

CRYSTAL AND MOLECULAR STRUCTURE OF HEPTACAIN HYDROCHLORIDE

František PAVELČÍK^a, Milan REMKO^b, Jozef ČIŽMÁRIK^b and Jaroslav MAJER^a

^a Department of Analytical Chemistry and

^b Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Comenius University, 832 32 Bratislava

Received January 2nd, 1985

The crystal and molecular structure of heptacain hydrochloride was determined from three-dimensional diffractometric data. The carbamate group was found to be rotated out of the benzene ring plane by 15.5°, whilst the piperidine ring is in a more stable chair conformation. The heptyloxy side chain is in a stable *all-trans* conformation. The structure was refined by the full matrix least-squares method to a final *R* value 0.1127 for the observed reflections.

1-[2-(2-Heptyloxyphenylcarbamoyloxy)ethyl]piperidinium chloride (heptacain hydrochloride) is a new Czechoslovak drug characteristic of considerable local-anaesthetic^{1,2} and antiarrhythmic effects³.

Our preceding papers concerned the stereochemical arrangement and electronic distribution of some basic esters of phenylcarbamic acid⁴⁻⁸ employing the quantum-chemical methods. Furthermore, the interaction of local anaesthetics with association loci in the biological membrane was studied in detail experimentally⁹ and theoretically¹⁰⁻¹⁴. This paper concerns the X-ray study of heptacain hydrochloride aiming to determine its crystal and molecular structure.

EXPERIMENTAL

Monocrystals of heptacain hydrochloride were separated from its chloroform solution by diffusion of benzene vapours. The plate-like crystal had approximate dimensions 0.8 . 0.35 . 0.09 mm. Its density was measured by a flotation method in the mixture consisting of tetrachloromethane and benzene. The preliminary lattice parameters and the symmetry were determined photographically on a Weissenberg goniometer. The systematic absences $h0l$ for $l = 2n + 1$ and $0k0$ for $k = 2n + 1$ unequivocally showed the space group $P2_1/c$. The lattice parameters were refined on a four-circle diffractometer $P2_1$ (Syntex) from diffraction angles of ten exactly centered reflections.

$a = 1.7097(40)$ nm	$V = 2.277(10)$ nm ³
$b = 1.1597(40)$ nm	$Z = 4$
$c = 1.1599(20)$ nm	$C_{21}H_{35}N_2O_3Cl$
$\beta = 98.11(20)^\circ$	$M_r = 399.0$
monoclinic	$\mu(\text{Mo } K_\alpha) = 1.52 \text{ cm}^{-1}$
$P2_1/c$	$D_o = 1.18(2) \text{ g cm}^{-3}$
$F(000) = 864$	$D_c = 1.16 \text{ g cm}^{-3}$

The integral intensities were measured with a graphite monochromator and Mo K_{α} radiation. The intensities were collected by a $\theta - 2\theta$ scan technique in the $0 < 2\theta \leq 50^{\circ}$ interval. The scan speed was changing in the $4.88 - 29.3^{\circ} \text{ min}^{-1}$ interval for the scan range starting at 1° below the calculated value for K_{α_1} and ending at 1° above the calculated value for K_{α_2} . The background was recorded at the end of each scan for a half of the scan reflection time. Two standard reflections scanned after each 98th measurement showed that no correction for the crystal decomposition or instrumental instability should be made.

Totally 4012 reflections were measured and after elimination of systematically absent and averaging equivalent reflections, the 3572 independent reflections were obtained 1643 of which with $|F| < 4\sigma(F)$ were considered as observed. The intensities were corrected for empirical absorption correction using the data from ψ scan.

