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SYNTHETIC AND CONFORMATIONAL ASPECTS OF TRIMETHYLAMMONIUM-METHYL SUBSTITUTED 2-OXAZOLINES AS POTENTIAL CHOLINERGICS

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Abstract—The effects of some structural features on the cholinergic activity of 2-oxazoline derivatives has been investigated. Improved synthetic approaches to the 2-oxazoline ring system are developed, and several new fluorinated 2-oxazolines are described. The extensive NMR data give insight into the rotameric behaviour of the substituents.

According to Triggle and Belleau[1] 2 - methyl - 5 - dimethylaminomethyl - 2 - oxazoline methiodide (the 2-oxazoline analog of Fourneau's dioxolane) equals acetylcholine in potency and thus ranks amongst the highly active cholinomimetics.

In this paper we describe the synthesis and report on the muscarinic activities of 2 - R - 5 - $CH_2N(Me_3)I$ - 2 - oxazolines (see Chart 1; R = Me (1a); CHF_2 (1c), CF_3 (1d) and C_6H_5 (1e)) and 2 - R - 4 - $CH_2N(Me_3)I$ - 2 - oxazolines (R = CH_2F (2b) and CF_3 (2d)).

R =
a CH_3
b CH_2F
c CHF_2
d CF_3
e C_6H_5

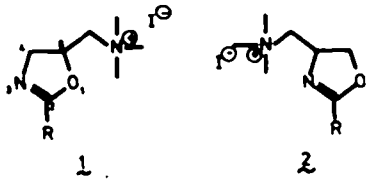


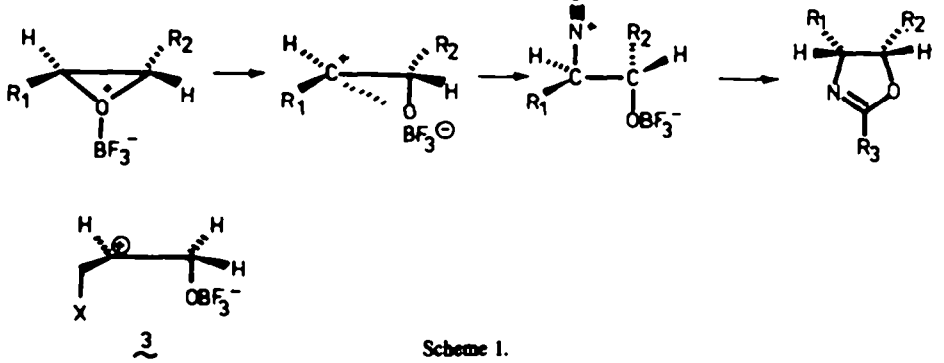
Chart 1.

The 2-phenyl derivative has been studied since it is known[2] that the introduction of a bulky substituent in a potent agonist is likely to afford good antagonistic properties.

Fluorinated analogs of drugs often exhibit peculiar properties.[3] Anteunis *et al.*[4] studied the activities of both enantiomers of *cis*-, and *trans*-2-CF_3-4-$CH_2N(Me_3)I$-1,3 - dioxolane in comparison to the 2-Me analogs. Fluorination of the 2-Me substituent lowers the cholinomimetic activities appreciably, although the 4-CH_2NMe_3I side chain preserves its rotameric preference.[5] Since 5-membered rings are flexible and the 2-CF_3 group has a pronounced tendency to adapt the (pseudo-) axial position,[6] the ring conformation has presumably been altered upon fluoromethylation. In the 2-oxazoline ring such a direct change of ring conformation is precluded (at least in the O_1–C_2–N_3–C_4 part of the ring) by the presence of the C=N double bond, and the "intrinsic" effect of the gradual fluorination of the 2-Me substituent on cholinergic activity would thus be revealed.

Synthesis. The key problem in the synthesis of compounds 1 and 2 (Chart 1) consists in the preparation of the appropriate 4 - (or 5-) CH_2X - 2 - R - substituted - 2 - oxazolines when X = OH, or Cl, or Br, and will now be considered in some detail. The conversion of the latter to the tetraalkylammonium salts involves standard procedures, described in detail in the Experimental.

From N-allylamides. A direct synthetic route to 5 - bromomethyl - 2 - oxazoline derivatives starts from the appropriate N-allylamide, through 1,2-addition of



Scheme 1.

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bromine and ring-closure of the dibromide in acetonitrile in the presence of silver carbonate at room temperature. Triggle and Belleau[1] described this approach originally for the synthesis of 2 - Me - 5 - CH_2Br - 2 - oxazoline from N-allyl-acetamide, but claimed that attempts to isolate the oxazoline were unsuccessful since rapid polymerization took place upon removal of the solvent. We found that flash-distillation allows the isolation of the oxazoline in good yield.

The same procedure was applied to the synthesis of the trifluoromethyl analog. The cyclisation of N - trifluoroacetyl - 2,3 - dibromopropylamine in Ag_2CO_3/MeCN requires a prolonged reaction time at elevated temperature and the yield of 2-CF_3-5-CH_2Br-2-oxazoline is considerably lower.

