Absolute Configuration and Conformational Analysis of (−)-(*R*)-Deprenyl and its Homologues

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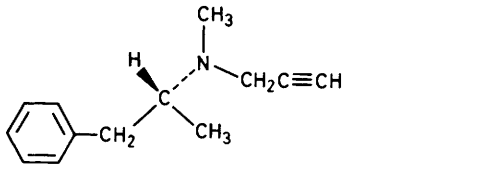
The absolute configuration of (−)-*N*,α-dimethyl-*N*-prop-2-ynylphenethylamine was determined using the isomorphous HCl and HBr salts. Beside *X*-ray analysis, the conformation of the free base, of the salt, and of the *C*-alkyl derivatives was studied by ^{1}H and ^{13}C n.m.r. techniques and potential-energy calculations. In the the solid state the extended conformer was observed, in solution the proportion of *gauche*-folded conformer increases with the bulkiness of R and decreases upon protonation of the nitrogen atom.

Deprenyl, *N*,α-dimethyl-*N*-prop-2-ynylphenethylamine (**1**), synthesized at the Chinoin Research Laboratories,[1] has been reported as a selective monoamine oxidase (MAO) type B inhibitor.[2] (−)-Deprenyl (other name, L-deprenyl) is a much more active inhibitor than the other enantiomer,[3] and highly selective on a special type of MAO, preferentially deaminating benzylamine,[4] *m*-iodobenzylamine, and β-phenylethylamine.[5] (−)-Deprenyl (international non-proprietory name, selegiline) has been introduced in the treatment of Parkinson's disease in combination with 3,4-dihydroxy-L-phenylalanine (L-dopa) and a pheripheral dopa-decarboxylase inhibitor.[6,7] (−)-Deprenyl is the active ingredient of JUMEX^R, an antiparkinsonic agent. This work describes the absolute configuration and the crystal structure of the HCl and HBr salts as well as the conformational analysis of (−)-deprenyl and its *C*-alkyl derivatives by n.m.r. spectroscopy, and potential-energy calculations on the parent compound.



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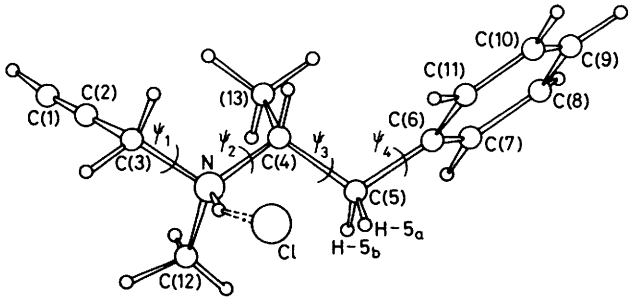

Figure 1. Molecular diagram of (−)-deprenyl·HCl with atomic numbering

Results and Discussion

X-Ray Studies.—*X*-Ray analyses of the isomorphous HCl and HBr salts of the resolved deprenyl were performed. The absolute configuration was established using the *R* value test;[8] in (−)-deprenyl ($[\alpha]_{20}^{D}$ −12°) the configuration of C(4) is *R* (Figure 1). This is an important observation since in amphetamine and its derivatives as well as in ephedrine the configuration of the analogous carbon atom is *S* for the more active, central nervous system stimulating enantiomer.[9,10] This is, however, in accord with the pharmacological observation on the enhanced central nervous system stimulating side-effect of the (+)-enantiomer of deprenyl.[3] Characteristic torsion angles are given in Table 1. As in other catecholamines,[11] the C(3), N, C(4), C(5), and C(6) atoms form an elongated, planar zig-zag chain. The two methyl groups as well as the ethynyl group are on one side of this plane while the anion (chloride or bromide) is on the other side. The difference in the distance of the counter ions ($N^+ \cdots Cl^-$ 3.03 Å, $N^+ \cdots Br^-$ 3.30 Å) is in accord with the hydrogen-bonding character of the two ions. The steric interactions between C(13) and the phenyl group, and between C(13) and the ethynyl group, are reduced by distortions from the ideal staggered conformation around the C(3)–N, N–C(4), C(4)–C(5), and C(5)–C(6) bonds.