STRUCTURE SOLUTION AND RESULTS

The structure was solved by "black box" direct methods of the SHELX76 program¹⁵ and completed with weighted Fourier syntheses of electron density. The structure was refined by the full matrix least-squares method. Positional and anisotropic temperature parameters for non-

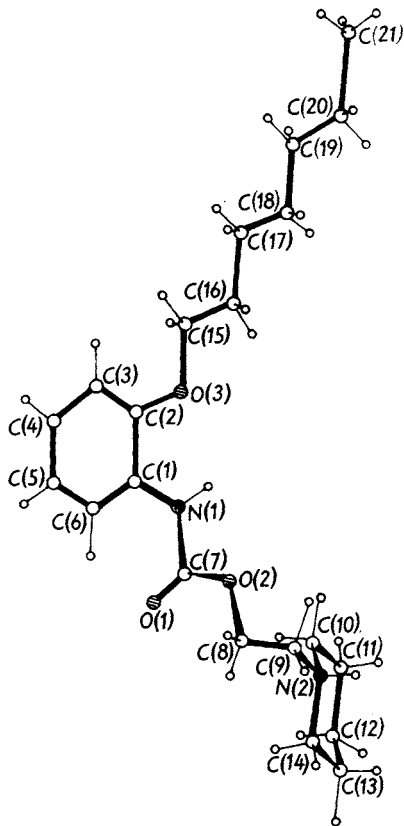


FIG. 1
Drawing of the heptacain molecule and the atomic numbering scheme

hydrogen atoms were refined. Hydrogen atoms in the calculated positions were employed for calculation of structure factors: only the overall isotropic temperature parameter of hydrogen atoms was refined. The function minimized was $\sum w(|F_o| - |F_c|)^2$ using the weighting scheme $w^{-1} = \sigma^2(F) + 0.0003 \cdot |F|^2$. The atomic scattering curves for neutral atoms¹⁶ were employed for calculation. The maximum shift in the least-square to *esd* ratio was found to be 0.2. The maximum residual electron density was 570 e nm^{-3} in proximity of the Cl atom. The final *R* value, where $R = \sum |\Delta F| / \sum |F_o|$ was 0.1127 and the weighted *wR* parameter value, where $wR = [\sum w|\Delta F|^2 / \sum w|F_o|^2]^{1/2}$ was 0.0925 for the observed reflections.

The refined positional parameters for the non-hydrogen atoms are presented in Table I, the anisotropic temperature parameters in Table II, the interatomic distances, angles and torsion angles in Table III. The perspective drawing of the molecule under study is shown in Fig. 1.

TABLE I

Final atomic coordinates ($\cdot 10^4$) for non-hydrogen atoms. Estimated standard deviations are given in parentheses

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
Cl(1)	5 517(2)	538(2)	-2 326(2)
O(1)	6 846(5)	527(6)	1 817(5)
O(2)	6 349(4)	2 174(5)	929(5)
O(3)	7 914(4)	3 978(6)	3 756(5)
N(1)	7 107(4)	2 321(6)	2 626(5)
N(2)	4 755(5)	2 688(6)	-713(5)
C(1)	7 550(6)	2 024(9)	3 736(7)
C(2)	7 982(6)	2 941(9)	4 310(7)
C(3)	8 395(6)	2 743(9)	5 414(7)
C(4)	8 412(6)	1 672(10)	5 900(8)
C(5)	7 990(6)	776(10)	5 320(8)
C(6)	7 567(6)	963(9)	4 204(7)
C(7)	6 788(6)	1 531(9)	1 789(8)
C(8)	5 950(6)	1 457(7)	-8(7)
C(9)	5 524(6)	2 277(8)	-912(7)
C(10)	4 768(6)	3 340(7)	436(6)
C(11)	3 978(7)	3 855(8)	491(7)
C(12)	3 321(7)	2 973(9)	386(8)
C(13)	3 330(7)	2 287(9)	-764(8)
C(14)	4 136(7)	1 799(9)	-825(7)
C(15)	8 357(7)	4 929(8)	4 287(8)
C(16)	8 260(7)	5 928(8)	3 468(7)
C(17)	8 753(6)	6 956(9)	3 927(7)
C(18)	8 703(7)	7 956(9)	3 087(8)
C(19)	9 239(6)	8 931(9)	3 536(8)
C(20)	9 237(7)	9 926(9)	2 655(8)
C(21)	9 705(8)	10 955(10)	3 155(9)

All calculations were carried out on an EC-1033 computer with SHELX76 program. Tables of observed and calculated structure factors are available from the authors on request.