In the process of the addition of bromine to β,γ-unsaturated amides neighboring group participation of the amide group (leading to 2-oxazoline product formation) competes with bromide ion attack and eventually solvent participation, at the stage of the intermediary bromonium ion. Replacement of Br_2 by N-bromosuccinimide (NBS) as the brominating agent, and the use of solvents of relatively low nucleophilicity (e.g. acetic acid) affords the 2-oxazoline derivatives in essentially quantitative yield in the case of N-allylbenzamides.[7] Although the O atom of the trifluoroacetamide group has a much lower nucleophilicity we attempted to exploit these findings to improve the synthesis of 2 - CF_3 - 5 - CH_2Br - 2 - oxazoline from N-allyl-trifluoro-acetamide. It was found that on simply heating a mixture of N-allyl acetamide or trifluoroacetamide and NBS (without solvent) an exothermic reaction takes place. The oxazoline can be distilled directly out of the reaction mixture at reduced pressure in essentially quantitative yield. This probably constitutes the most simple, high-yield synthetic route to 2 - R - 5 - CH_2Br - 2 - oxazolines in general.

From epoxides and nitriles. A potentially attractive approach to the synthesis of 2-oxazolines is the ring-enlargement of epoxides with nitriles in the presence of acids. Yields are improved if boron trifluoride ether complex is used as the acid[8] instead of concentrated sulfuric acid[9,10] or tin tetrachloride.[11,12] The observed regio- and stereospecificities of this reaction were reconciled[8] with a BF_3 assisted unimolecular opening of the epoxide ring by the nitrile nitrogen, wherein the oxygen substituent acts as a neighbouring group that maintains stereochemistry. After C–C rotation the oxazoline is formed (Scheme 1).

The condensation of 1 - chloro - 2,3 - epoxypropane with acetonitrile and with benzonitrile in the presence of BF_3–Et_2O has been achieved, and affords, exclusively 5 - substituted - 2 - oxazoline derivatives (Experimental). From mono-alkyl (or aryl) substituted oxiranes the 4 - substituted - 2 - oxazolines are normally obtained. However if the second atom of the side chain is an electronegative element (e.g. O, Cl) as here, the developing carbocation (3) is relatively destablized, directing the attack of the nucleophile to the non-substituted epoxide carbon, and 5 - substituted - 2 - oxazolines were formed exclusively.†

The reaction of 1 - chloro - 2,3 - epoxypropane with trifluoroacetonitrile and BF_3-Et_2O was unsuccessful. Only polymeric material was recovered, presumably because of the decreased nucleophilicity of the nitrile nitrogen. A similar limitation, encountered during the condensation of oxiranes with fluorinated aldehydes or ketones in acidic conditions, was evaded[13] using tetraethylammonium bromide (TEAB) as the catalyst, a procedure originally described by Nerdel[14] for non-fluorinated carbonyl compounds. By heating 1 - chloro - 2,3 - epoxypropane with the appropriate fluorinated nitrile for 2–4 hr at 150° in a glass-pressure tube in the presence of TEAB, the 5 - chloromethyl - 2 - (mono-, di- or tri-)fluoromethyl - 2 - oxazolines were obtained in this case too in satisfactorily yields.

The mode of action of the catalyst is depicted in Scheme 2.

This mechanism accounts for the observed regiospecificity (exclusively 5 - substituted - 2 - oxazolines are obtained), and is consistent with the observed stereochemistry in the analogous TEAB catalysed condensation of *cis* - 2,3 - epoxybutane with, e.g. hexafluoroacetone, where only *cis* - 4,5 - diMe - 2,2 - bis - CF_3 - 1,3 - dioxolane is formed,[13] i.e. with net retention.

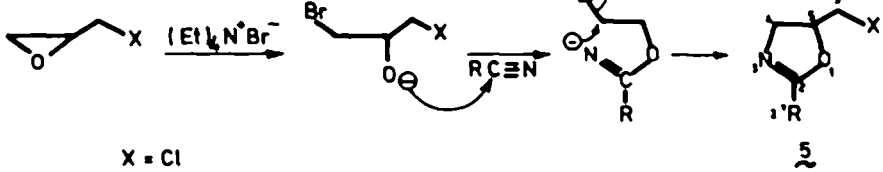
When fluorinated nitriles are allowed to react with 1 - hydroxy - 2,3 - epoxy-propane (glycidol) in the presence of TEAB,‡ exclusively 4-CH_2OH-substitued 2-oxazolines are formed. Again a striking analogy exists with the condensation of glycidol with fluorinated carbonyl compounds. R-Glycidol reacts with trifluoroacetaldehyde to give the optically pure R-dioxolane[15] (inversion). This observation was rationalized[15] by a mechanism (Scheme 3) that accounts very well for the regiospecificity, i.e. 4-substituted oxazolines are formed exclusively in the fluoronitrile reactions described in this study (Scheme 4).

Unlike the highly acidic hemiacetal of Scheme 3, that can electrophilically assist the oxirane ring opening, the iminoester formed in Scheme 4 needs the catalytic effect of TEAB. Table 1 summarizes the formation of 2-oxazolines from epoxides and nitriles that were achieved in this work.

