238. The Four Diastereomeric Thio-Analogues of (±)-Muscarine[1])[2])

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Die vier diastereomeren Thioanalogen des (±)-Muscarins

Zusammenfassung

Im Zusammenhang mit pharmakologischen Arbeiten über die chemische Natur des cholinergischen Rezeptors haben wir die reinen (±)-Thiomuscarinjodide **4a–d** hergestellt und ihre relativen Konfigurationen an C(2), C(3) und C(5) an den *nor*-Basen **3a–d** in ^{1}H-NMR.-Spektren mit Lanthanidverschiebung aufgeklärt. Auf der Stufe der 3-Hydroxyamide **2** wurden die vier Diastereomere chromatographisch voneinander getrennt.

1. Introduction. – Studies on muscarine analogues and derivatives proved to be a useful tool in the investigations on the chemical nature of active sites of the cholinergic receptor [3] [4]. Generally, substitution of the oxygen by sulfur effects different bond angles, bond lengths and electronic structure which afford important information on both the nature and topography of the receptor's active sites.

For this reason we investigated the sulfur analogues **4a–d** of muscarine from a chemical and pharmacological point of view. Although the synthesis of a mixture of the stereoisomeric thiomuscarines was performed several years ago [5], the separation into pure diastereomers was not achieved at that time, only the relationships of the C(3)- and C(5)-substituents were established.

In this paper we report the preparation of the pure diastereomers and the elucidation of the relative configurations of the four (±)-thiomuscarines **4a–d**. The pharmacological results have been published elsewhere [6].

2. Syntheses and separations. – Previous work in the muscarine series established the retention of the configurations at C(2) and C(5) of the *nor*-bases during hydride reductions of the corresponding 3-oxo-compounds [7]. Unexpectedly, enolization at C(2) does not occur under the reaction conditions. This finding is *not* confirmed in the thiomuscarine series (see *Scheme*). The sulfur heteroatom probably

[1]) 41st communication on muscarine and related compounds; 40th comm. [1]; 39th comm. [2].

[2]) This work was presented in part at the 13th Congress of the Italian Chemical Society, Merano 1978.

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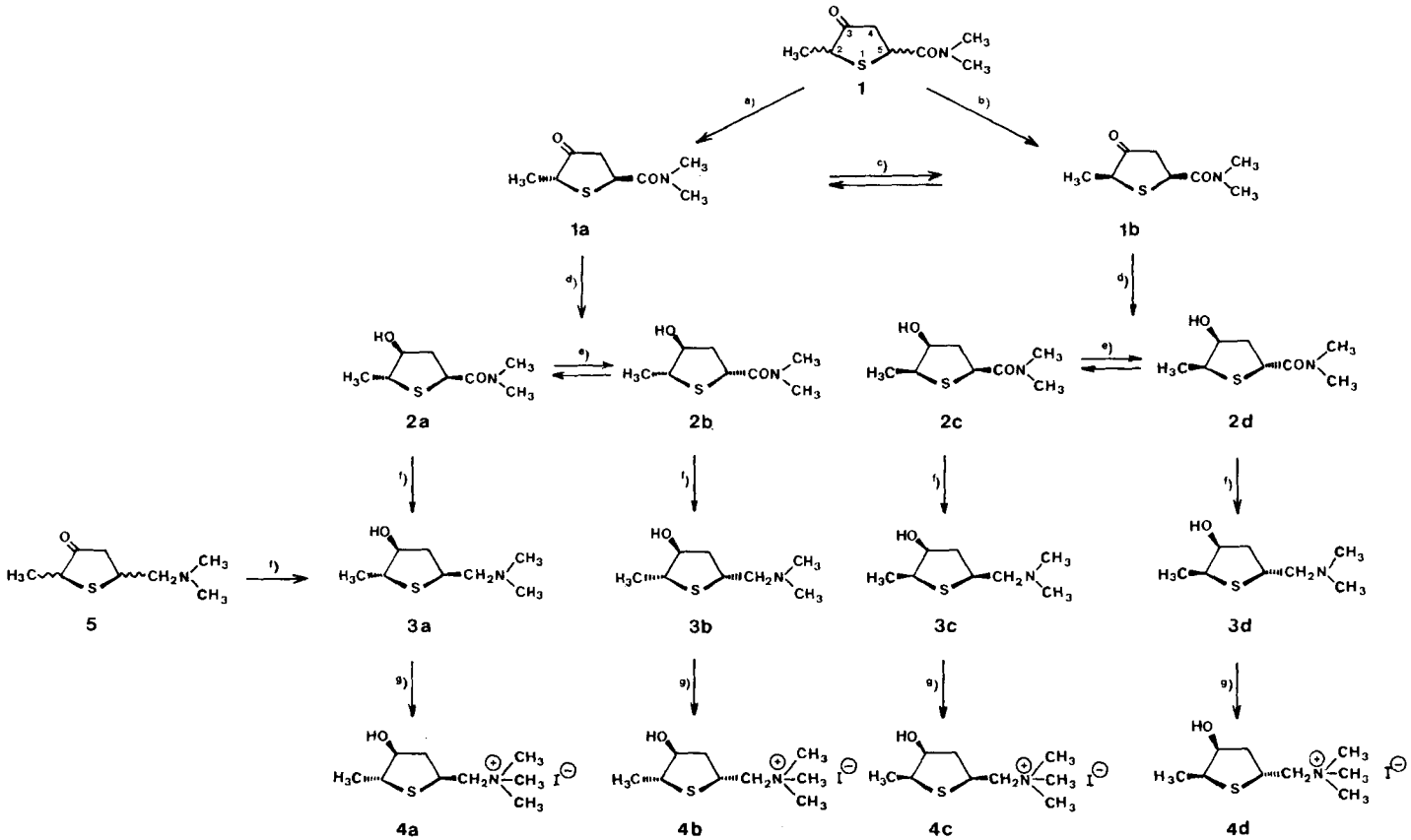
Scheme (only 1 enantiomer drawn)



