reaction was followed by tlc (Eastman 6060 silica gel, 5% EtOH in C_6H_6). When the reaction was complete (2–4 hr), the mixture was cooled and allowed to stir overnight. The precipitated solids were filtered off and washed with Et_2O. The filtrate was concentrated under reduced pressure and the residue was dissolved in anhydrous Et_2O. After filtration and concentration of the ethereal solution, the residual oil was distilled to give the free bases 9–13 and 17–19. Crude 15 and 16 were not distilled but were dissolved in anhydrous Et_2O and treated with HCl gas to give the salt of 15 and 16. See Table I for details.

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Supplementary Material Available. The results of the antagonist testing will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-453.

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A Cyclopentane Analog of Muscarone

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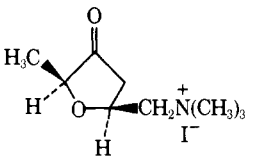
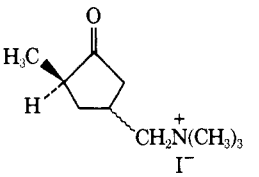
Muscarine and related compounds have played a major role in studies on cholinergic receptors. Among the other compounds, muscarones are particularly interesting because of their activity which is higher than that of muscarine and because of a different importance of steric factors on the activity.[1] For instance, muscarone and *allo*-muscarone have nearly the same potency and D(−)-muscarone is about three times more active than L(+)-muscarone while in the muscarine series the L(+)-muscarine is a hundred times more potent than D(−)-muscarine and the other stereoisomers.[1]

Various rationalizations of these facts have been proposed by Waser,[2] Belleau,[3] and recently by Pauling.[4] Although Belleau's theory seemed more consistent with the current knowledge of cholinergic receptors, no definite conclusions could be drawn.

Therefore, it appeared to us of some importance to have a compound such as 1 which, by substitution of the ether oxygen with a methylene group, would allow us to check the role of both the ether and the keto group on the activity and cast further light on the problem. This paper reports the synthesis and some preliminary pharmacological data of compound 1.



(±)-muscarone



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While concluding this research, a paper[5] reporting the synthesis and pharmacological evaluations of a cyclopentane analog of muscarine appeared. The results of this work, which challenge the current theories of muscarinic receptors, prompted us to publish our results as a contribution to a further understanding of the problem.

Chemistry. The synthesis of compound 1 was achieved through the pathways shown in Scheme I. Although time consuming, if compared to that involving the amide 2, synthesis through compounds 9, 11, and 12 was performed to explore the possibility that more hindered compounds could bring to the separation of cis and trans isomers.

Because of the strongly equilibrating conditions used in the synthesis of the starting material, 4-methyl-3-oxocyclopentane-1-carboxylic acid,[6,7] the nmr spectrum showed it to be a mixture of cis and trans isomers (roughly 60:40) that could not be separated by chromatography.