† The BNC-28 minicomputer version of the LAOCOON3 quantum chemical algorithm.

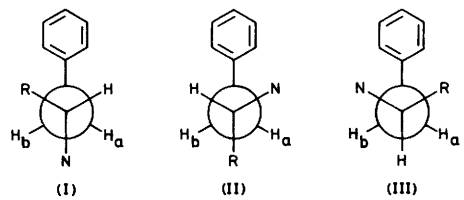

Figure 2. The Newman projection of the three stable rotamers around the C(4)–C(5) bond

N.m.r. Studies.—In order to get some information on the conformation in solution, the ^{1}H n.m.r. spectra of deprenyl and its 4-alkyl derivatives were studied in detail. ^{1}H N.m.r. spectral data and those of amphetamine[12] are given in Table 2. The coupling constant analysis was checked by spectra, simulated with the ITRCAL program.† The change of the chemical-shift difference of the diastereoisotopic benzyl protons (5-H_a, 5-H_b), as well as their coupling constants, refers to different conformational distributions around the C(4)–C(5) bond. The three stable rotamers are given in Figure 2.

Table 1. Characteristic torsion angles (°). E.s.d.s are given in parentheses and the definition of torsion angles used in conformational analysis

Atoms	Definition	(−)-Deprenyl·HBr	(−)-Deprenyl·HCl
C(2)–C(3)–N–C(4)	ψ_1	78.7(6)	79.0(3)
C(2)–C(3)–N–C(12)		−54.1(6)	−53.6(3)
C(3)–N–C(4)–C(5)	ψ_2	167.3(7)	168.3(3)
C(3)–N–C(4)–C(13)		−66.2(7)	−64.8(3)
C(12)–N–C(4)–C(5)		−62.4(7)	−62.0(3)
C(12)–N–C(4)–C(13)		64.1(7)	64.9(3)
N–C(4)–C(5)–C(6)	ψ_3	−165.0(8)	−168.1(3)
C(13)–C(4)–C(5)–C(6)		68.2(7)	65.1(3)
H(4)–C(4)–C(5)–H(5a)		78	72(2)
H(4)–C(4)–C(5)–H(5b)		−169	−169(2)
C(4)–C(5)–C(6)–C(7)	ψ_4	−107.2(8)	−104.7(3)
C(4)–C(5)–C(6)–C(11)		72.1(9)	74.7(3)
H(5a)–C(5)–C(6)–C(11)		−49	−53(2)
H(5b)–C(5)–C(6)–C(7)		13	14(2)

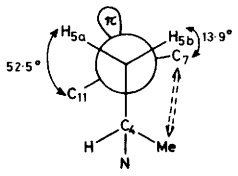

Figure 3. The Newman projection across the C(5)–C(6) bond showing the distortion of the phenyl group toward the hydrogen atoms in the solid-state structure

the steric effect of the nitrogen atom is not so pronounced. A significant decrease in the amount of conformer (**I**) can be observed in the methyl, ethyl, isopropyl series. This is due to the interaction of the alkyl and phenyl in rotamer (**I**).

Some conclusions can be drawn concerning the conformation around the C(5)–C(6) bond by analysis of the $^2J_{5\text{-}H_2}$ values (Table 2). The increase in the absolute values in methyl, ethyl, isopropyl series from 12.8 to 15.1 Hz can be explained by the enhanced π–$\sigma_{C(5)\text{-}H}$ interaction. The Newman projection of this bond for deprenyl·HCl in the solid state is shown in Figure 3. The difference between the C(7)–C(6)–C(5)–H(5b) and C(11)–C(6)–C(5)–H(5a) torsion angles is 39°. The distortion should be even larger for the bulkier ethyl and isopropyl derivatives, which give rise to an enhanced electronic π–$\sigma_{C(5)\text{-}H}$ interaction resulting in increased coupling constants. It is worth mentioning that the enzyme-inhibitory activity decreases in the same series.[15]

Table 2. Characteristic ^{1}H n.m.r. data (δ_{TMS} 0.00; J/Hz)