a) Crystallization from cyclohexane. b) SiO_2-chromatography. c) Room temperature, base. d) $NaBH_4$ (see *Table 3*, exper. part). e) Elevated temperature, base (see *Table 4*, exper. part). f) $LiAlH_4$ in ether. g) CH_3I in ether.

increases the acidity of the H–C(2) so that facile epimerization of the oxo-compounds **1** under these conditions is observed even at room temperature (see *Table 3*, experiments 1, 2 and 10, exper. part).

Since the mixture of 3-oxo-compounds **5** [5] after $LiAlH_4$ reduction only yields 3 diastereomers (lacking the *'epi-allo'*-**3d**, see exper. part), we used the thiophan-3-one amides **1** as starting materials. The pure *trans* (= *'allo'* [7])-isomer **1a** is easily obtained by crystallization from the mixture whereas the *cis*-isomer **1b** can be isolated only with difficulty by column chromatography on silica gel[3]). $NaBH_4$ reduction of the keto-amides **1** afforded the four diastereomeric hydroxy-amides **2** which in turn were separated by column chromatography on silica gel. Analogous to earlier observations [5] the two pairs **2a/2c** (intramolecular hydrogen bond) and **2b/2d** behaved very similarly on silica gel and were isolated together in a first separation step. Succeeding chromatography yielded the pure compounds which, after

Table 1. ^1H-*NMR. spectra of the* nor-*bases* **3a–d** *in* CCl_4 (δ in ppm, J in Hz, TMS = 0)

	3a	**3b**
H–C(2)	3.19 ($d\times q$, $J_{2,3}=4$, $J_{2,CH_3}=7$)	3.14 ($d\times q$, $J_{2,3}=3.5$, $J_{2,CH_3}=7$)
H–C(3)	3.81 ($d\times d\times d$, $J_{3,4c}=5$, $J_{3,4t}=4$, $J_{3,2}=4$)	3.95 (br. *'qa'*, $\Sigma J=12$)
H_{cis}–C(4)[a])	1.72 ($d\times t$, *A*-part, $J_{AM}=13$, $J_{4c,3}=5$, $J_{4c,5}=5$)	1.72 ($d\times d\times d$, *A*-part, $J_{AB}=13$, $J_{4c,3}\approx 4$, $J_{4c,5}\approx 8$)
H_{trans}–C(4)[a])	*ca.* 2.30 (*M*-part, hidden)	2.05 ($d\times d\times d$, *B*-part, $J_{AB}=13$, $J_{4t,3}\approx 4{,}5$, $J_{4t,5}\approx 6{,}5$)
H–C(5)	3.52 ($d\times d\times t$, $J_{5,4c}\approx 5$, $J_{5,4t}=8$, $J_{5,CH_2}\approx 5$)	3.53 (br. *'qi'*, *X*-part, $\Sigma J=28$)
H_3C–C(2)	1.22 (*d*, $J_{CH_3,2}=7$)	1.25 (*d*, $J_{CH_3,2}=7$)
N–CH_2	2.44 (*'d'*, *AA'*-part, $\frac{1}{2}\lvert J_{AX}+J_{A'X}\rvert=5$)	2.33 ($d\times d$, *A*-part, $J_{AB}=12$, $J_{AX}\approx 6.5$) 2.49 ($d\times d$, *B*-part, $J_{AB}=12$, $J_{BX}\approx 7$)
$N(CH_3)_2$	2.32 (*s*, 6 H)	2.21 (*s*, 6 H)
	3c	**3d**
H–C(2)	3.36 ($d\times q$, $J_{2,3}=4$, $J_{2,CH_3}=7$)	3.46 ($d\times qa$, $J_{2,3}=4$, $J_{2,CH_3}=7$)
H–C(3)	3.97 ($d\times d\times d$, $J_{3,4c}\approx 3$, $J_{3,4t}\approx 4$, $J_{3,2}=4$)	4.20 ($d\times d\times d$, $J_{3,4c}=4$, $J_{3,4t}=3$, $J_{3,2}=4$)
H_{cis}–C(4)[a])	1.89 ($d\times t$, *A*-part, $J_{AB}=13$, $J_{4c,3}\approx 3$, $J_{4c,5}\approx 3$)	1.58 ($d\times d\times d$, *A*-part, $J_{AM}=13$, $J_{4c,3}=4$, $J_{4c,5}=9$)
H_{trans}–C(4)[a])	2.19 ($d\times d\times d$, *B*-part, $J_{AB}=13$, $J_{4t,3}\approx 4$, $J_{4t,5}\approx 8.5$)	*ca.* 2.10 (*M*-part, hidden)
H–C(5)	3.50 ($d\times d\times t$, $J_{5,4c}\approx 3$, $J_{5,4t}\approx 8.5$ $J_{5,CH_2}\approx 4.5$)	3.70 (*'qi'*, *X*-part, $\Sigma J=30$)
H_3C–C(2)	1.27 (*d*, $J_{CH_3,2}=7$)	1.26 (*d*, $J_{CH_3,2}=7$)
N–CH_2	2.48 (*'d'*, *AA'*-part, $\frac{1}{2}\lvert J_{AX}+J_{A'X}\rvert=5$)	2.35 ($d\times d$, each, *AB*-part, $J_{AB}=12$, 2.48 $J_{AX}\approx J_{BX}\approx 7$)
$N(CH_3)_2$	2.32 (*s*, 6 H)	2.21 (*s*, 6 H)