NMR-data of the 2-oxazolines. The limited amount of NMR data on 2-oxazolines available in the literature[8,10,16–19] reveal some useful correlations with molecular structure, and allow unambiguous assignments

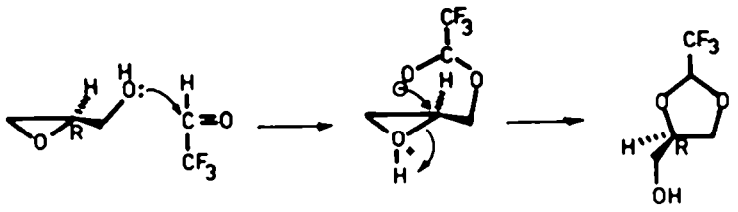
†Also for R_1 = H, R_2 = 4-MeC$_6$H$_4$OCH$_2$, R_3 = Me (Scheme 1) only the formation of the 5-substituted 2-oxazoline has been reported.[8]

‡The reaction does not proceed without the TEAB catalyst.

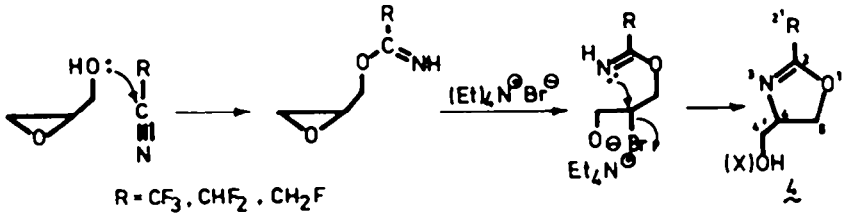


X = Cl
R = CF_3, CHF_2, CH_2F

Scheme 2.



Scheme 3.



Scheme 4.

Table 1. Synthesis of 4-, and 5-CH_2X-2-R-2-oxazolines from epoxides and nitriles

X*	R*	Catalyst	Temperature (°C) (reaction time, hrs)	% Yield oxazoline	Product	Boilingpoint/ mm Hg
Cl	C_6H_5	$BF_3.Et_2O$	[a] (1 hr)	22	5	71-73°/0.1
Cl	CH_3	$BF_3.Et_2O$	[a] (1 hr)	62	5	84°/21
Cl	CF_3	$BF_3.Et_2O$	[a] (1 hr)	—	polymer	—
Cl	CF_3	TEAB	150°C (2 hrs)[b]	28	5	152°/760
Cl	CHF_2	TEAB	150° (2 hrs)[b]	66	5	89-90°/24
Cl	CH_2F	TEAB	150° (4 hrs)[b,c]	33	5	
Cl	CH_3 or C_6H_5	TEAB	150° (4 hrs)[b]	—	d	
OH	CF_3	TEAB	150° (2 hrs)[b]	46	4	103-105°C/23
OH	CHF_2	TEAB	150° (0,5 hr)[b]	56	4	108-111°C/23
OH	CH_2F	TEAB	70°	93	4	92°C/14

a. Exothermic reaction, no external heating used.

b. In a sealed glass pressure tube.

c. Solvent benzene.

d. Only starting materials recovered.

*. X and R refer to structures 4 and 5 in Schemes 2 and 4.

of the present oxazolines as proposed in Tables 2 and 3.

Conformational aspects. In 2-oxazolines the C=N double bond imposes the O_1–C_2–N_3–C_4 atoms into one plane, leaving only a flipping of the C-5 top as the only rotational degree of freedom in the ring. Principally the vicinal ^1H–^1H coupling constants in the 4-5 fragment contain information about the "buckle" (i.e. torsion angle around C4–C5 bond) of these C_s (envelope) conformers. Unfortunately the factors that influence these couplings in the oxazoline ring system are at present[19] not well understood. It is however reasonable to assume that (as in cyclopentene[20] and 2,3-dihydrofurane[21]) the angle of buckle is *ca.* 20° with a very low barrier to inversion <2.0 J/mol or 0.5 kcal/mol).

Rotameric distribution of the fluoromethyl- and difluoromethyl substituents in 2,5-substituted 2-oxazolines. In all 2-oxazolines studied a ^5J (2', 4) long range coupling of the homoallylic type has been observed between the 4-protons and the fluor and/or H atoms of

Table 2. ^{1}H-300 MHz NMR data of 2-R_f-4-CH_2X-2-oxazolines (4) in solvent $CDCl_3$, shifts (δ) in ppm downfield relative to TMS unless otherwise indicated;[a] coupling constants (J) in Hz

R_f	X	δ							J						
		H4	H4'A	H4'B	H5A	H5B	H2'	X	$^2J(4'A,4'B)$	$^3J(4,4'A)$	$^3J(4,4'B)$	$^2J(5A,5B)$	$^3J(4,5A)$	$^3J(4,5B)$	$\lvert^5J(4,2')\rvert$
CF_3	OH	4.45	3.90	3.67	4.6	4.46	—	2.83	a						
CF_3	Br	4.55	3.61	3.49	4.46	4.44	—	—	a	3.5	6.7				
CF_3	NMe_2	4.43	2.62	2.40	4.60	4.30	—	2.28	-12.4	5.0	8.4	-8.0	a		1.6
CF_3	$^+NMe_3$[b]	4.35	3.86	3.65	4.52	4.36	6.23[c]	2.9	-11.6	3.4	3.9	a			
CH_2F	OH	4.31	3.84	3.62	4.43	4.27	4.99[d]		-11.6	3.4	4.1	-7.5[e]	8.0[e]	6.0[e]	1.2
CH_2F	Br	4.55	3.60	3.42	4.46	4.26	5.01[f]	—	-10.4	3.7	7.0	-8.6	9.4	7.0	1.1(H,H) 2.2(H,F)
CH_2F	NMe_2	4.31	2.58	2.34	4.44	4.13	4.98[f]	2.21	-12.3	5.45	8.35	-8.3	9.0	7.4	1.0(H,H)
CH_2F	$^+NMe_3$[g]	1.5	0.28	0.28	1.81	1.35	1.81[f]	0.0	a			-8.8	10.1	8.2	

