Cholinergic Compounds. 9. Cyclohexane Analogues of Deoxamuscarine and Derivatives[1]

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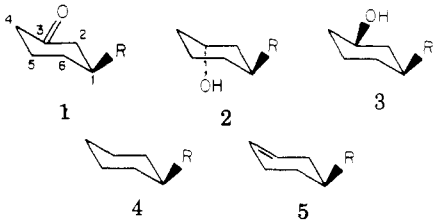
The synthesis of some cyclohexane analogues of deoxamuscarine is reported. Stereochemical aspects are discussed on the basis of IR and NMR spectra. Muscarinic activity, measured on guinea pig ileum, shows a sharp drop when comparison is made with the cyclopentyl analogues.

In order to better understand the structure–activity relationships within the deoxamuscarine (**16**)[2,3] and deoxamuscarone (**14**)[4] series of agonists, it was of interest to extend our investigations to cyclohexane analogues **1–3**.

With these new analogues the most serious structural alteration is that the methyl substituent of the cyclopentyl compounds now forms part of the enlarged ring and finds itself at the end of the "5-atom chain" (which is important for cholinergic activity).[5] Such analogues may contribute to a better understanding of the role of the C-7 methyl of muscarine analogues and, hence, may help clarify the chemistry of the cholinergic receptor.

In order to complete our SAR studies in this field,[6] the methiodide derivatives **4**[7] and **5** were also investigated.



R = $CH_2N^+(CH_3)_3I^-$; spatial position is referred to R

Chemistry. Methiodide derivatives **1–3** were synthesized starting from the lactone of 3-hydroxycyclohexane-1-carboxylic acid (**6**), easily prepared by reduction of 3-hydroxybenzoic acid[8] (Scheme I).

Ketoamine **9** was synthesized by oxidation of **8** or **13** avoiding, in this way, protection of the carbonyl group of 3-oxocyclohexane-1-carboxylic acid[9,10] when used as starting material. Besides, the synthesis of **11** was carried out through inversion at position 3 of **7**, avoiding the tedious separation of the cis and trans isomers of 3-hydroxycyclohexane-1-carboxylic acid.[11]

In order to confirm the structure of **12**, obtained through this inversion reaction, *cis*-3-acetoxy-1-(*N*,*N*-dimethylcarboxamido)cyclohexane was synthesized from alcohol **7** by treatment with acetic anhydride.

Finally, 3-dimethylaminomethylcyclohex-1-ene methiodide (**5**) was obtained starting from the corresponding dimethylamide of 3-cyclohexene-1-carboxylic acid.[12]

Stereochemistry. The configuration of these compounds was clearly established by the reaction sequences shown in Scheme I. As regards the more stable conformations, examination of relative hindrance[13,14] between groups at positions 1 and 3 suggests a sharp preference for chair conformations with the two functional groups assuming the equatorial orientation in the cis series but one axial (3-OH) and one equatorial (position 1) orientation in the trans series (conformer A). Using the tosyl derivative **10** and lactone **6**[15] as models, the NMR spectra

Scheme I

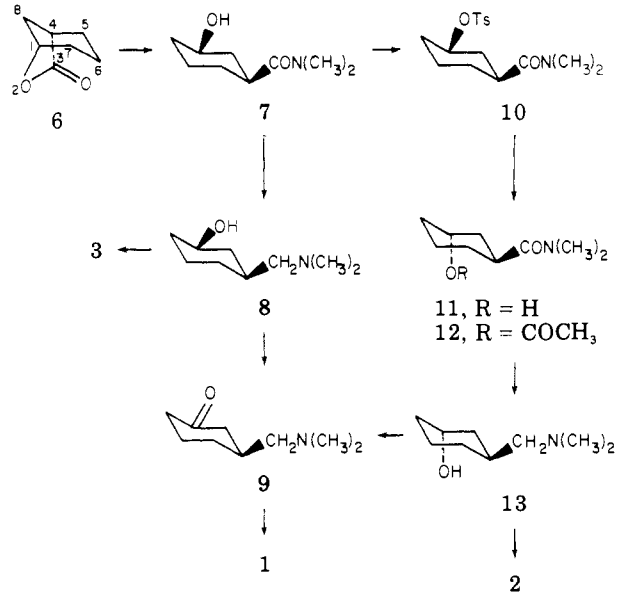


Table I. IR and NMR Data at Position 3 of Some Compounds of the Cyclohexyl Series