a) *Cis*- resp. *trans*-relative to HO–C(3).

3) For this reason only **1a** was used in the pure form in preparative experiments whereas reductions of the *cis*-isomer were performed with **1a/1b** mixtures (see *Table 3*, exper. part).

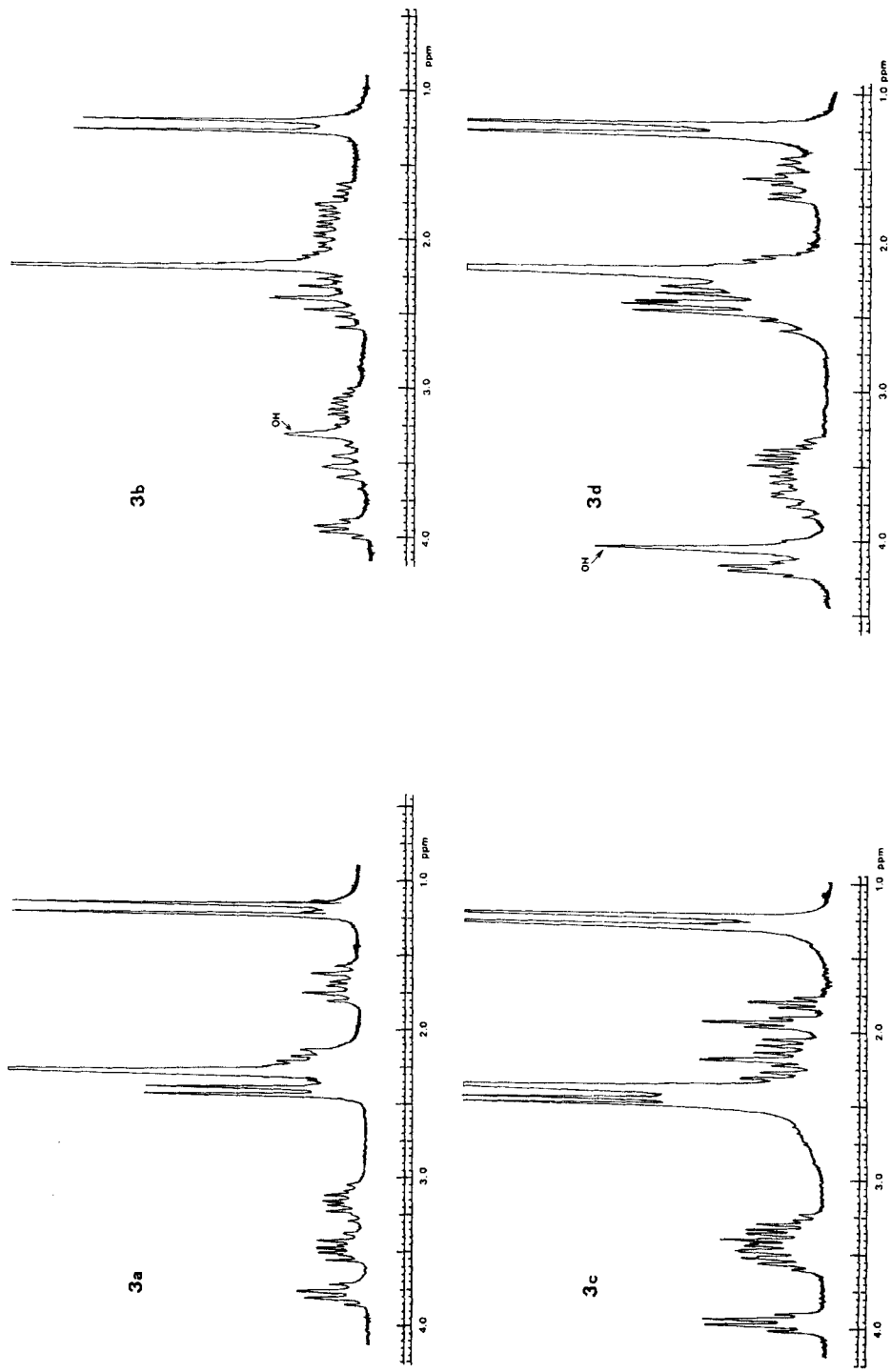