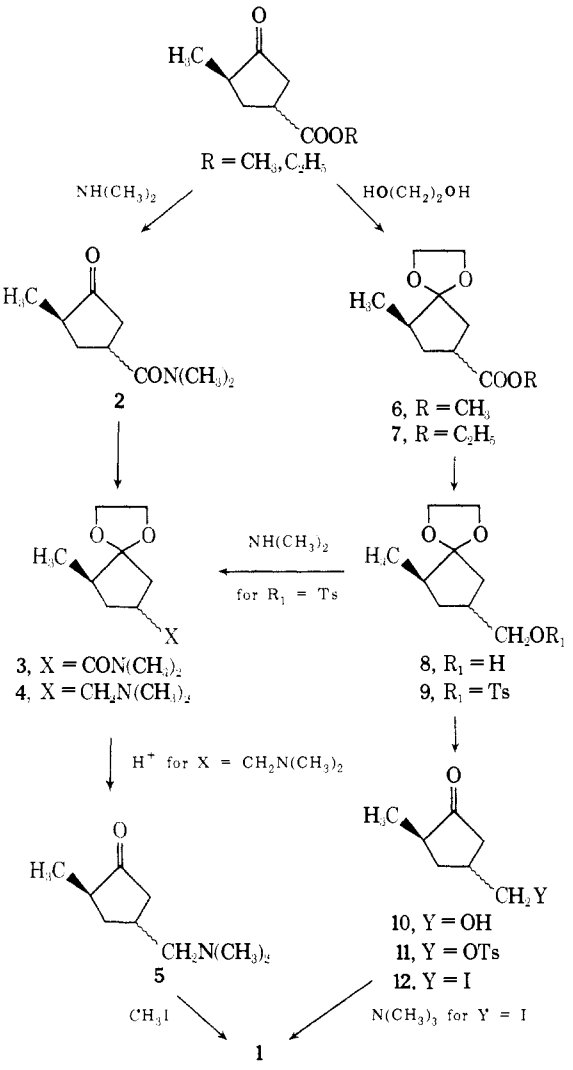
Although Hardegger, *et al.*,[8] report that, in a very similar case, complete conversion into the trans isomer was observed, the reaction of 4-methyl-3-oxo-1-carbomethoxycyclopentane with dimethylamine gave a mixture of cis and trans isomers of 2. The same was found for 3 whose nmr spectrum, as well as that of 6 and 7, shows a double doublet for 4-CH_3, while 4, 5, and in general all compounds where the substituent in 1 is not a carbonyl group show a single doublet. Yet this cannot be considered evidence of the presence of a single isomer as a consequence of isomerization but it is probably due to the equivalence of 4-CH_3 in the two isomers.

This was confirmed by nmr spectrum of *p*-toluenesulfonate 11 which again shows the double doublet, while its starting material (10) does not.

Consequently, compound 1 should be considered a mixture of cis and trans isomers. Because of the overlapping of the signals, even at 100 MHz, the ratio of the two isomers could not be directly obtained but it is safe to say that it should not be different from that of the equilibrated starting material.

Repeated efforts to evidence the isomers by tlc at every

Scheme I



stage of the synthesis were unsuccessful even for the more hindered compounds. Nor was it possible to separate the iodomethylate (1), the hydrochloride, and the oxalate[8] of the nor base 5 by fractional crystallization from a number of solvents.

For these reasons a stereospecific synthesis of the two isomers has been planned and is in progress.

Finally, reaction of 11 with dimethylamine did not give 5 but a different compound which will be published later.

Pharmacology.† Biological activity of compound 1 has been assayed on four *in vitro* muscarinic preparations: guinea pig terminal ileum, rat jejunum, guinea pig ductus deferens, and guinea pig auricles according with standard procedures.

Guinea pigs or Wistar rats, Marini breeding, weighting *ca.* 250 g, were decapitated and the organs suspended in oxygenated Tyrode solution at 38° or in Ringer Locke medium at 31° (guinea pig auricles). Contractions were elicited every 3 min by injecting 0.1 ml of the drug solution or of acetylcholine standard into a 10-ml bath and recorded by means of an isotonic recording apparatus.

The compound showed unit intrinsic activity and gave typical dose-effect curves. The results reported in Table I show that in all preparations compound 1 presents about the same activity as acetylcholine.

† The pharmacological tests were performed by Professor L. Rossini and Dr. M. L. Cingolani Belli of the Medical School of Ancona University, Italy.

Table I. Cholinergic Activity of Compound 1[a]

Preparation	Rel potency[b]
Guinea pig ileum	0.2[c] 2.4[d]
Rat jejunum	2.4
Guinea pig ductus deferens	0.5
Guinea pig auricles	1.1

[a] Ratios were calculated from the ED_{50}'s obtained through the regression of the angular transformate of the fractional effects *vs.* the log concentration of the agonists. The statistical significance ($p \leq 0.05$) of the values of the slopes of the straight lines and of parallelism was checked. Experiments were repeated a minimum of four times. Standard error of the mean values of ED_{50}'s was less than 10%. [b] Acetylcholine equal to 1.0. [c] 15-sec incubation. [d] 3-min incubation.

Also, compound 1 showed nicotinic activity confirmed in assays on the blood pressure of the pithed[9] rat and antiacetylcholinesterase activity in rat erythrocytes.[10] This might explain the slow kinetics shown by guinea pig ileum during contraction.