Compound	Solvent	Frequency (MHz)	$\delta_{4\text{-}H}$	$\delta_{5\text{-}Ha}$	$\delta_{5\text{-}Hb}$	$^2J_{5\text{-}H_2}$	$J_{4.5a}$	$J_{4.5b}$
Deprenyl·HCl	$CDCl_3$[b]	250	3.71	3.56	2.80	−12.8	3.1	11.4
Deprenyl·HCl	D_2O	80	3.93	3.18	2.88	−13.3	5.0	9.5
Deprenyl	$CDCl_3$	250	2.98	3.05	2.38	−13.0	4.1	9.8
4-Et-deprenyl·HCl	$CDCl_3$[b]	100	3.72	3.48	3.04	−13.5	4.2	9.4
4-Pr^i-deprenyl·HCl	$CDCl_3$	100	3.70	3.35	3.18	−15.1	7.4	4.2
Amphetamine·HCl[a]	$CDCl_3$	270		3.22	2.84		5.13	9.16
Amphetamine·HCl[a]	D_2O	270		2.92	2.94		7.5	6.9
Amphetamine[a]	$CDCl_3$	270		2.50	2.69		8.06	5.50
Amphetamine[a]	D_2O	270		2.55	2.70		7.70	6.23

[a] Taken from ref. 12. [b] With a drop of D_2O.

For the estimation of the conformational distribution, as a first step, the diastereoisotopic protons should be assigned unambiguously. For this purpose we have used data for *erythro*- and *threo*-[β-^{2}H]amphetamine.[12] In $CDCl_3$ 5-H_b of the amphetamine HCl salt resonated at higher frequency than 5-H_a. An even more extreme chemical-shift difference was detected in a $CDCl_3$ solution of deprenyl·HCl between the benzylic protons. Applying the above assignment, the coupling constants $J_{4.5b}$ 11.4, $J_{4.5a}$ 3.1 Hz were derived. With the extended Karplus-type equation, taking into account the electronegativity of the substituents,[13] we calculated the coupling constants as a function of the torsion angle of the C(4)–C(5) bond. Good agreement was obtained between the experimental and calculated coupling constants using the torsion angle derived from the *X*-ray analysis.* This indicates that in $CDCl_3$ the HCl salt of deprenyl is exclusively in conformation (**I**). In all other cases the measured coupling constants can be explained in terms of conformational equilibria. Numerical values are summarized in Table 3, together with data for amphetamine.[12] Values for conformer distribution should be considered to be approximate, with a possible error of *ca.* 10%.[14] Comparing the conformational distribution of deprenyl·HCl and amphetamine·HCl in $CDCl_3$ the increase in rotamer (**I**) is noticeable in deprenyl. This is understable since the nitrogen atom is substituted by a propynyl group. In D_2O and in the case of the free base the proportion of rotamer (**II**) increases, as found for amphetamine. This is presumably due to the fact that in aqueous media in the fully ionized salt or in the case of the base,

Table 3. Rotameric distribution[a]

Compound	Solvent	Ratios [%] (I)	(II)	(III)
Deprenyl·HCl	$CDCl_3$	100	0	0
Deprenyl·HCl	D_2O	77	23	0
Deprenyl	$CDCl_3$	81	13	6
4-Et-deprenyl·HCl	$CDCl_3$	76	14	10
4-Pr^i-deprenyl·HCl	$CDCl_3$	13	52	35
Amphetamine·HCl[b]	$CDCl_3$	76	21	3
Amphetamine·HCl[b]	D_2O	45	53	2
Amphetamine[b]	$CDCl_3$	27	61	12
Amphetamine[b]	D_2O	36	56	8

[a] Calculated assuming J(antiperiplanar) 11.4 and J(synclinal) 3.1 Hz, obtained from the conformationally homogeneous deprenyl·HCl salt in $CDCl_3$. [b] Taken from ref. 12.