Fig. 1. ^1H-*NMR. spectra of the* NOR-*bases in* CCl_4

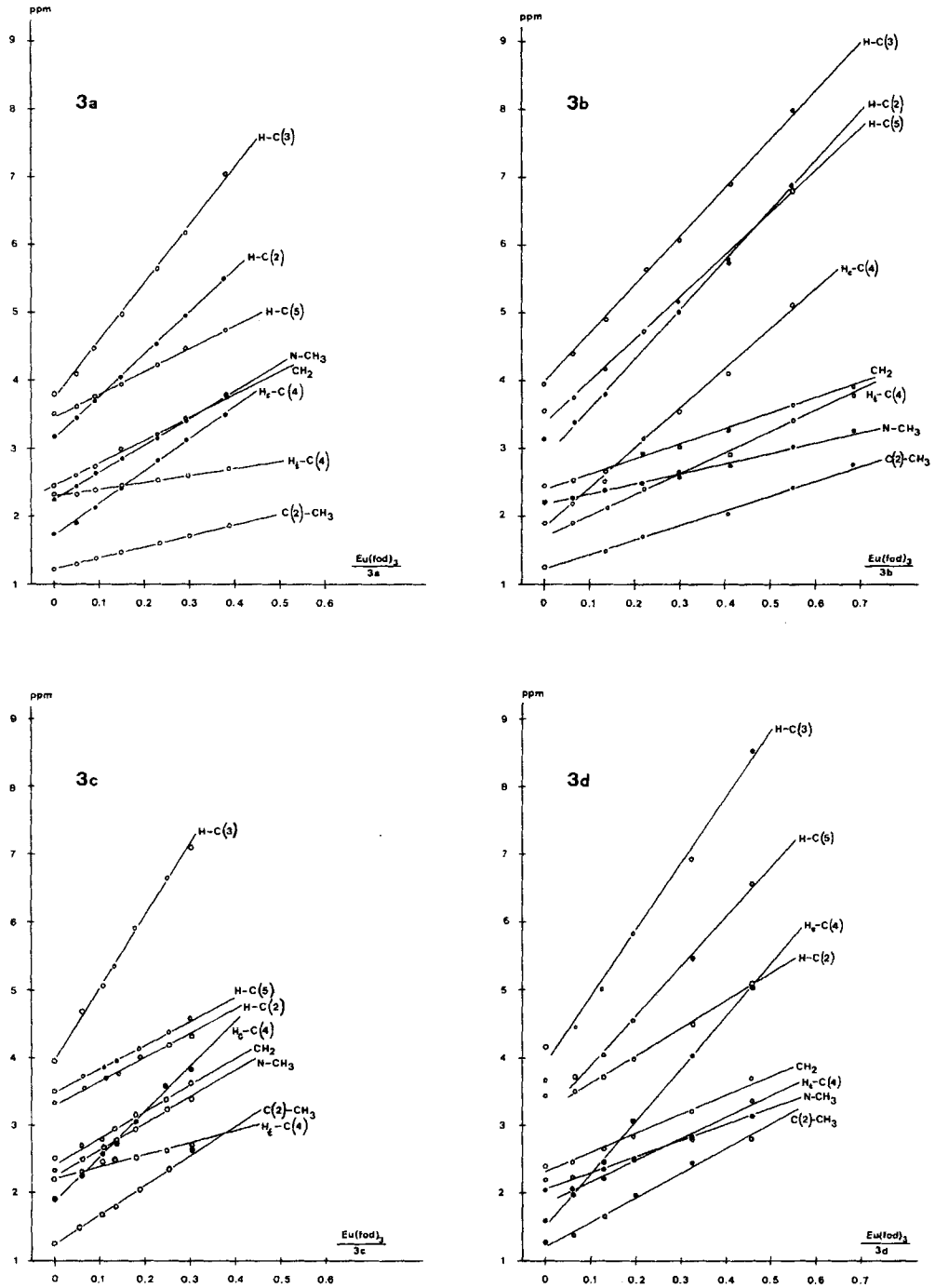


Fig. 2. *Relative LIS. rates of the* nor-*bases*

Table 2. *Relative paramagnetic shift rates of the* nor-*bases* **3a–d** (approximately calculated slopes (°) from *Fig. 2*)