DISCUSSION

Heptacain hydrochloride molecules exist in their ionized forms. Nitrogen atom of the tertiary amine N(2) is protonized with HCl.

As far as the structural feature is considered, the spatial arrangement of the main chain bearing the piperidine ring and that of the side aliphatic chain with respect to the aromatic ring are of interest. The N—H fragment of the carbamate grouping

TABLE II

Coefficients of anisotropic temperature factors ($\cdot 10^4$). Estimated deviations are given in parentheses. The temperature factor is of the form $T = \exp[-2\pi^2(U_{11}a^2h^2 + \dots + 2U_{12}a*b*hk)]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1(1)	1 752(32)	651(19)	356(13)	--107(14)	--117(16)	53(23)
O(1)	1 358(74)	505(47)	624(43)	--44(43)	--328(44)	7(54)
O(2)	962(57)	467(43)	512(37)	--26(33)	--333(38)	--7(41)
O(3)	1 173(66)	647(49)	448(37)	20(37)	--219(40)	--96(49)
N(1)	985(70)	440(51)	419(40)	50(37)	--254(45)	33(50)
N(2)	757(67)	572(56)	285(39)	--8(38)	--214(43)	74(59)
C(1)	765(86)	595(72)	465(56)	--2(56)	--170(58)	--28(68)
C(2)	1 015(95)	648(78)	355(52)	48(56)	--129(59)	--85(73)
C(3)	1 230(102)	670(81)	396(56)	--90(57)	--294(62)	40(76)
C(4)	889(94)	850(91)	519(63)	117(65)	--243(62)	67(78)
C(5)	1 092(104)	757(85)	597(67)	241(62)	--94(69)	--82(79)
C(6)	1 102(98)	550(74)	498(61)	35(54)	--178(63)	29(71)
C(7)	826(90)	440(67)	540(63)	6(60)	--145(61)	--92(72)
C(8)	877(84)	504(64)	561(57)	--93(51)	--312(60)	--70(63)
C(9)	694(86)	719(80)	447(56)	--54(53)	--156(60)	165(70)
C(10)	949(93)	495(66)	288(47)	15(46)	--155(57)	64(67)
C(11)	949(96)	586(72)	443(57)	3(53)	--82(63)	78(79)
C(12)	903(98)	738(84)	716(71)	33(67)	38(70)	59(77)
C(13)	793(93)	694(82)	747(74)	23(63)	--185(70)	--133(75)
C(14)	830(93)	710(82)	479(58)	--68(54)	--248(63)	--52(79)
C(15)	1 387(117)	543(70)	578(64)	--119(59)	--239(70)	--81(78)
C(16)	1 198(104)	646(79)	515(59)	4(57)	--159(66)	14(75)
C(17)	1 088(101)	670(77)	535(62)	--80(60)	--143(65)	--46(74)
C(18)	1 103(101)	729(81)	569(62)	41(64)	--191(68)	50(79)
C(19)	892(90)	826(86)	527(60)	112(63)	--50(61)	5(77)
C(20)	1 165(115)	839(85)	649(69)	35(66)	--214(71)	--193(81)
C(21)	1 215(117)	1 138(117)	828(82)	370(84)	--217(77)	--259(102)

is rotated out of the benzene ring plane by 15.5°. This value well corresponds with theoretical calculations for a simpler model compound — methyl 2-methoxyphenyl-carbamate (I). The PCILO calculations of this compound^{4,5} afforded the value 30°,

TABLE III

Interatomic distances (nm), bond angles (°), and torsion angles (°) with standard deviations in parentheses