In the ^{1}H n.m.r. spectra of the salts in $CDCl_3$ the peaks are broadened; nevertheless upon adding 1 drop of D_2O to the solution the signals become sharp. On the other hand adding a catalytic amount of trifluoroacetic acid (TFA) to the solution

* The range of $J_{4.5a}$ (calculated) for torsion angles H(4)–C(4)–C(5)–H(5a) = 72 ± 4° is 3.0—2.2 Hz. The range of $J_{4.5b}$ (calculated) for torsion angles H(4)–C(4)–C(5)–H(5b) = −169 ± 4° is 11.3—11.7 Hz.

Table 4. ^{13}C N.m.r. chemical shifts of deprenyl·HCl (δ_{TMS} 0.0)

Solvent	T/°C	$\delta_{C(1)}$	$\delta_{C(2)}$	$\delta_{C(3)}$	$\delta_{C(4)}$	$\delta_{C(5)}$	$\delta_{C(6)}$	$\delta_{C(7),(11)}$	$\delta_{C(8),(10)}$	$\delta_{C(9)}$	δ_{NMe}	δ_{CMe}
CD_3OD	25	81.2	73.6	44.1	63.2	37.7	137.2	129.8	130.4	128.2	35.2	13.3
CD_3OD	−80	81.4	74.4	43.2 44.2	61.3	35.7 38.5	137.6	130.2	130.9	127.0	34.7 36.0	11.2 14.0
$CDCl_3$	25	80.3	72.3	43.3	61.8	37.3	136.2	129.0	129.4	127.3	36.5	13.5
$CDCl_3$ + TFA	25	79.8	71.5	42.4 43.3	61.5	36.1 37.5	135.5	128.5	128.9	126.9	35.4 36.4	12.0 13.9

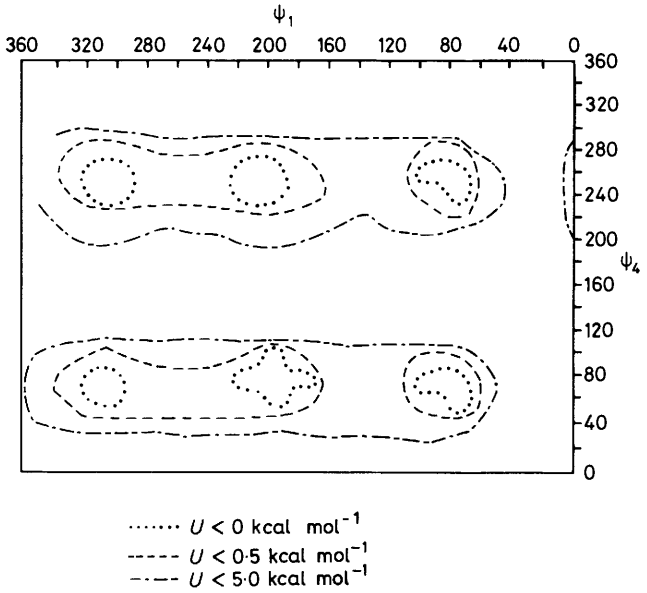

Figure 4. Potential-energy map, horizontal axis, ψ_1 = C(2)–C(3)–N–C(4), vertical axis ψ_4 = C(4)–C(5)–C(6)–C(7). Boundaries for ···· $U > 0$ kcal mol^{-1} (0 kJ mol^{-1}), – – – – $U > 0.5$ kcal mol^{-1} (2.1 kJ mol^{-1}), — · — · — $U > 5.0$ kcal mol^{-1} (21 kJ mol^{-1})

interconversion of them in $CDCl_3$ is accelerated by adding D_2O and slowed down by TFA, on the n.m.r. time-scale.

Supposing that the amine–salt interconversion is fast, the rate of the interchange can be described according to Saunders and Yamada [16] by equation (1).

$$k_{interchange} = k_{inversion} \cdot \frac{[amine]}{[salt] + [amine]} \quad (1)$$

D_2O and TFA change the free amine and salt relation, and, hence the rate of the intechange.

The same can be concluded from the ^{13}C n.m.r. spectra of deprenyl·HCl (Table 4), namely both the lowering of the temperature and the addition of TFA causes the doubling of the same signals, supporting the presence of the diastereoisomeric salt pair.