Compd	$\nu_{3\text{-OH}}$, cm^{-1}	^1H NMR, 3-H Solvent	δ, ppm	$W_{1/2}$[a]	W[b]
8	3330	$CDCl_3$	3.88	19	30
3	3360	D_2O	3.80	20	~30[c]
13	3350	$CDCl_3$	4.28	11	18
2	3375	D_2O	4.23	11	18
10		$CDCl_3$	4.50	22	40
		^1H NMR, 1-H			
6		$CDCl_3$	4.68	13	23

[a] Half-height width in hertz. [b] Base width in hertz. [c] Signal partially obscured.

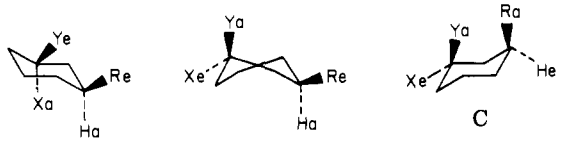
confirmed these conformations as judged from chemical shift data and line width of the proton on the OH-bearing carbon[14,16] (Table I). Furthermore, the stretching frequency of the OH at position 3 was greater for the trans compound than for the corresponding cis isomer,[17] as would be expected. Therefore, it is possible to exclude the existence of skew-boat forms (conformer B) in the trans series and of conformers like C in the cis series.

However, the spatial arrangement of the OH and N-bearing carbon in the cyclopentyl series may assume pseudoequatorial positions,[13,18-20] a possibility which is difficult to prove. However, the difference in the relative positions of the hydroxyl and the side chain of the two cyclic systems is rather small, so that the major difference

Table II. Comparative Biological Activity of Cyclohexyl and Cyclopentyl Analogues of Muscarone, Muscarine, and Derivatives on Guinea Pig Terminal Ileum[a,b]

Cyclohexyl series		Cyclopentyl series		
Compd	EPMR[c,d]	Compd	EPMR	Ref
1	507	14	0.5	4
2	2 897	15	50	5
3	>10 000	16	9.8	3
4[f]	203	17	454	1
5	269	18	221[e]	5
		19	500	23
		20	100	23
		21	3590[e]	5
		22	100	2
		23	16	6
		24	30	6
		25	11	6

[a] Significance of the EPMR's averages was estimated by the t test at $p \leq 0.05$ level. [b] More details on these experiments are reported in cited references. [c] EPMR = equipotent molar ratios: average number of molecules of compound required to equal at 50% level the effects obtained by the reference (AcCh). [d] AcCh (chloride or bromide) taken equal to 1.0. [e] Further tests have shown that the activity previously reported was incorrect. [f] This compound was synthesized according to Baumgarten et al. (ref 7).

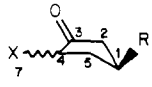


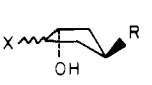
A B C

8, R = $CH_2N(CH_3)_2$; X = H; Y = OH
3, R = $CH_2N^+(CH_3)_3$; X = H; Y = OH
13, R = $CH_2N(CH_3)_2$; X = OH; Y = H
2, R = $CH_2N^+(CH_3)_3$; X = OH; Y = H
10, R = $CON(CH_3)_2$; X = H; Y = p-$CH_3C_6H_4SO_3^-$

lies in the relative arrangements about carbon 7 [4-methyl in the cyclopentyl and methylene (position 4) in the cyclohexyl series].

