32. Preparation of Optically Active Secondary Amines by Thermal Decomposition of (Methylbenzyl)urea Analogs: Absolute Configuration of (+)- and (−)-Mecamylamine

Preliminary Communication[1][2]

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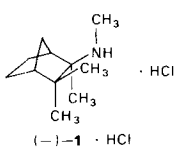
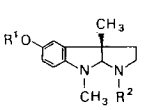
Thermolysis of the (α-methylbenzyl)urea diastereoisomers **4** and **5** of (±)-mecamylamine ((±)-**1**) and **6** and **7** of (±)-1-noreseroline *O*-methyl ether ((±)-**3**) in refluxing alcohol afforded optically pure amines in high yield, besides optically pure carbamates of (α-methylbenzyl)amine which can be recycled. The absolute configuration of (−)-mecamylamine hydrochloride ((−)-**1** · HCl) was determined by X-ray diffraction analysis.

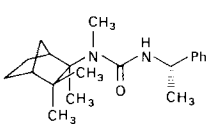
Classical chemical resolutions of (±)-mecamylamine (= *N*-methyl-(2-*endo*,3,3-trimethylbicyclo[2.2.1]hept-2-*exo*-yl)amine; (±)-**1**) [1], used in form of the racemate as an antihypertensive agent [2], and of (±)-eserethole (= 5-ethoxy-1,2,3,3a-8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indole; (±)-**2**) [3], required for the synthesis of (−)-physostigmine [4] and its (+)-enantiomer [5], are not very practical. We now report on a better method for preparing these optically active amines, obtained in high yield and of excellent optical purity.



(−)-**1** · HCl



	R^1	R^2
(−)-**2**	C_2H_5	CH_3
(−)-**3**	CH_3	H



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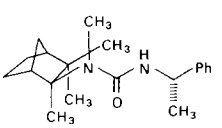

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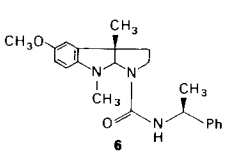

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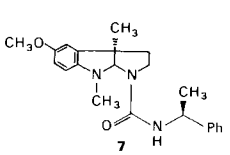

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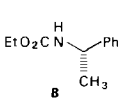

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[1] The full paper will be published elsewhere.
[2] Patent application has been filed.

The crucial reaction is a thermal fragmentation of (α-methylbenzyl)urea diastereoisomers **4** and **5**, and **6** and **7**, respectively, in refluxing alcohols. The ureas were readily obtained from (±)-**1** and (±)-**3** (instead of (±)-**2**), respectively, with (−)-(*S*)-(α-methylbenzyl)isocyanate [6] in $CHCl_3$ at 0° and separated by flash chromatography. Urea **4** (m.p. 91.5–92.0° from hexane; $[\alpha]_D = -71.8°$ ($CHCl_3$); faster moving isomer an TLC (silica gel, Et_2O/hexane 1:5)) and its diastereoisomer **5** (m.p. 108.0–108.5° from $(i\text{-}Pr)_2O$; $[\alpha]_D = +44.1°$ ($CHCl_3$)) decomposed both when refluxed in 2M NaOEt in EtOH for 1 h. Workup and recrystallization afforded 32% of amine hydrochloride (+)-**1**·HCl ($[\alpha]_D = +20.1°$ ($CHCl_3$)) and 32% of (−)-**1**·HCl ($[\alpha]_D = -20.0°$ ($CHCl_3$)), respectively, as essentially optically pure products. Ethyl (−)-*N*-(α-methylbenzyl)carbamate (**8**) was the only recognizable by-product, identical with a reference sample made from (−)-(α-methylbenzyl)amine and ethyl chloroformate.

Carbamates such as **8**, or analogs obtained in other examples, can be reconverted into optically active (α-methylbenzyl)isocyanates by hydrolysis to the corresponding (α-methylbenzyl)amines [7] and reaction of the latter with phosgene [8].

Fragmentation of these (α-methylbenzyl)ureas does not necessarily require sodium alkyl oxide suggesting that the reaction proceeds by a hetero-*Grob* fragmentation with formation of the secondary amine and trapping of the (α-methylbenzyl)isocyanate fragment with the alcohol.

Similarly (±)-**3**, prepared by a variant of the *Julian* total synthesis of (−)-physostigmine [3], afforded urea **7** ($[\alpha]_D = +182.9°$ ($CHCl_3$)) as the faster and **6** ($[\alpha]_D = -40.0°$ ($CHCl_3$)) as the slower moving diastereoisomer. The 1-noreseroline *O*-methyl ether (−)-**3** (oxalate: m.p. 156–159°; $[\alpha]_D = -77.2°$ (CH_3OH)) and its enantiomer (+)-**3** (oxalate: m.p. 151–153°; $[\alpha]_D = +68°$ (CH_3OH)) were obtained from **6** and **7**, respectively, after refluxing in 1-pentanol for 1 h in the presence of 1M sodium pentyl oxide, besides the pentyl-ester analog of **8**.