[a] The tightly coupled 5-spin system could not be analysed completely.
[b] Solvent D_2O, shifts in ppm downfield against HOD.
[c] $^2J(H,F)$ = 52.7 Hz.
[d] $^2J(H,F)$ = 46.1 Hz.
[e] Not analysed properly, the coupling constants given are first order approximations.
[f] $^2J(H,F)$ = 46.4 Hz.
[g] Solvent formamide; shifts in ppm downfield against $^+NMe_3$.
[h] Protons are labeled as indicated for structure 4 in Scheme 4. A and B refer to low respectively high field.

Table 3. ^{2}-300 MHz NMR data of 2-R-5-CH_2X-2-oxazolines (5) in solvent $CDCl_3$, shifts (δ) in ppm downfield relative to TMS and coupling constants (J) in Hz, unless otherwise indicated[a]

R	X	δ							J						
		H4A	H4B	H5	H5'A	H5'B	H2'	X	$^2J(4A,4B)$	$^3J(4A,5)$	$^3J(4B,5)$	$^2J(5'A,5'B)$	$^3J(5'A,5)$	$^3J(5'B,5)$	$\lvert^5J(4,2')\rvert$
CH_3	Br	3.95	3.66	4.77	3.46		2.00		-14.5	9.6	7.2	—	5.3	5.3	1.45
CH_3	Cl	3.93	3.68	4.74	3.60		1.99		-14.5	9.6	6.8	—	5.3	5.3	1.45
CH_3	NMe_2	3.89	3.43	4.65	2.57	2.33	1.97	2.26	-14.0	9.7	7.6	-13.2	8.4	4.0	1.45
CH_3	$^+NMe_3$[c]	-0.63	-1.2	0.53	-0.92	-1.13	-2.8	-1.47	-14.4	10.2	7.6	-14.6	10.0	1.9	1.45
CF_3	Br	4.11	3.93	5.07	3.59	3.53	—	—	-15.6	9.6	7.0	-11.1	5.5	4.0	1.8
CF_3	Cl[d]	4.13	3.95	5.00	3.68		—	—	-15.6	9.7	7.0	—	5.0	5.0	1.8
CF_3	NMe_2	4.12	3.72	4.93	2.63	2.50	—	2.32	-15.2	9.7	7.8	-13.6	7.2	4.7	1.8
CF_3	$^+NMe_3$[c]	-0.38	-0.96	0.81	-0.84	-1.08	—	-1.51	-15.4	10.4	8.1	-14.6	10.0	1.8	1.8
CHF_2	Cl	4.11	3.92	4.98	3.70	3.65	6.22[e]		-15.6	10.1	6.9	-12.0	5.6	4.4	3.0(H,F)
CHF_2	NMe_2	4.06	3.72	4.86	2.60	2.46	6.22[e]	2.32	-15.1	9.7	7.1	-13.3	7.1	4.4	3.0(H,F)
CHF_2	$^+NMe_3$[c]	-0.46	-1.01	0.73	-0.89	-1.10	1.72[b]	-1.50	-15.4	10.2	7.6	-14.5	10.1	1.2	3.0(H,F)
CH_2F	Cl	4.06	3.84	4.89	3.66	3.63	5.0[c]		-14.8	9.7	6.8	-11.6	5.2	4.7	1.3(H,H) 3.0(H,F)
C_6H_5	Cl	4.18	3.94	4.93	3.67		—	—	-15.2	9.6	6.6	—	5.6	5.6	—
C_6H_5	NMe_2	4.13	3.72	4.83	2.64	2.50		2.39	-14.7	9.6	7.8	-13.0	7.6	4.6	—
C_6H_5	$^+NMe_3$[c]	-0.52	-1.05	0.57	-0.98	-1.1		-1.84	-15.0	10.1	7.4	-14.4	10.3	1.2	—

[a] $^2J(H,F)$ = 52.4 Hz; [b] $^2J(H,F)$ = 52.2 Hz; [c] $^2J(H,F)$ = 45.8 Hz
[d] Solvent CCl_4; [e] The protons are labeled as indicated on structure 5, in Scheme 2.

the 2-substituent. The relevant data are reproduced in Table 4.

The angular dependence of homoallylic coupling appears to be well documented both theoretically and empirically.[22,23]

If θ denotes the angle measured from the C_2–C_5–N_3–C_4 plane of the C_2–H (or C_2–F) bond (Fig. 1) and θ' that from the C_4–H bond, the angular dependence of $^5H(H_2, H_4)$ and $^5J(F_2, H_4)$ is expected to follow $^5J = A \cdot \sin^2\theta \cdot \sin^2\theta'$. The σ–π overlap (and so the magnitude of the coupling) is maximum for $\theta = 90°$ and the minimum for $\theta = 180°$. Homoallylic couplings across heteroatoms

Table 4. ^5J (2', 4) proton–proton (HH) and proton–fluorine (HF) homoallylic long range coupling constants (in Hz) in 5-CH_2X-2-R-2-oxazolines