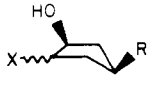
Pharmacological Results and Discussion. Compounds 1–5 were assayed on the guinea pig ileum preparation. The potency ratios, relative to AcCh, are assembled in Table II. The large drop in activity, with these substances when compared with the corresponding cyclopentyl analogues 14–25, shows that the cyclopentane

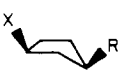




14, X = CH_3 (deoxamuscarone)
15, X = H

16, X = CH_3, cis (deoxamuscarine)
17, X = CH_3, trans (*epi-allo*-deoxamuscarine)
18, X = H





19, X = CH_3, cis (*epi*-deoxamuscarine)
20, X = CH_3, trans (*allo*-deoxamuscarine)
21, X = H

22, X = CH_3
23, X = H

24, X = CH_3
25, X = H

R = $CH_2N^+(CH_3)_3I^-$; spatial position is referred to R

nucleus is a better carrier of activity than the cyclohexane ring. Furthermore, the observation that the quaternary ammonium group and the oxygenated functions in these two series of compounds are in almost identical positions further confirms the importance of the C-7 methyl for muscarinic activity.[5] In fact, by comparing the EPMR's of compounds 1–3 with that of the corresponding demethyl derivatives 15, 18, and 21, it can be concluded that the ring methylene of the cyclohexane ring is unable to contribute significantly to the biological activity.

Compounds of the cyclohexyl series, as well as those of the cyclopentane series,[6] lacking an oxygenated function in 3, merit special consideration. Thus, compounds 4 and 5 are the most active of the series and their potency does not drop dramatically when compared to the corresponding cyclopentane derivatives 22–25, in contrast to the preceding cases. This result seems to confirm Triggle's statement,[21] particularly for n-pentyltrimethylammonium iodide,[22] that cholinergic compounds lacking an oxygenated function interact at the receptor level with an accessory receptor site of reduced polarity. Comparison of the EPMR's supports the reduced specificity of this site as compared to the polar recognition site.

Experimental Section

All melting points were taken in sealed capillaries on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer in Nujol mull for solids and neat for liquids. NMR spectra were measured on a Jeol C-60 HL spectrometer using Me_4Si or DSS as internal standards. Chromatographic separations were performed on a silica gel column (Kieselgel 40, 0.063–0.200 mm, Merck). Where analyses are indicated using symbols, the analytical results are within ±0.4% of the theoretical values.

cis-**3-Hydroxy-1-(*N,N*-dimethylcarboxamido)cyclohexane (7).** 3-Oxo-2-oxabicyclo[3.2.1]octane (6,[8] 8.0 g) and dimethylamine (20 ml) were heated in a sealed tube for 24 h at 80 °C. Work-up of the mixture[23] gave pure 7 as a pale yellow oil that was used without further purification: 85% yield; IR 3380 (OH) and 1625 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.00–2.30 (m, 8, cyclohexane protons), 2.73 (m, 1, 1-H), 3.05 (s, 3, NCH_3), 3.17 (s, 3, NCH_3), 3.73 (m, 2, 3-H and 3-OH, $W_{1/2}$ = 20 Hz). Anal. ($C_9H_{17}NO_2$) C, H, N.

cis-**3-Hydroxy-1-(*N,N*-dimethylaminomethyl)cyclohexane (8).** A solution of 7 (3.6 g) in dry ether (100 ml) was added to a stirred and cooled (ice–water bath) suspension of $LiAlH_4$ (2.0 g) in dry ether (100 ml) and then refluxed for 4 h. When cooled, the excess $LiAlH_4$ was decomposed with EtOAc (50 ml) and water (5 ml). The solution was decanted, the white solid was washed with EtOAc (2 × 50 ml), and the organic layer dried over Na_2SO_4. Evaporation of solvent gave 8 which was distilled: 70% yield; bp 96–100 °C (8 mm); IR 3330 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.50–2.30 (m, 11, cyclohexane and 1-CH_2 protons), 2.48 [s, 6, $N(CH_3)_2$], 3.88 (m, 1, 3-H), 4.28 (s, 1, OH). Anal. ($C_9H_{19}NO$) C, H, N.

trans-**3-Hydroxy-1-(*N,N*-dimethylaminomethyl)cyclohexane (13).** 13 was obtained, as described for 8 starting from 11 or 12, as a colorless oil: 70–75% yield; IR 3350 cm^{-1} (OH); NMR (CCl_4) δ 1.00–2.80 (m, 11, cyclohexane and 1-CH_2 protons), 2.40 [s, 6, $N(CH_3)_2$], 3.96 (s, 1, 3-OH), 4.28 (m, 1, 3-H). Anal. ($C_9H_{19}NO$) C, H.