Potential-energy Calculations.—Potential-energy calculations were performed using the EENYC program by Motherwell,[17] where the constants were those given by Giglio.[18] The analysis of the rotation of the terminal groups is given in Figure 4. The propynyl group can rotate quite freely while a higher barrier hinders rotation around the C(5)–C(6) bond. Around ψ_1 the ideal values would be 60, 180, and 300°, while for ψ_4 90 and 270°. The minima are displaced by 20 and 10°, respectively, in accordance with the *X*-ray data (see Table 1).

As the molecule can rotate freely around C(3)–N, (ψ_1), the

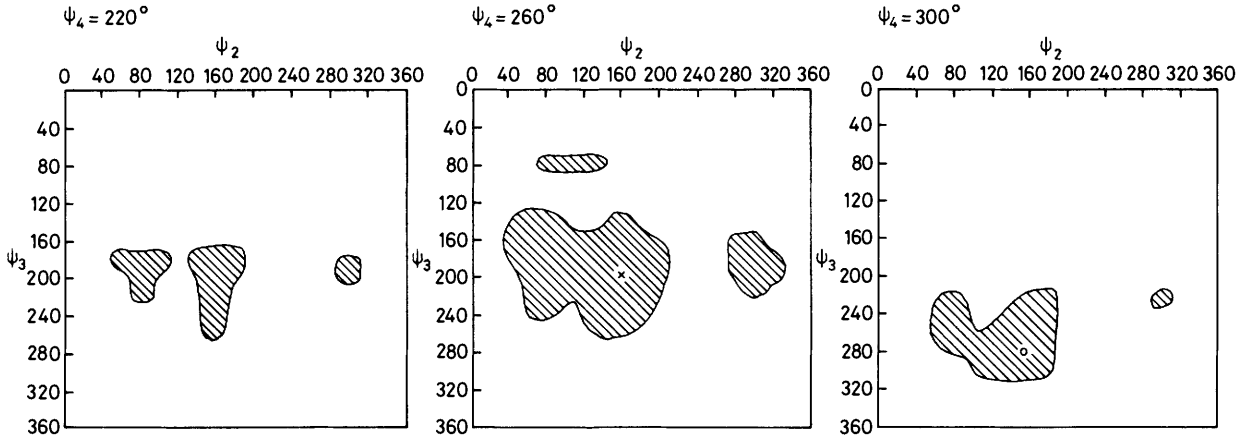

Figure 5. Percentage map for (−)-deprenyl. The area should encompass 99% of the molecule at 37 °C, at sections ψ_4 = 220, ψ_4 = 260, ψ_4 = 300°. ×, Potential-energy minimum for extended conformer. ○, Potential-energy minimum for *gauche* folded conformer

causes a doubling of the peaks, but the separation is only observable at *C*-methyl and at *N*-methyl. These signals are of equal intensity, and the *N*-methyl signals are doublets with 4.8 Hz splitting, due to the coupling with the NH proton. So the signals come from the diastereoisomeric salt pair, and the conformation of the molecule can be analysed by changing only the other three torsion angles ψ_2, ψ_3, and ψ_4. Part of the potential map is reproduced in Figure 5. Using the well known method [19] the contours encompass 99% of the molecule at the physiological temperature (12 kJ mol^{-1} above the minimal