R \ X	Br		Cl		NMe_2		$^+NMe_3$	
	HH	HF	HH	HF	HH	HF	HH	HF
CH_3	1.45	—	1.45	—	1.45	—	1.45	—
CF_3	—	1.8	—	1.8	—	1.8	—	1.8
CHF_2			~0	3.0	~0	3.0	~0	3.0
CH_2F			1.3	3.0				

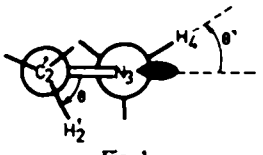
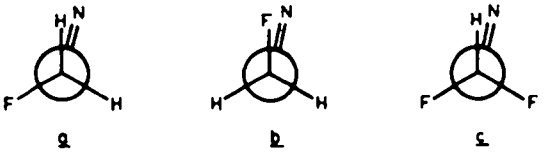


Fig. 1.

are in general susceptible to electronic influences. The latter are not believed to be responsible for the gross trends in Table 4 since in the protonated species of 2 - methyl - 2 - oxazolines an increase of only 0.4 Hz was observed compared to the non-protonated species. In 2 - Me - 2 - thiazolines the same long range coupling increases only by 0.2 Hz relative to the 2-oxazoline case.[22]

The ^5J (H, F) homoallylic coupling of 3.0 Hz observed in the 2-CH_2F derivatives indicates the predominance of the rotamer that eclipses one hydrogen atom with the C=N double bond (Fig. 2a), but is incompatible for a rotamer in which fluorine is eclipsed (see Fig. 2b).

In the CHF_2-derivatives logically both F atoms take equivalent, coupling-favouring, positions (Fig. 2c) and the same coupling value ^5J (H, F) of 3.0 Hz is expected and observed. In the 2-CF_3-oxazolines one of the three atoms is necessarily in an eclipsed position, unfavourable for coupling. One expects ^5J (H, F) to be two thirds of 3.0 Hz = 2.0 Hz, where 1.8 Hz is found experimentally. The observed interproton long range couplings support this. In the 2-CHF_2 case ^5J (H, H) ≈ 0, conform to structure c, and in the CH_2F derivatives the averaged ^5J (H, H) is indeed smaller (1.3 Hz) than in the 2-CH_3-case (1.45 Hz), where respectively one of two and two of three protons are situated favourably for homoallylic long range coupling.



a b c

Fig. 2.

Rotameric preference of the $-CH_2-\dot{N}Me_3$ *side chain in* 5 - $CH_2\dot{N}Me_3I$ - 2 - R - 2 - *oxazolines.* Of the three rotamers of the $CH_2-\dot{N}Me_3$ side chain (Fig. 3) the one that places the N^+Me_3 group over the ring (III) is for steric reasons not expected to be populated to a significant extent.

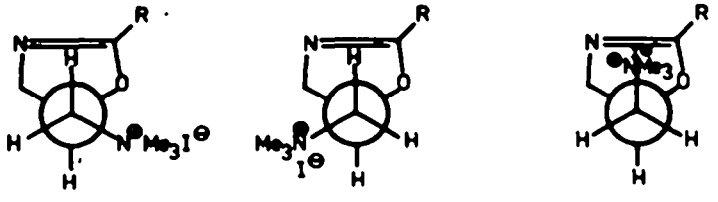
This follows also from the high ratio of ^3J (5, 5'A)/^3J (5, 5'B) ≈ 5–8 (Table 5) which assures that one of the rotamers I or II and *not* a mixture of these is present.

The low value of the gauche coupling ^3J (5, 5'B) (1.2–1.9 Hz) is typical[5,24] for the lowering effect of the electronegative O atom expected for rotamer I. The rigid *trans* - 3,9 - dimethyl - 2,4 - dioxa - 9 - aza - bicyclo-[4,4,0]decane methiodide has a situation around the bond exactly as in rotamer II, and possesses a ^3J (gauche) of 4.3 Hz.[5,24]

Considering the data in Table 5, we conclude that the 5-$CH_2\dot{N}Me_3I$-side shain takes exclusively the rotamer I, with the $^+NMe_3$ moieties gauche to the ring-O atom probably because of an energetically favourable interaction between these groups. Vicinal ^{13}C, ^{14}N scalar coupling data give a firm and independent proof for the unique population of rotamer I. A recent study[25] of twelve appropriate rigid or anancomeric tetraalkylammonium iodides revealed a torsion angle dependence

Table 5. ^3J (5, 5'A) and ^3J (5, 5'B) (in Hz) in 2-R-5-$CH_2\dot{N}Me_3I$-2-oxazolines in D_2O

R	^3J(5,5'A) (anti)	^3J(5,5'B) (clinal)
CH_3	10.0	1.9
CF_3	10.0	1.8
CHF_2	10.1	1.2
C_6H_5	10.3	1.2



I II III

Fig. 3.

with typical values of 1.5–2.0 Hz for anti (180°) coupling and about ≤0.5 Hz for gauche (60°) couplings. We have obtained ^3J (^{13}C, ^{14}N) for 2 - methyl - 5 - trimethylammonium methyl - 2 - oxazoline-iodide. The relevant ^{13}C parameters are gathered in Table 6.