3-Oxo-1-(*N,N*-dimethylaminomethyl)cyclohexane (9). A solution of CrO_3 (1.08 g) in 4.5 M H_2SO_4 (50 ml) was slowly added to a stirred solution of 8 or 13 (1.7 g) in 4.5 M H_2SO_4 (5 ml). After standing at room temperature overnight, the solution was concentrated in vacuo, made basic with 5 N NaOH, and extracted with CH_2Cl_2. Evaporation of the dried (Na_2SO_4) extract gave 9 which was distilled: 73% yield; bp 98–100 °C (10 mm); IR 1715 cm^{-1} (CO); NMR (CCl_4) δ 1.00–3.00 (m, 11, cyclohexane and 1-CH_2 protons), 2.15 [s, 6, $N(CH_3)_2$]. Anal. ($C_9H_{17}NO$) C, H, N.

cis-**3-Hydroxy-1-(*N,N*-dimethylcarboxamido)cyclohexane *p*-Toluenesulfonate (10).** Tosyl chloride (8.75 g) was added to a stirred and cooled (ice bath) solution of compound 7 (4.0 g) in pyridine (40 ml). After 3 h at 0 °C, the solution was left at room temperature overnight. After the usual work-up[3] 10 was obtained as a white solid which was purified by recrystallization from EtOAc–petroleum ether: 75% yield; mp 119–120 °C; IR 1635 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.00–2.20 (m, 8, cyclohexane protons), 2.20–2.80 (m, 1, 1-H), 2.45 (s, 3, $PhCH_3$), 2.90 (s, 3, NCH_3), 2.99

(s, 3, NCH_3), 4.50 (m, 1, 3-H, $W_{1/2}$ = 22 Hz), 7.20–8.00 (m, 4, aromatics). Anal. ($C_{16}H_{23}NO_4S$) C, H, N.

trans-**3-Hydroxy-1-(*N*,*N*-dimethylcarboxamido)cyclohexane (11) and *trans*-3-Acetoxy-1-(*N*,*N*-dimethylcarboxamido)cyclohexane (12).** Compound **10** (2.0 g) and potassium acetate (2.94 g) were heated under reflux for 20 h in dimethylformamide (75 ml) containing water (2.5 ml). The solution was then evaporated in vacuo to dryness; the residue was treated with a saturated solution (2 ml) of $NaHCO_3$ and extracted several times with CH_2Cl_2. After evaporation of the solvent, an oil was obtained which was separated into three main fractions by column chromatography using ethyl acetate as the eluting phase. The first fraction was an unidentified product of elimination (28% yield). The second fraction was **12** obtained as a colorless oil: 35% yield; IR 1735 (ester CO) and 1640 cm^{-1} (amide CO); NMR ($CDCl_3$) δ 1.00–2.50 (m, 8, cyclohexane protons), 2.12 (s, 3, CH_3), 2.50–3.40 (m, 1, 1-H), 3.10 [s, 6, $N(CH_3)_2$], 5.18 (m, 1, 3-H, $W_{1/2}$ = 9 Hz). Anal. ($C_{11}H_{19}NO_3$) C, H.