	3a	**3b**	**3c**	**3d**
H–C(2)	45	50	30	30
H–C(3)	55	50	55	55
H_{cis}–C(4)	35	40	45	50
H_{trans}–C(4)	10	25	20	25
H–C(5)	25	40	30	45
H_3C–C(2)	15	20	40	30
N–CH_2	25	20	35	25
N(CH_3)$_2$	30	10	35	20

reduction to the corresponding *nor*-bases **3** with $LiAlH_4$, were converted to the crystalline thiomuscarine-iodides **4**.

The assignment of the relative configurations was achieved unambiguously with ^{1}H-NMR. lanthanide induced shift [8] experiments on the racemic *nor*-bases **3** (see next section).

The presence of the amide function has stereochemical consequences: the distributions of the reduction products **2** (see *Table 3*, exper. part) suggest a favoured attack of the hydride reagent *trans* to the amide group at low temperature followed by epimerization at C(5) at higher temperature. In fact, the latter proved to be a good way of obtaining the isomers **2b** and **2d** through epimerization of **2a** and **2c** respectively according to [9], thus eliminating impurities that are formed during reductions at high temperature (see exper. part).

3. Assignment of the relative configurations. – The ^{1}H-NMR.-spectra of the (±)-*nor* bases **3a–d** vary distinctly from each other (see *Fig. 1* and *Table 1*). The full analysis of these spectra was made with extensive multiple resonance experiments, however, the assignment of the relative configurations on the basis of the coupling constants is not possible in such five-membered ring systems. Their unequivocal establishment was achieved by lanthanide induced shift (=LIS.) experiments [8] in the ^{1}H-NMR.-spectra with Eu(fod)$_3$[4]). *Figure 2* and *Table 2* clearly show the differences in pairs of the paramagnetic shift rate; hence follow the *cis*- respectively *trans*-relationships between OH and CH_3, OH and H–C(5) *etc.* Moreover, a comparison of the relative shift rates of protons adjacent to the nitrogen atom with those close to the oxygen atom shows the stronger influence of the shift reagent on the latter; *i.e.* the Eu^{3+} preferably coordinates with the hydroxy group and allows the deduction of the relative configurations in the thiophane ring as depicted.

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4) Eu(fod)$_3$ = Europium(III)-*tris*-(1,1,1,2,2,3,3-heptafluor-7,7-dimethyl-4,6-octadionate).

Experimental Part

General. The IR. spectra were recorded on a *Perkin-Elmer* 257 spectrophotometer, the ^{1}H-NMR. spectra at 100 MHz on a *Varian* HA-100 spectrometer using TMS as internal standard ($\delta=0$). Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.063 to 0.200 mm, *Merck*). The GC. analysis of the amines **3** was effected on a *Carlo Erba* Fractovap Model G 1 type AID (FID) on a glass-capillary column 20 m × 0.4 mm packed with Emulphor 0/1% KOH at 105°, 0.5 at H_2 flow 5–30 ml/min, injector temperature 180°. Relative areas of the peaks were determined with a *Carlo Erba* Digital Integrator Model 72. Melting points were taken on a *Büchi* 510 apparatus in sealed capillaries and are uncorrected.

1. *2-Methyl-3-oxo-5-*N,N*-dimethylamido-tetrahydrothiophenes* **1a** *and* **1b**. A solution of 2-methyl-3-oxo-tetrahydrothiophene-5-carboxylic acid (12 g, 0.07 mol) [5] and triethylamine (12.2 ml, 0.09 mol) in chloroform (200 ml) was added to a cooled and stirred solution of ethyl chloroformate (8.3 ml; 0.09 mol) in chloroform (80 ml). After 30 min an excess of dimethylamine in ether (60 ml of 33% solution) was added and the mixture allowed to stand for 1 h. The solution was then washed with 2N HCl, saturated $NaHCO_3$-solution, H_2O and dried over Na_2SO_4. Evaporation of the solvent gave a solid that was purified by chromatography with ethyl acetate/cyclohexane 7:3 as eluent: 9.1 g (65%) *ca.* 3:1 *trans/cis* mixture **1**.

The *trans*-isomer **1a** was obtained by drying the mixture on a porous plate and crystallization from cyclohexane: colourless prisms, m.p. 83–84°. – IR. ($CHCl_3$): 1730, 1635 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1,44 (*d*, $J=7$ Hz, 3 H, H_3C–C(2)); 2,56 (*d* × *d*, *A*-part, $J_{AB}=17$ Hz, $J_{AX}=2$ Hz, 1 H, H–C(4)); 3,04 (*d* × *d*, *B*-part, $J_{AB}=17$ Hz, $J_{BX}=7$ Hz, 1 H, H–C(4)); 2,97 and 3,08 (each *s*, each 3 H, $N(CH_3)_2$); 3,60 (*qa*, $J=7$ Hz, 1 H, H–C(2)); 4,11 (4 lines, *X*-part, $|J_{AX}+J_{BX}|=9$ Hz, 1 H, H–C(5)).