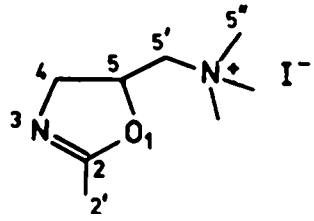
The vicinal coupling of 1.5 Hz (a typical anti ^3J (^{13}C, ^{14}N) between ring carbon C_4 and the tetraalkylammonium ^{14}N encloses the gauche relation between the latter and the ring oxygen, in accordance with our conclusion based on proton NMR.

Pharmacological results and conclusions

The cholinergic activity of the quaternary ammonium - 2 - oxazolines was tested[34] on isolated ileum segments of caviae, by the method of cumulative dose-activity curves. The results are given in Table 7.

The spasmogenic effects of 1a, 1d and 1e can be suppressed by atropine, so these compounds have cholinergic activity. Judged on the CD_{50} values in Table 7, 2 - Me - 2 - CH_2NMe_3I - 2 - oxazoline is 3 times less active than acetylcholine, although on guinea pig ileum as the

Table 6. ^{13}C-NMR parameters of 2-CH_3-5-$CH_2\overset{+}{N}Me_3I^-$-2-oxazoline in solvent D_2O at 70°



Carbon n°	δ[a] (ppm)	Rel. Int.	Multiplicity[b]	$^3J(C_4,{}^+N)$ (Hz)	$^1J(C,{}^+N)$
2'	23.0	20	q	—	—
4	44.4	69	t	1.5	—
5''	55.4	232	q	—	3.9
5	65.7	53	d	—	—
5'	69.6	62	t	—	3.4

[a] Shifts downfield relative to TMS (from 1,4-dioxane as the internal standard: +67,4 ppm).

[b] q = quartet; d = doublet; t = triplet due to C–H coupling in off-resonance experiment.

Table 7. Cholinergic activities of 2-R-4- and 2-R-5-trimethyl-ammoniummethyl-2-oxazoline-iodides on isolated ileum segments of caviae

Compound	CD_{50}[b]		Intrinsic activity[d]
	mg/l	R/Ach[c]	(i.a.)
4a CH_3	0.06	3.1	0.95
4c CHF_2[f]	inactive[e]		
4d CF_3	0.5	25	0.86
4e C_6H_5	0.63	31	1.05
5b CH_2F[f]	inactive[e]		
5d CF_3[f]	inactive[e]		
Ach[b]	0.02	1	1

[a] Tests performed by Janssen Pharmaceutica, Beerse, Belgium.

[b] CD_{50} is the concentration in mg/l corresponding to 50% of the maximum acetylcholine (Ach) contraction.

[c] R/Ach = CD_{50}/CD_{50}(Ach).

[d] i.a. is the maximal contraction, relative to the maximal contraction caused by Ach.

[e] >100 mg/l.

[f] decomposes in hydrolytic solvents.

test organ,[1] using as criterium the minimum concentration of this drug to elicit a response, it manifests the same muscarinic activity as acetylcholine.

Replacement of the 2-Me group (in **1a**) by the more bulky 2-phenyl substituent (**1e**) causes a tenfold increase in CD_{50}, while the intrinsic activity remains. Clearly the phenyl substituent in the 2-position of the oxazoline ring is not bulky enough to cause antagonistic action.

Substitution of the 2-Me group in **1a** by a trifluoromethyl group (**1d**) decreases muscarinic activity considerably. A similar trend exists in the 1,3-dioxolane-series.[4]

The $^1H,^1H$-vicinal coupling data (Table 5) of **1a** (^3J (5, 5'A) = 10 Hz, ^3J (5, 5'B) = 1.9 Hz) and of **1d** (10 Hz and 1.8 Hz) assure that the conformation of the 5-trimethylammoniummethyl side chain is identical in both products. Since the $O_1C_2N_3C_4$ region of the ring is flat, and the vicinal coupling constants around C_4–C_5 (Table 2) only slightly change, also the geometry of the oxazoline ring is expected to be very similar in compounds **1a** and **1d**. It follows from this study that the fall in muscarinic activity upon fluorination of the 2-Me side chain in the 2-oxazolines is not mediated by conformational effects perceivable in the ground state of these drugs. The reason for the decrease in activity can at present only vaguely be guessed. The introduction of the highly electronegative trifluoromethyl group may influence the electronic distribution in the 2-oxazoline ring system, which in turn affects the drug-receptor interaction.

The tested 4-CH_2NMe_3I-substituted 2-oxazolines (**2b** and **2d**) were totally inactive, presumably because of their instability towards hydrolytic solvents.

EXPERIMENTAL

Apparatus. PMR spectra were obtained from a HR 300 MHz Varian spectrometer at 18°, at ~0.2 M concentration. Spectral parameters (*J*, *δ*) have been refined by simulation with the SIMEQ 16/II program,[26] on a Varian 620-L, computer. ^{13}C-spectra were taken on a VARIAN XL-100 (12 in. wide gap) spectrometer equipped with a 620-L/16K computer. The spectra were run at 70° with 300 mg of the salt in 2 ml D_2O. 4% 1,4-dioxane was added as an internal reference. Broad-band proton decoupling was achieved by square wave modulation[27] using a 75 Hz oscillator frequency and a 4 V output level. Spectral widths were 2500 Hz, with an acquisition time of 1.6 sec, corresponding to 0.6 Hz per data point.