Table 5. Fractional co-ordinates ($\times 10^4$) with e.s.d.s in parentheses

	(−)-Deprenyl·HBr			(−)-Deprenyl·HCl		
Atom	*x*	*y*	*z*	*x*	*y*	*z*
Br/Cl	3 256(1)	3 981(1)	413(1)	3 243(1)	3 986(1)	401(1)
N	3 186(5)	916(3)	834(2)	3 194(2)	1 001(2)	785(1)
C(1)	3 253(8)	−2 234(5)	22(3)	3 260(4)	−2 258(3)	7(2)
C(2)	3 292(7)	−1 079(5)	44(2)	3 313(3)	−1 061(2)	19(1)
C(3)	3 311(7)	362(4)	63(2)	3 380(3)	414(2)	35(1)
C(4)	4 987(6)	882(4)	1 256(2)	4 992(3)	946(2)	1 226(1)
C(5)	4 806(7)	1 733(5)	1 943(2)	4 727(4)	1 827(2)	1 900(1)
C(6)	6 662(7)	2 023(4)	2 272(2)	6 588(4)	2 055(2)	2 281(1)
C(7)	7 185(7)	1 403(5)	2 918(3)	7 014(4)	1 371(2)	2 914(1)
C(8)	8 886(8)	1 637(6)	3 223(3)	8 716(4)	1 556(3)	3 257(1)
C(9)	10 077(9)	2 468(5)	2 891(3)	10 033(4)	2 410(3)	2 974(1)
C(10)	9 579(9)	3 113(6)	2 261(3)	9 638(4)	3 112(3)	2 362(1)
C(11)	7 878(9)	2 874(5)	1 952(3)	7 915(5)	2 934(3)	2 010(1)
C(12)	1 543(7)	369(5)	1 221(3)	1 471(3)	465(3)	1 142(1)
C(13)	5 640(8)	−499(5)	1 421(3)	5 629(4)	−475(3)	1 393(1)
H(N)	2 930	1 953	840	2 910	1 930	660
H(1)	3 281	−3 248	16	3 340	−3 340	0
H(3A)	4 469	722	−171	4 570	840	−160
H(3B)	2 228	725	−238	2 210	650	−320
H(4)	6 004	1 231	932	6 140	1 340	910
H(5A)	4 122	2 569	1 803	4 160	2 770	1 820
H(5B)	3 964	1 237	2 296	3 790	1 310	2 250
H(7)	6 243	821	3 171	5 950	690	3 150
H(8)	9 237	1 157	3 689	9 160	820	3 650
H(9)	11 368	2 685	3 122	11 290	2 540	3 250
H(10)	10 461	3 724	2 000	10 690	3 790	2 140
H(11)	7 473	3 333	1 478	7 600	3 510	1 520
H(12A)	1 753	−593	1 343	1 720	−540	1 360
H(12B)	1 322	845	1 700	1 250	1 090	1 480
H(12C)	400	436	921	310	390	750
H(13A)	6 844	−487	1 686	6 910	−460	1 700
H(13B)	4 703	−966	1 740	4 590	−840	1 680
H(13C)	5 786	−1 034	962	5 830	−1 050	910

energy). It can be seen that the folded conformation (ψ_3 300°) can exist at the physiological temperature if the phenyl group is rotated by 40° around ψ_4 compared with the value obtained for the extended conformer (ψ_3 = 190°).

Conclusions.—In the R = H, Me, Et, and Pr^i series maximal MAO inhibitory activity was observed with R = Me;[16] therefore steric and electronic effects should determine the activity.[20] In this respect the relative populations of the conformers may be an important factor. The proportion of conformer (**II**) increases with the bulkiness of R and decreases upon protonation of the nitrogen atom.

Conformational changes are coupled; changes in ψ_3 affect ψ_4 strongly due to the interaction between R and the phenyl group. For R = Me the minimum-energy conformers are at ψ_3 −168, ψ_4 −105° (extended form); ψ_3 280°, ψ_4 −60° (folded form). The relative position of the phenyl group toward the covalently bound flavin component of the mitochondrial MAO[21] might be an important factor of the selectivity.

The known absolute configuration of (−)-deprenyl might help to solve the controversial question on the stereospecificity of monoamine oxidase.[22]

Experimental

^{1}H N.m.r. spectra were recorded on a JEOL PS-100 instrument at 100 MHz in the continuous wave mode on a Bruker WP-80 instrument at 80 MHz and on a Bruker WM-250 instrument at 250 MHz in the Fourier transform mode. As internal standard tetramethylsilane (TMS) was used for $CDCl_3$ solutions and 3-(trimethylsilyl)[$^2H_4$]propionic acid sodium salt (TSS) for D_2O solutions. ^{13}C N.m.r. spectra were recorded on a Bruker WP-80 instrument at 20.115 MHz, in saturated solutions using TMS as internal reference. The temperature dependence of the spectrum was studied in 15% CD_3OD solution at 25 MHz on a JEOL FX instrument.