$C_8H_{13}NO_2S$ (187.25) Calc. C 51.31 H 7.00 N 7.48% Found C 51.23 H 6.84 N 7.52%

The *cis*-isomer **1b** was enriched by chromatography with petroleum ether/ethyl acetate/acetone/methanol 30:5:2:2, followed by distillation afforded **1b** in *ca.* 80–90% purity as a colourless oil, b.p. 115–116°/0.2 Torr. – IR. ($CHCl_3$): 1735, 1640 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.44 (*d*, $J=7$ Hz, 3 H, H_3C–C(2)); 2.68 (*d* × *d*, *A*-part, $J_{AB}=17$ Hz, $J_{AX}=7$ Hz, 1 H, H–C(4)); 3,13 (*d* × *d*, *B*-part, $J_{AB}=17$ Hz, $J_{BX}=4.5$ Hz, 1 H, H–C(4)); 2,97 and 3,10 (each *s*, each 3 H, $N(CH_3)_2$); 3.58 (*qa*, $J=7$ Hz, 1 H, H–C(2)); 4.18 (4 lines, *X*-part, $|J_{AX}+J_{BX}|=11.5$ Hz, 1 H, H–C(5)).

$C_8H_{13}NO_2S$ (187.25) Calc. C 51.31 H 7.00 N 7.48% Found C 51.41 H 6.93 N 7.38%

2. *Reduction of* **1** *to the hydroxy-amides* **2a–d** (Table 3). The reduction was performed on the *trans* isomer **1a** (*Table 3*, experiments 1–5 and 10) or on *trans/cis* mixtures (*Table 3*, experiments 6–9). The conditions used are reported in *Table 3* as well as the yields. The reducing agent was added in small quantities to the amide (experiments 2–4, 7–9); on the contrary, for the experiments 1, 5, 6 and 10, the amide solution was added dropwise to the reducing agent.

Table 3

Exp. No.	Substrate	Reagent	Molar ratio Substr./ Reagent	Solvent	Conditions	Total yields	Relative yields %			
							2a	**2b**	**2c**	**2d**
1	**1a**	$NaBH_4$	1:1	Pyridine	RT., 5 h	64	57	–	43	–
2	**1a**	id.	1:1	*i*-PrOH	RT., 2 h	88	60	3	33	4
3	**1a**	id.	1:1	*i*-PrOH	100°, 2 h	70	35	15	25	25
4	**1a**	id.	1:1	*i*-PrOH	100°, 5 h	60	30	20	20	30
5	**1a**	id.	1:1	MeOH/H_2O 2:1	0°, 10 h	82	96	–	–	4
6	**1a/1b** 1:4	id.	1:1	MeOH/H_2O 2:1	0°, 10 h	70	15	5	80	–
7	**1a/1b** 1:1	id.	1:1	*i*-PrOH	RT., 2 h	85	47	2	47	4
8	**1a/1b** 1:1	id.	1:1	*i*-PrOH	100°, 2 h	65	30	17	30	23
9	**1a/1b** 1:1	id.	1:1	*i*-PrOH	100°, 5 h	50	23	24	23	30
10	**1a**	$NaBH(OCH_3)_3$	1:3	MeOH	RT., 1 h	80	62	3	32	3

The reactions were worked up in the usual way: evaporation of the solvent, decomposition of the residue with diluted hydrochloric acid, extraction with $CHCl_3$, washed with saturated $NaHCO_3$-solution, H_2O and dried over Na_2SO_4. The hydroxy-amides **2a–d** were purified by chromatography; best results were obtained by separation of the **2a/2c** and **2b/2d** couples with $CHCl_3$/ethyl acetate/EtOH 17:2:1. The two couples were in turn separated with $CHCl_3$/petroleum ether/EtOH/conc. NH_3-solution 50:50:5:1 and ethyl acetate/EtOH 9:1 respectively.

– 'allo'-*Isomer* **2a**. Colourless oil. – IR. ($CHCl_3$); 3300, 1630 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.36 (*d*, J=7 Hz, 3 H, H_3C–C(2)); 2.26 (*d*×*d*×*d*, *A*-part, J_{AB}=14 Hz, $J_{4,5}$=7.5 Hz, $J_{4,3}\approx$4.5 Hz, 1 H, H–C(4)); 2.47 (br. *d*×*d*, *B*-part, J_{AB}=14 Hz, $J_{4,5}$=2.5 Hz, $J_{3,4}\approx$1.5 Hz, 1 H, H–C(4)); 2.97 and 3.08 (each *s*, each 3 H, $N(CH_3)_2$); 3.53 (*d*×*q*, $J_{2,3}$=2 Hz, J_{2,CH_3}=7 Hz, 1 H, H–C(2)); 4.16 (*m*, 5 lines, *X'*-part, $w_{1/2}$=9 Hz, 1 H, H–C(3)); 4.37 (4 lines, *X*-part, $|J_{AX}+J_{BX}|$=10 Hz, 1 H, H–C(5)).