Synthesis

2 - *Methyl* - 5 - *bromomethyl* - 2 - *oxazoline* was obtained from N - acetyl - 2,3 - dibromopropylamine[28] and acetonitrile with silver carbonate, essentially as described[1] except in the work-up. After filtration of the ppt of silver bromide, the acetonitrile was evaporated under reduced pressure, and the residue flash-distilled immediately, b.p. 85°/20 mm Hg (lit.[35] m.p. 103°). yield: 76% (5.3 g).

2 - *Methyl* - 5 - *chloromethyl* - 2 - *oxazoline*. BF_3-ether (14.1 g; 0.1 mole) was added to a soln of 9.2 g (0.1 mole) 1 - chloro - 2,3 - epoxypropane in 100 ml acetonitrile, while stirring. The reaction was exothermic. After all the complex had been added, stirring was continued for 1 hr. The mixture was poured into $NaHCO_3$ aq and stirred for 2 hr. The chloroform extract was dried over Na_2SO_4, evaporated at 40° under vacuum and the residue fractionated, b.p. 84°/21 mm Hg (lit.[9] 73–5°/9 mm Hg). Yield: 62% (8.2 g).

2-*Methyl*-5-*dimethylaminomethyl*-2-*oxazoline*. A soln of 2.66 g (0.02 mole) of 2 - methyl - 5 - chloromethyl - 2 - oxazoline and 2.7 g (0.06 mole) dimethylamine in 20 ml of dry benzene was heated for 3 hr at 150° in a glass sealed pressure tube. The mixture was distilled, b.p. 78–80°/21 mm Hg (lit.[1] 57–8°/5 mm Hg). Yield: 91% (2.1 g).

2 - *Methyl* - 5 - *trimethylammoniummethyl* - 2 - *oxazoline iodide*. MeI (1.42 g; 0.01 mole) was added to a soln of 1.42 g (0.01 mole) of the dimethylamino derivative in 10 ml dry acetone and left to stand overnight. The white crystals had m.p. 134° (lit.[1] 134.5–135°). Yield: 92% (2.6 g). Iodine analysis: calc. 68.9%; exp. 68.0%.

2 - *Trifluoromethyl* - 5 - *bromomethyl* - 2 - *oxazoline* (n.c.†). N-Allyl-trifluoroacetamide[29] was brominated according to the procedure described[28] for N-allylacetamide, m.p. 98°, yield: 90%. Treatment of the dibromide with silver carbonate in acetonitrile for 6 hr gave the title compound in 36% yield, b.p. 79°/20 mm Hg.

2 - *Trifluoromethyl* - 5 - *dimethylaminomethyl* - 2 - *oxazoline* (n.c.). A soln of 2.32 g of 2 - CF_3 - 5 - CH_2Br - 2 - oxazoline and 20 ml of 50% dimethylamine in benzene was kept at room temp overnight. The residue was evaporated and fractionated, b.p. 73–78°/20 mm Hg, yield: 1.54 g (71%).

2 - *Trifluoromethyl* - 5 - *trimethylammoniummethyl* - 2 - *oxazoline iodide* (n.c.). A soln of 1.32 g of 2-CH_3-5-Me_2NCH_2-2-oxazoline and 0.95 g (1 equiv) MeI in 25 ml dry ether was kept overnight, yielding 1.92 g (84%) of white crystals, m.p. 203°. Iodine analysis: calc. 53.3%, exp. 52.5%.

2 - *Phenyl* - 5 - *chloromethyl* - 2 - *oxazoline*. This was achieved as described for 2 - CH_3 - 5 - chloromethyl - 2 - oxazoline replacing acetonitrile by benzonitrile, yield: 21%. b.p. 71–73°/0.1 mm Hg (lit.[36] m.p. 25°).

2 - *Phenyl* - 5 - *dimethylaminomethyl* - 2 - *oxazoline* (n.c.). The procedure described for 2 - CH_3 - 5 - Me_2NCH_2 - 2 - oxazolidine was used, yield: 87%, b.p. 113–117°/0.6 mm Hg.

2 - *Phenyl* - 5 - *trimethylammoniummethyl* - 2 - *oxazoline iodide* (n.c.). Alkylation with MeI in ether as described for 2 - CF_3 - 5 - Me_3NCH_2 - 2 - oxazoline iodide was performed, yield: 93%, m.p.: 228°. Iodine analysis: calc. 51.56%, exp. 51.4%.

2 - *Trifluoromethyl* - 5 - *chloromethyl* - 2 - *oxazoline* (n.c.). A mixture of 9.2 g (0.1 mole) 1 - chloro - 2,3 - epoxypropane, 9.5 g (0.1 mole) trifluoroacetonitrile[30] and 200 mg tetraethylammonium bromide (TEAB) was heated at 250° for 2 hr in a sealed glass pressure tube. The mixture was distilled at atmospheric pressure, b.p. 152°, yield: 5.2 g (28%).

2 - *Trifluoromethyl* - 5 - *dimethylaminomethyl* - 2 - *oxazoline* (n.c.). The method was exactly as described for the corresponding 2-Me derivative, yield: 66%, b.p. 73–78°/20 mm Hg.

2 - *Difluoromethyl* - 5 - *chloromethyl* - 2 - *oxazoline* (n.c.). Difluoroacetonitrile was prepared according to Swarts,[31] then as for 2 - CF_3 - 5 - CH_2Cl - 2 - oxazoline, yield: 66%, b.p.: 89–90°/24 mm Hg.