Interatomic distances			
C(1)—C(2)	0.1407(11)	C(10)—C(11)	0.1486(11)
C(1)—C(6)	0.1344(11)	C(10)—N(2)	0.1529(9)
C(1)—N(1)	0.1440(9)	C(11)—C(12)	0.1513(12)
C(2)—C(3)	0.1391(10)	C(12)—C(13)	0.1554(12)
C(2)—O(3)	0.1361(10)	C(13)—C(14)	0.1500(12)
C(3)—C(4)	0.1363(12)	C(14)—N(2)	0.1470(11)
C(4)—C(5)	0.1385(12)	C(15)—C(16)	0.1492(11)
C(5)—C(6)	0.1407(11)	C(15)—O(3)	0.1428(9)
C(7)—N(1)	0.1389(10)	C(16)—C(17)	0.1514(11)
C(7)—O(1)	0.1169(10)	C(17)—C(18)	0.1509(11)
C(7)—O(2)	0.1379(10)	C(18)—C(19)	0.1502(11)
C(8)—C(9)	0.1523(10)	C(19)—C(20)	0.1541(12)
C(8)—O(2)	0.1459(8)	C(20)—C(21)	0.1506(12)
C(9)—N(2)	0.1448(10)		

Bond angles			
C(2)—C(1)—C(6)	121.4(8)	C(10)—C(11)—C(12)	113.2(9)
C(2)—C(1)—N(1)	114.7(9)	C(11)—C(12)—C(13)	108.5(8)
C(6)—C(1)—N(1)	124.0(9)	C(12)—C(13)—C(14)	110.8(8)
C(1)—C(2)—C(3)	118.4(9)	C(13)—C(14)—N(2)	112.7(9)
C(1)—C(2)—O(3)	116.1(8)	C(16)—C(15)—O(3)	108.7(7)
C(3)—C(2)—O(3)	125.4(9)	C(15)—C(16)—C(17)	112.4(8)
C(2)—C(3)—C(4)	120.6(10)	C(16)—C(17)—C(18)	113.6(8)
C(3)—C(4)—C(5)	120.2(9)	C(17)—C(18)—C(19)	112.3(8)
C(4)—C(5)—C(6)	119.7(10)	C(18)—C(19)—C(20)	113.0(8)
C(1)—C(6)—C(5)	119.5(9)	C(19)—C(20)—C(21)	112.7(8)
N(1)—C(7)—O(1)	127.9(9)	C(1)—N(1)—C(7)	124.9(8)
N(1)—C(7)—O(2)	105.6(8)	C(9)—N(2)—C(10)	113.6(7)
O(1)—C(7)—O(2)	126.4(9)	C(9)—N(2)—C(14)	114.4(8)
C(9)—C(8)—O(2)	106.6(7)	C(10)—N(2)—C(14)	110.2(7)
C(8)—C(9)—N(2)	117.0(8)	C(7)—O(2)—C(8)	112.3(6)
C(11)—C(10)—N(2)	109.6(7)	C(2)—O(3)—C(15)	118.3(7)

TABLE III
(Continued)

Torsion angles

C(21) - C(20) - C(19) - C(18)	173·8(10)
C(20) - C(19) - C(18) - C(17)	176·2(9)
C(19) - C(18) - C(17) - C(16)	-176·3(9)
C(18) - C(17) - C(16) - C(15)	176·7(9)
C(17) - C(16) - C(15) - O(3)	-176·3(8)
C(16) - C(15) - O(3) - C(2)	173·8(8)
C(15) - O(3) - C(2) - C(1)	-178·4(9)
O(3) - C(2) - C(1) - N(1)	1·1(12)
C(2) - C(1) - N(1) - C(7)	164·5(9)
C(1) - N(1) - C(7) - O(1)	-3·1(16)
C(1) - N(1) - C(7) - O(2)	174·0(8)
N(1) - C(7) - O(2) - C(8)	-178·2(7)
O(1) - C(7) - O(2) - C(8)	-1·0(14)
C(7) - O(2) - C(8) - C(9)	-177·5(8)
O(2) - C(8) - C(9) - N(2)	-83·6(9)
C(8) - C(9) - N(2) - C(10)	59·2(10)
C(8) - C(9) - N(2) - C(14)	-68·6(9)
C(9) - N(2) - C(10) - C(11)	172·7(7)
N(2) - C(10) - C(11) - C(12)	58·3(9)
C(10) - C(11) - C(12) - C(13)	-56·0(10)
C(11) - C(12) - C(13) - C(14)	53·3(11)
C(12) - C(13) - C(14) - N(2)	-56·5(10)
C(13) - C(14) - N(2) - C(10)	57·9(8)
C(14) - N(2) - C(10) - C(11)	-57·4(8)