$C_8H_{15}NO_2S$ (189.26) Calc. C 50.76 H 7.99 N 7.40% Found C 50.79 H 8.04 N 7.53%

– *'Thiomuscarine'-isomer* **2b**. Colourless prisms (from cyclohexane), m.p. 75.5–76.5°. – IR. ($CHCl_3$): 3400, 1630 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.32 (*d*, J=7 Hz, 3 H, H_3C–C(2)); 2.07 (*d*×br.*d*, *A*-part, J_{AM}=13 Hz, $^3J\approx$6.5 and *ca.* 1 Hz, 1 H, H–C(4)); 2.65 (*d*×*d*×*d*, *M*-part, J_{AM}=13 Hz, $^3J\approx$6 and 4 Hz, 1 H, H–C(4)); 2.95 and 3.02 (each s, each 3 H, $N(CH_3)_2$); 3.35 (*qi*-like, $w_{1/2}\approx$25 Hz, 1 H, H–C(2)); 4.20 (*m*, 5 lines, *X*- and *X'*-parts, $w_{1/2}$=21 Hz, 2 H, H–C(3) and H–C(5)):

$C_8H_{15}NO_2S$ (189.26) Calc. C 50.76 H 7.99 N 7.40% Found C 50.81 H 8.07 N 7.58%

– 'epi'-*Isomer* **2c**. Colourless oil. – IR. ($CHCl_3$): 3300, 1630 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.40 (*d*, J=7 Hz, 3 H, H_3C–C(2)); 2.14 (*d*×*d*×*d*, *A*-part, J_{AM}=14 Hz, $^3J\approx$9 and 4 Hz, 1 H, H–C(4)); 2.61 (br.*d*, *M*-part, J_{AM}=14 Hz, $^3J\approx$1.5 Hz, 1 H, H–C(4)); 2.97 and 3.04 (each *s*, each 3 H, $N(CH_3)_2$); 3.64 (*d*×*q*, $J_{2,3}$=3.5 Hz, J_{2,CH_3}=7 Hz, 1 H, H–C(2)); 4.28 (*m*, *X*- and *X'*-parts, $w_{1/2}$=12 Hz, 2 H, H–C(3) and H–C(5)).

$C_8H_{15}NO_2S$ (189.26) Calc. C 50.76 H 7.99 N 7.40% Found C 50.65 H 7.82 N 7.20%

– 'epi-allo'-*Isomer* **2d**. Colourless prisms (from cyclohexane), m.p. 80–82°. – IR. ($CHCl_3$): 3400, 1630 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.32 (*d*, J=7 Hz, 3 H, H_3C–C(2)); 2.14 (*d*×*d*×*d*, *A*-part, J_{AB}=13 Hz, $J_{4,5}$=8.5 Hz, $J_{4,3}$=4 Hz, 1 H, H–C(4)); 2.57 (*d*×*d*×*d*, *B*-part, J_{AB}=13 Hz, $J_{4,5}$=8.5 Hz, $J_{4,3}$=4 Hz, 1 H, H–C(4)); 2.95 and 3.03 (each *s*, each 3 H, $N(CH_3)_2$); 3.57 (*d*×*q*, $J_{2,3}$=3.5 Hz, J_{2,CH_3}=7 Hz, 1 H, H–C(2)); 4.33 (4 lines, *X*-part, $|J_{AX}+J_{BX}|$=15.5 Hz, 1 H, H–C(5)); 4.42 (*m*, 4 lines, $w_{1/2}\approx$9 Hz, 1 H, H–C(3)).

$C_8H_{15}NO_2S$ (189.26) Calc. C 50.76 H 7.99 N 7.40% Found C 50.62 H 7.91 N 7.39%

3. *Reduction of 2-methyl-3-oxo-5-(*N,N*-dimethylaminomethyl)-tetrahydrothiophene* (**5**) *to the* nor*-bases* **3a–c**. The reduction of **5** [5] (about 1:1 *cis/trans* mixture) was performed according to *Eugster & Allner* [5]. Only three isomeric compounds (**3a–c**) were obtained which were separated by chromatography with $CHCl_3$/EtOH/conc. NH_3-solution 50:9:1.2. It is worthy of note that the isomers **3a** and **3b** are chromatographically identical to those already described, for which steric relationships between the groups at C(3) and C(5) were clearly established (*cis* and *trans* respectively) [5].