2 - *Difluoromethyl* - 5 - *dimethylaminomethyl* - 2 - *oxazoline* (n.c.). Starting from 2 - CHF_2 - 5 - CH_2Cl - 2 - oxazoline, the procedure described for 2 - CH_3 - 5 - Me_2NCH_2 - 2 - oxazoline was used, yield: 80%, b.p.: 76–78°/18 mm Hg.

2 - *Difluoromethyl* - 5 - *trimethylammoniummethyl* - 2 - *oxazoline iodide* (n.c.). Starting from the 5-dimethylaminomethyl compound the procedure was as described for 2 - CF_3 - 5 - Me_2NCH_2⊕I - 2 - oxazoline, yield: 81%, m.p.: 132°. Iodine analysis: calc. 57.6%, exp. 54.3%.

2 - *Fluoromethyl* - 5 - *chloromethyl* - 2 - *oxazoline* (n.c.). Monofluoroacetonitrile was prepared as described by Buckle *et al.*[32] and then the procedure was as described for 2 - CF_3 - 5 - CH_2Cl - 2 - oxazoline except that 40 ml of benzene was added to the mixture of starting materials and that trifluoroacetonitrile was replaced by monofluoroacetonitrile. The reaction time was 4 hr, yield: 33%, b.p. 92°/25 mm Hg.

Attempted synthesis of 2 - *fluoromethyl* - 5 - *dimethylaminomethyl* - 2 - *oxazoline*. 2 - CH_2F - 5 - CH_2Cl - 2 - oxazoline (1.51 g; 0.01 mole) and dimethylamine (1.35 g; 0.03 mole) in 10 ml dry benzene was heated for 3 hr at 150° in a sealed glass pressure tube. A compound boiling at 87–88°/20 mm Hg (1.2 g) was obtained and not identified. Since the ^1H NMR spectrum showed no absorption at fields lower than 3.8 ppm (rel. to TMS) this product was not a 2-oxazoline derivative.

† n.c. = new compound.

2 - *Trifluoromethyl* - 4 - *hydroxymethyl* - 2 - *oxazoline* (n.c.). A mixture of 3.7 g (0.05 mole) 1 - hydroxy - 2,3 - epoxypropane (glycidol)[33] and 4.75 g (0.05 mole) trifluoroacetonitrile with 50 mg TEAB was heated at 150° for 2 hr in a sealed glass preasure tube. Distillation gave the title compound, yield 46%, b.p. 102–105°/23 mm Hg.

2 - *Trifluoromethyl* - 4 - *bromomethyl* - 2 - *oxazoline* (n.c.). CBr_4 (5.68 g; 0.02 mole) was slowly added to a mixture of 3.38 g 2 - CF_3 - 4 - CH_2OH - 2 - oxazoline (0.02 mole) and 5.24 g (0.02 mole) triphenylphosphine in 20 ml benzene. The reaction was exothermic. The product was distilled directly out of the mixture, yield: 2.7 g (58%). b.p.: 76–78°/22 mm Hg.

2 - *Trifluoromethyl* - 4 - *dimethylaminomethyl* - 2 - *oxazoline* (n.c.). Starting with 2 - CF_3 - 4 - CH_2Br - 2 - oxazoline and using the procedure described for 2 - CF_3 - 5 - Me_2NCH_2 - 2 - oxazoline, the yield was 92%, b.p.: 68°/15 mm Hg.

2 - *Trifluoromethyl* - 4 - *trimethylammoniummethyl* - 2 - *oxazoline iodide* (n.c.). Starting from 2 - CF_3 - 4 - Me_2NCH_2 - 2 - oxazoline and proceeding as for 2 - CF_3 - 5 - CH_2NMe_3I - 2 - oxazoline the yield was 62%, m.p.: 165°. Iodine analysis: calc. 53.3%, exp. 51.2%.

2 - *Difluoromethyl* - 4 - *hydroxymethyl* - 2 - *oxazoline* (n.c.) Following the same procedure as described for 2 - CF_3 - 4 - CH_2OH - 2 - oxazoline, but replacing trifluoroacetonitrile[30] by difluoroacetonitrile[31] and reaction time of 0.5 hr the yield was 56%, b.p.: 108–111°/23 mm Hg.

2 - *Fluoromethyl* - 4 - *hydroxymethyl* - 2 - *oxazoline* (n.c.). Glycidol (3.7 g; 0.05 mole) and monofluoroacetonitrile[32] (2.95 g; 0.05 mole) was heated at 70° in the presence of 50 mg TEAB. The reaction was exothermic. Distillation gave 6.2 g of the title compound at 92°/14 mm Hg, yield: 93.2%.

2 - *Fluoromethyl* - 4 - *bromomethyl* - 2 - *oxazoline* (n.c.). Starting from 2 - CH_2F - 4 - CH_2OH - 2 - oxazoline and proceeding as described for 2 - CF_3 - 4 - CH_2Br - oxazoline the yield was 53%, b.p. 73°/18 mm Hg.

2 - *Fluoromethyl* - 4 - *trimethylammoniummethyl* - 2 - *oxazoline iodide* (n.c.). 2 - CH_2F - 4 - CH_2Br - 2 - oxazoline (0.98 g; 0.005 mole) was dissolved in 10 ml dry benzene, trimethylamine (0.59 g; 0.01 mole) was added and the mixture left overnight at room temp, yielding 0.76 g (60%) of crystals which decomposed on heating before melting.

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