More details on these experiments as well as a complete pharmacological profile of the compound will be published later. Nevertheless, these preliminary results, together with those of Sundelin, *et al.*,[5] suggest further examination of the role played by ether oxygen in muscarine and muscarone. The current theories on the cholinergic receptors need to be consequently revised.

Experimental Section

All melting points were taken in capillary tubes on a Büchi apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 257 spectrophotometer. The nmr spectra were measured on a Jeol JMH-MH-60 and a Varian HA-100 spectrometer using TMS or DSS as internal standards. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

Starting Materials. 4-Methyl-3-oxocyclopentane-1-carboxylic acid was synthesized according to Giuliano, *et al.*,[6b] and its methyl and ethyl esters by using standard methods. Their nmr shows that the substances are mixtures of cis and trans isomers, roughly in 60:40 ratio, that did not change when the mixture was equilibrated by heating with sodium methoxide.

4-Methyl-3-oxo-1-(*N,N*-dimethylcarboxamido)cyclopentane (2). Anhydrous dimethylamine (10 ml) was added to 4-methyl-3-oxo-1-carbomethoxycyclopentane (5.0 g) and heated for 48 hr at 95–100° in a sealed tube. The reaction product was dissolved in ether and washed with 2 *N* HCl (10 ml) and cold water. Evaporation of the solvent gave an oil that was distilled under reduced pressure: bp 139–140° (7 mm); 73% yield; ir (neat) 1640 (amidic CO), 1740 cm^{-1} (CO); nmr (CCl_4) δ 1.06 and 1.10 (d, 3 H, 4-CH_3, trans and cis forms, $J \cong 6.5$ Hz), 2.00–3.50 (m, 6 H, cyclopentane protons), 3.03 and 3.26 ppm [s, 6 H, $N(CH_3)_2$]. *Anal.* ($C_9H_{15}NO_2$) C, H, N.

4-Methyl-3,3-ethylenedioxy-1-(*N,N*-dimethylcarboxamido)cyclopentane (3). A mixture of 2 (0.06 mol), ethylene glycol (0.18 mol), and *p*-toluenesulfonic acid (1.0 g) in 600 ml of benzene was refluxed under vigorous stirring and removal of the reaction water. After 6–10 hr the benzene was washed (saturated $NaHCO_3$ solution) and dried (Na_2SO_4). Evaporation of the solvent gave an oil that was distilled under reduced pressure: bp 135–137° (4 mm); 65% yield; ir (neat) 1640 cm^{-1} (CO); nmr (CCl_4) δ 0.90 and 0.97 (d, 3 H, 4-CH_3, trans and cis forms, $J \cong 6.5$ Hz), 1.50–2.50 (m, 5 H, 2-, 4-, and 5-H), 2.97 and 3.12 [s, 6 H, $N(CH_3)_2$], 3.34–3.97 (m, 1 H, 1-H), and 3.97 ppm (s, 4 H, ethylenedioxy). *Anal.* ($C_{11}H_{19}NO_3$) C, H, N.

4-Methyl-3,3-ethylenedioxy-1-(*N,N*-dimethylaminomethyl)cyclopentane (4). A. To a suspension of $LiAlH_4$ (0.01 mol) in dry ether (100 ml) was added, with stirring and cooling, a solution of 3 (0.01 mol) in dry ether (100 ml). The suspension was then refluxed for 5 hr. When cooled, the excess of $LiAlH_4$ was decomposed with ethyl acetate (50 ml) and H_2O (5 ml). The solution was decanted, the white solid was washed twice with ethyl acetate (50 ml), and the organic solution dried (Na_2SO_4). Evapo-

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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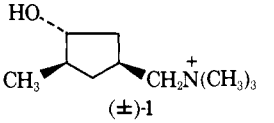
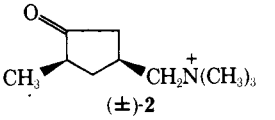
Earlier we reported[1,2] on the stereospecific synthesis of the carbocyclic analog of muscarine which we term desethermuscarine [(±)-**1**]. The unusually high activity found for (±)-**1** suggests that the role of the ether oxygen is not as critically important as has been assumed previously.[3] However, 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.

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