– 'allo'-*Isomer* **3a**. Colourless prisms (from petroleum ether), m.p. 35°; yield 43.0%; Rf[5]) 0.61; t_R[6]) 17.8 min. – IR. (nujol): 3360 cm^{-1}. – ^{1}H-NMR.: see *Table 1.*

$C_8H_{17}NOS$ (175.28) Calc. C 54.81 H 9.78 N 7.99% Found C 54.75 H 9.67 N 7.79%

– *'Thiomuscarine'-Isomer* **3b**. Colourless oily crystals, m.p. *ca.* 20°; yield 9.4%; Rf[5]) 0.52; t_R[6]) 25.0 min. – IR. (nujol): 3390. – ^{1}H-NMR.: see *Table 1.*

$C_8H_{17}NOS$ (175.28) Calc. C 54.81 H 9.78 N 7.99% Found C 54.93 H 9.85 N 8.03%

– 'epi'-*Isomer* **3c**. Colourless prisms (from petroleum ether), m.p. 56–57°; yield 44.6%; Rf[5]) 0.67; t_R[6]) 11.0 min. – IR. (nujol): 3370 cm^{-1}. – ^{1}H-NMR.: see *Table 1.*

$C_8H_{17}NOS$ (175.28) Calc. C 54.81 H 9.78 N 7.99% Found C 54.82 H 9.62 N 7.83%

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[5]) SiO_2, analytical plate, $CHCl_3$/EtOH/conc. NH_3-solution 50:9:1.2.

[6]) Note the congruence of the elution sequence with the muscarine series [10].

4. *Reduction of* **2** *to the* nor-*bases* **3a-d**. A solution of **2d** (0.55 g; 2.9 mmol) in dry ether (55 ml) was added dropwise to a cooled slurry of $LiAlH_4$ (0.27 g, 7.1 mmol) in dry ether (55 ml). The reaction mixture was then refluxed for 4 h. When cooled, the excess of $LiAlH_4$ was decomposed with EtOAc (40 ml) and water (10 ml). The solution was decanted, the white solid was washed twice with EtOAc and the organic solution dried over Na_2SO_4. Evaporation of the solvent gave 400 mg (78%) *'epi-allo'*-isomer **3d** as a pale yellow low melting solid, m.p. *ca.* 20°; Rf[5]) 0.51; t_R[6]) 18.6 min. – IR. (nujol): 3430 cm^{-1}. – ^{1}H-NMR.: see *Table 1*.

$C_8H_{17}NOS$ (175.28) Calc. C 54.81 H 9.78 N 7.99% Found C 54.79 H 9.85 N 7.81%

Similarly, the isomers **3a**, **3b** and **3c** were obtained starting from **2a**, **2b** and **2c** respectively.

5. *Epimerization of the amides* **2a** *and* **2c**. A solution of 1.9 g (0.01 mol of the amides **2a** or **2a/2c** (1:1 mixture)) in 90 ml of abs. 2-propanol was refluxed for 5 h with 540 mg (0.01 mol) of $NaOCH_3$ according to [9]. The solvent was evaporated and the residue decomposed with diluted hydrochloric acid, extracted with $CHCl_3$ and the pure compounds isolated by chromatography (see section 2). This procedure is a good way to obtain **2b** and **2d** without impurities that are formed during reduction at high temperature and that complicate the chromatographic separation.

Table 4

Substrate	Total yield %	Relative yields %			
		2a	**2b**	**2c**	**2d**
2a	76	52	48	–	–
2a/2c (1:1)	82	29	24	24	23

6. *Methiodides* **4a-d**. Excesses of CH_3I (0.7 ml each) were added to the solutions of the *nor*-bases (300 mg each) in 20 ml abs. ether. After standing for two days at room temperature colourless precipitates were obtained.

– (±)-allo-*Thiomuscarine-iodide* (**4a**): 435 mg (80%), m.p. 172–173°. – IR. (nujol): 3390 cm^{-1}.

$C_9H_{20}IONS$ (317.22) Calc. C 34.07 H 6.35 N 4.42% Found C 33.98 H 6.51 N 4.31%

– (±)-*Thiomuscarine-iodide* (**4b**): 380 mg (70%), m.p. 162–164°. – IR. (nujol): 3360 cm^{-1}.

$C_9H_{20}IONS$ (317.22) Calc. C 34.07 H 6.35 N 4.42% Found C 33.98 H 6.60 N 4.18%

– (±)-epi-*Thiomuscarine-iodide* (**4c**): 380 mg (70%), m.p. 186–187°. – IR. (nujol): 3400 cm^{-1}.

$C_9H_{20}IONS$ (317.22) Calc. C 34.07 H 6.35 N 4.42% Found C 34.11 H 6.45 N 4.53%

– (±)-epi-allo-*Thiomuscarine-iodide* (**4d**): 380 mg (70%), m.p. 183–184°. – IR. (nujol): 3400 cm^{-1}.

$C_9H_{20}IONS$ (317.22) Calc. C 34.07 H 6.35 N 4.42% Found C 34.01 H 6.35 N 4.38%

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