Both mecamylamine (+)- and (−)-**1** when tested as hydrochloride salts in assays measuring neuromuscular transmission showed interesting differences [9], indicating that their absolute configuration be of interest. Single-crystal X-ray analysis of (−)-**1**·HCl is summarized below and establishes (−)-**1** as (1*S*,2*R*,4*R*)-*N*-methyl-(2,3,3-trimethylbicyclo[2.2.1]hept-2-yl)amine.

X-Ray Analysis of (−)-1·HCl. Mecamylammonium chloride, $C_{11}H_{22}ClN$, of m.p. 258–261° (from 2-propanol) crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 7.515(1)$, $b = 11.704(2)$, $c = 13.825(3)$ Å, and $Z = 4$. The calculated density is 1.11 mg·mm^{-3}. The 1574 unique reflections with $|F_o| > 3\sigma F$ include 640 *Bijvoet* pairs. Data was collected on a *Nicolet-R3m* diffractometer using Cu$K\alpha$ radiation with an incident beam monochromator. The structure was solved by direct methods [10] and the absolute configuration [11] of the compound was determined. The 136 parameters refined in the least-squares refinement include the atom coordinates and anisotropic thermal parameters for all but the H-atoms. The atom coordinates of the ammonium H-atoms were refined, and all other H-atoms used a riding model with C–H = 0.96 Å and $U(H) = 1.2\ U_{eq}(C)$. The function minimized was $\sigma w(|F_o| - |F_c|)^2$. The final *R* factor was 0.031 and $R_w = 0.037$ with an error in an observation of unit weight of 1.23, as compared to the values for the incorrect enantiomorph of $R = 0.049$, $R_w = 0.062$ and $S = 2.06$.

The absolute configuration of the molecule *(Fig.)* is given by chiral centers C(1), C(3), and C(6) (arbitrary numbering). C(1) and C(3) are *R*, and C(6) is *S*. The isomer of mecamylammonium chloride formed is the *exo*-isomer. Bond distances and angles[3]) are

[3]) Lists of bond distances, angles, and fractional coordinates, have been deposited with the *Crystallographic Data Centre*, Cambridge University, University Chemical Lab, Cambridge CB2 1EW, England.

Table 1. *Atom Coordinates* ($\times 10^4$) *and Temperature Factors* ($Å^2 \times 10^3$)[a])

Atom	*x/a*	*y/b*	*z/c*	U_{eq}[b])
C(1)	2260(3)	4461(2)	3590(1)	40(1)
C(2)	1430(3)	5472(2)	4209(2)	46(1)
C(3)	3127(4)	6097(2)	4555(2)	66(1)
C(4)	4055(4)	6736(2)	3725(2)	79(1)
C(5)	4773(4)	5755(2)	3108(2)	72(1)
C(6)	4280(3)	4679(2)	3684(2)	56(1)
C(7)	4439(4)	5115(3)	4707(2)	70(1)
C(8)	377(4)	5065(2)	5094(2)	60(1)
C(9)	192(4)	6247(2)	3633(2)	72(1)
C(10)	1581(4)	4373(2)	2551(2)	61(1)
N(11)	1837(2)	3315(2)	4056(1)	40(1)
C(12)	2647(4)	2277(2)	3619(2)	56(1)
Cl	2087(1)	2500	3837(1)	50(1)

[a]) Arbitrary numbering, see *Fig.*
[b]) Equivalent isotropic *U* defined as $\frac{1}{3}$ of the trace of the orthogonalized U_{ij} tensor.

Table 2. *Bond Lengths* (Å)[a])

C(1)–C(2)	1.588(3)	C(1)–C(6)	1.545(3)
C(1)–C(10)	1.528(3)	C(1)–N(11)	1.521(3)
C(2)–C(3)	1.546(4)	C(2)–C(8)	1.534(3)
C(2)–C(9)	1.524(4)	C(3)–C(4)	1.537(4)
C(3)–C(7)	1.529(4)	C(4)–C(5)	1.529(4)
C(5)–C(6)	1.536(4)	C(6)–C(7)	1.509(4)
N(11)–C(12)	1.487(3)		

[a]) Arbitrary numbering, see *Fig.*

Table 3. *Bond Angles* (deg.)[a])