X-*Ray Analysis of* (−)-*Deprenyl*·HBr.—$C_{13}H_{17}N$·HBr, M = 268.20, orthorhombic, a = 7.266(2), b = 10.171(3), c = 18.360(2) Å, V = 1 357 Å^3, Z = 4, D_c = 1.31 g cm^{-3}, space group $P2_12_12_1$. Intensities of 1 554 reflections, 1 103 with $I \geqq 2\sigma(I)$ were collected on an Enraf–Nonius CAD-4F diffractometer with graphite-monochromated Cu-K_α radiation (λ = 1.5418 Å), $\omega/2\theta$ scan mode, $2\theta_{max}$ = 150°, $h,k,l \geqq 0$ from a cubic crystal with an approximate dimension of 0.2 mm. No decay was observed during the exposure (3 check reflections). Cell constants were determined by least squares from the setting angles of 25 centred reflections. The structure was determined by the usual heavy-atom techniques after location of the Br atom from the Patterson map (R = 0.30). Full-matrix least squares refinement of the positional and anisotropic vibrational parameters of non-hydrogen atoms resulted in R = 0.055. The hydrogen atom positions (except of HN) were generated from observed geometries and checked then in a difference electron density map in which the co-ordinates of the NH atom could also be determined. Both enantiomers were refined; refinement for (*S*)-enantiomer concluded at R = 0.046, R_w 0.057, while the (*R*)-enantioner could be further refined to R = 0.029, R_w = 0.032 for 1 103 reflections. Accordingly, in (−)-deprenyl·HBr the configuration of C(4) is *R*. The other enantiomer could be

rejected at a significance level much lower than 0.005. R_w is defined as $[\Sigma\Delta^2/\Sigma wF_o^2]^{\frac{1}{2}}$ where $w = [\sigma(F) + 0.01F^2]^{-1}$.

X-*Ray Analysis of* (−)-*Deprenyl*·HCl.—$C_{13}H_{17}N$·HCl, $M = 223.75$, orthorhombic, $a = 7.108(1)$, $b = 9.880(1)$, $c = 18.558(1)$ Å, $V = 1\,303$ Å^3, $Z = 4$, $D_c = 1.140$ g cm^{-3}, space group $P2_12_12_1$. Intensities of 2 169 reflections, 1 547 with $I \geqq 3\sigma(I)$ were collected on an Enraf–Nonius CAD-4F diffractometer with graphite-monochromated Mo-K_α radiation ($\lambda = 0.7107$ Å), $\omega/2\theta$ scan mode, $2\theta_{max} = 25°$, $h,k,l \geqq 0$ from a cubic crystal with an approximate dimension of 0.3 mm. No decay was observed during the exposure (three check reflections). Cell constants were determined by least squares from the setting angles of 25 centred reflections.

The structure of the HCl salt was obtained from the isomorphism of the two salts ($R = 0.44$). Full-matrix refinement of the positional and anisotropic vibrational parameters of the non-hydrogen atoms resulted in $R = 0.065$. All hydrogen atoms could be located from a difference electron density map and were included isotropically in the final refinement cycles. At this stage the reliability values were calculated for both enantiomers: (*R*)-enantiomer, $R = 0.044$, $R_w = 0.071$; (*S*)-enantiomer, $R = 0.045$, $R_w = 0.073$. The (*R*)-enantiomer could be refined to $R = 0.035$, $R_w = 0.047$ for 1 547 reflections.

Scattering factors and anomalous dispersion coefficients were taken from ref. 23. No absorption correction was applied in either case. All calculations were performed on a PDP 11/34 (64K) computer with an Enraf–Nonius SDP-34 system with some local modifications. Atomic co-ordinates for the two salts are given in Table 5. Anisotropic thermal parameters for non-hydrogen atoms are deposited as Supplementary Publication No. SUP 56365 (4 pp.).*

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* For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1986, Issue 1.

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