The third fraction, recovered by washing the column with methanol, was **11** obtained as a colorless oil: 30% yield; IR 3390 (OH) and 1635 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.10–2.20 (m, 8, cyclohexane protons), 2.60–3.40 (m, 1, 1-H), 3.10 (s, 3, NCH_3), 3.25 (s, 3, NCH_3), 4.32 (m, 1, 3-H, $W_{1/2}$ = 9 Hz). Anal. ($C_9H_{17}NO_2$) C, H.

cis-**3-Acetoxy-1-(*N*,*N*-dimethylcarboxamido)cyclohexane.** Compound **7** (0.5 g) and acetic anhydride (5 ml) were left at room temperature overnight. The solution was then decomposed with water and extracted with ether to give a colorless oil which was used without further purification: 90% yield; IR 1730 (ester CO) and 1640 cm^{-1} (amide CO); NMR ($CDCl_3$) δ 1.10–2.20 (m, 8, cyclohexane protons), 2.10 (s, 3, CH_3), 2.65 (m, 1, 1-H), 2.98 (s, 3, NCH_3), 3.10 (s, 3, NCH_3), 4.78 (m, 1, 3-H, $W_{1/2}$ = 19 Hz). Anal. ($C_{11}H_{19}NO_3$) C, H.

3-(*N*,*N*-Dimethylaminomethyl)cyclohex-1-ene. This compound was obtained as described for the case of **8** starting from 3-(*N*,*N*-dimethylcarboxamido)cyclohex-1-ene:[12] 72% yield; NMR (CCl_4) δ 1.00–2.30 (m, 9, cyclohexane and 1-CH_2 protons), 2.13 [s, 6, $N(CH_3)_2$], 5.57 (m, 2, CH=CH). Anal. ($C_9H_{17}N$) C, H.

3-Oxo-1-dimethylaminomethylcyclohexane Methiodide (1), *trans*-3-Hydroxy-1-dimethylaminomethylcyclohexane Methiodide (2), *cis*-3-Hydroxy-1-dimethylaminomethylcyclohexane Methiodide (3), and 3-Dimethylaminomethylcyclohex-1-ene Methiodide (5). The general procedure, described for **1**, was as follows. An excess of CH_3I (5 ml) was added to a solution of **9** (1.5 g) in ether (50 ml). After standing at room temperature overnight a white solid was obtained which was recrystallized from anhydrous EtOH–Et_2O: 90% yield; mp 200–202 °C; IR 1710 cm^{-1} (CO); NMR (D_2O) δ 1.10–2.80 (m, 9, cyclohexane protons), 3.30 [s, 9, $^+N(CH_3)_3$], 3.55 (m, 2, 1-CH_2). Anal. ($C_{10}H_{20}INO$) C, H, N.

Methiodides **2**, **3**, and **5** were obtained similarly starting from **13**, **8**, and 3-(*N*,*N*-dimethylaminomethyl)cyclohex-1-ene, respectively, and recrystallized from the same solvent.

Compound **2**: 93% yield; mp 166–168 °C; IR 3370 cm^{-1} (OH); NMR (D_2O) δ 1.00–2.20 (m, 9, cyclohexane protons), 3.33 [s, 9, $^+N(CH_3)_3$], 3.45 (d, 2, 1-CH_2), 4.23 (m, 1, 3-H). Anal. ($C_{10}H_{22}INO$) C, H, N.

Compound **3**: 95% yield; mp 204–206 °C; IR 3360 cm^{-1} (OH); NMR (D_2O) δ 0.80–2.30 (m, 9, cyclohexane protons), 3.13 [s, 9, $^+N(CH_3)_3$], 3.23 (d, 2, 1-CH_2), 3.80 (m, 1, 3-H). Anal. ($C_{10}H_{20}INO$) C, H, N.

Compound **5**: 92% yield; mp 235–237 °C; NMR (D_2O) δ 1.30–2.50 (m, 7, cyclohexane protons), 3.15 [s, 9, $^+N(CH_3)_3$], 3.30 (d, 2, 1-CH_2), 5.73 (m, 2, CH=CH). Anal. ($C_{10}H_{20}IN$) C, H, N.

Pharmacological testing was carried out on guinea pig ileum as previously described.[1,3-6,23] In order to allow a general comparison of the results, the techniques and the statistical evaluation of the bioassays were kept uniform. Each value of the potency ratio represents the average of a minimum of four determinations with AcCh and the experimental compounds.

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References and Notes

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