C(2)–C(1)–C(6)	102.6(2)	C(2)–C(1)–C(10)	115.1(2)
C(6)–C(1)–C(10)	114.7(2)	C(2)–C(1)–N(11)	110.3(2)
C(6)–C(1)–N(11)	108.4(2)	C(10)–C(1)–N(11)	105.6(2)
C(1)–C(2)–C(3)	101.3(2)	C(1)–C(2)–C(8)	113.6(2)
C(3)–C(2)–C(8)	109.0(2)	C(1)–C(2)–C(9)	113.7(2)
C(3)–C(2)–C(9)	112.6(2)	C(8)–C(2)–C(9)	106.7(2)
C(2)–C(3)–C(4)	111.9(2)	C(2)–C(3)–C(7)	102.6(2)
C(4)–C(3)–C(7)	100.2(2)	C(3)–C(4)–C(5)	102.2(2)
C(4)–C(5)–C(6)	104.0(2)	C(1)–C(6)–C(5)	109.2(2)
C(1)–C(6)–C(7)	102.2(2)	C(5)–C(6)–C(7)	101.0(2)
C(3)–C(7)–C(6)	94.2(2)	C(1)–N(11)–C(12)	117.6(2)

[a]) Arbitrary numbering, see *Fig.*

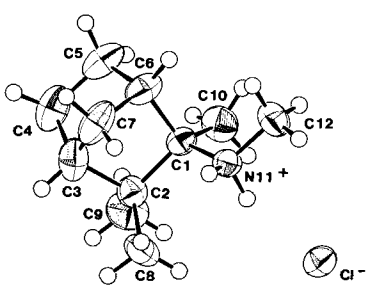

Figure. *Structure and absolute configuration of (−)-mecamylamine hydrochloride* ((−)-**1**·HCl). Thermal ellipsoid plot enclosing 50% probability of (−)-**1**·HCl. Arbitrary numbering.

Table 4. *Anisotropic Temperature Factors* ($Å^2 \times 10^3$)[a])[b])

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	38(1)	44(1)	39(1)	5(1)	1(1)	–3(1)
C(2)	50(1)	41(1)	45(1)	1(1)	–1(1)	1(1)
C(3)	86(2)	55(1)	58(2)	–1(1)	–12(2)	–19(2)
C(4)	85(2)	60(2)	90(2)	15(2)	–12(2)	–26(2)
C(5)	51(2)	84(2)	82(2)	25(2)	5(2)	–19(2)
C(6)	38(1)	59(1)	73(2)	13(1)	3(1)	–2(1)
C(7)	59(2)	78(2)	75(2)	23(2)	–28(1)	–26(2)
C(8)	71(2)	52(2)	56(2)	–9(1)	16(1)	9(1)
C(9)	74(2)	65(2)	77(2)	12(2)	0(2)	20(2)
C(10)	72(2)	70(2)	40(1)	2(1)	–2(1)	–1(1)
N(11)	37(1)	44(1)	38(1)	–3(1)	1(1)	1(1)
C(12)	62(2)	47(1)	59(1)	10(1)	–1(1)	9(1)
Cl	44(1)	58(1)	47(1)	3(1)	–1(1)	–6(1)

[a]) The anisotropic temperature factor exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + \cdots + 2hka^*b^*U_{12})$.

[b]) Arbitrary numbering, see *Fig.*

Table 5. *H-Atom Coordinates* ($\times 10^4$) *and Temperature Factors* ($Å^2 \times 10^3$)[a])

Atom	x/a	y/b	z/c	U_{eq}
H(3)	2835	6604	5077	87
H(4a)	3228	7198	3368	94
H(4b)	5001	7209	3965	94
H(5a)	6039	5818	3033	90
H(5b)	4218	5751	2482	90
H(6)	4962	4023	3493	74
H(7a)	5038	4574	5182	85
H(7b)	5618	5366	4868	85
H(8a)	1117	4631	5525	71
H(8b)	–652	4623	4924	71
H(8c)	8	5757	5409	71
H(9a)	746	6523	3053	87
H(9b)	–121	6881	4039	87
H(9c)	862	5826	3468	87
H(10a)	1664	5111	2252	74
H(10b)	369	4115	2532	74
H(10c)	2322	3841	2209	74
H(12a)	2278	1623	3988	71
H(12b)	3915	2361	3665	71
H(12c)	2315	2174	2954	71
H(11a)	2169(29)	3306(17)	4628(15)	48
H(11b)	541(29)	3255(17)	4045(15)	48

[a]) Arbitrary numbering, see *Fig.*

those normally expected. There are two H-bonds in which the N-atom in the molecule acts as a donor to Cl^-, $N^+(11)–H(11B)\cdots Cl^-$ and $N^+(11)–H(11A)\cdots Cl^-$ ($-x$, $1/2 + y$, $1/2 - z$). For the former H-bond, the $H\cdots Cl^-$ and $N^+\cdots Cl^-$ distances and the $N^+–H\cdots Cl^-$ angle are 2.18(2) Å, 3.114(5) Å, and 159.8(2.2)° respectively for the latter H-bond these values are 2.39(2) Å, 3.170(5) Å, and 157.1(2.1)°, respectively.

Further examples of successful conversions of biologically interesting secondary amines into their optical enantiomers by the (α-methylbenzyl)isocyanate method have been accomplished, and full experimental details will be reported elsewhere.

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