and the *ab initio* calculations⁷ 0°; nevertheless, considering the very flat energetic profile the anticipated arbitrary angle can be in the $\pm 20^\circ$ interval⁷. A little higher value (36·5°) of the carbamate group rotation out of the benzene ring plane was found for ethyl 2-[(2-hydroxy-3-isopropylamino)propoxy]carbanilate hydrochloride by X-ray analysis¹⁷. The carbamate N—H group is in a *cis* position in regard to oxygen O(3) as a result of a weak intramolecular hydrogen bonding, stabilizing the *cis* isomer towards the *trans* one. The carbamate group itself is not planar with a very little deviation from planarity (the dihedral angle C(1)—N(1)—C(7)—O(2) = -3·1°). Similarly, the *ab initio* and PCILO calculations^{4,5,7} for model *I* also showed the most stable conformers to be *cis* with an intramolecular hydrogen bonding N(1)—H...O(3). According to PCILO calculations^{4,5}, the deviation from planarity in *I* was a little greater (5—10°).

Considering conformation around C(7)—O(2) and C(2)—C(8) bonds, the cation requires a *trans* arrangement. On the other hand, conformation around the C(8)—C(9) bond is close to *gauche* arrangement of the O(2)—C(8)—C(9)—N(2) fragment with a dihedral angle -83.6° . Value -70.2° was found for this dihedral angle in the structurally close O—C—C—N fragment of procain hydrochloride¹⁸. The *gauche* conformation is like presumed around the C(9)—N(2) bond. The piperidine ring was found in the more stable chair conformation similarly as with the simple unsubstituted piperidine cation¹⁹. The heptyloxy side chain is in *all-trans* form, the *O*-alkoxy group lies virtually in the benzene ring plane.

The crystal structure is bound together by ionic and van der Waals forces. A strong hydrogen bonding exists between the chlorine anion and hydrogen of the piperidine nitrogen with the distance Cl(1)...N(2) = 0.3053(11) nm.

REFERENCES

1. Čižmárik J., Borovanský A., Švcc P.: Acta Fac. Pharm. Univ. Comenianae 29, 53 (1976)
2. Čižmárik J., Borovanský A., Švcc P.: Pharmazie 33, 297 (1978).
3. Kozlovský J., Čižmárik J., Pešák M., Inczinger F., Borovanský A.: Arzneim.-Forsch. 32, 1032 (1982).
4. Remko M., Čižmárik J.: Eur. J. Med. Chem. 15, 556 (1980).
5. Remko M., Frecer V., Čižmárik J.: Arch. Pharm. (Weinheim) 316, 9 (1983).
6. Remko M., Sekerka I., van Duijnen P. Th.: Arch. Pharm. (Weinheim) 317, 45 (1984).
7. Remko M., van Duijnen P. Th.: J. Mol. Struct., Theocchem. 105, 1 (1983).
8. Remko M., Čižmárik J.: Acta Fac. Pharm. Univ. Comenianae, in press.
9. Remko M., Liptaj T., Veselovská J., Čižmárik J.: This Journal 49, 1695 (1984).
10. Remko M., Frecer V., Čižmárik J.: This Journal 48, 533 (1983).
11. Remko M., van Duijnen P. Th.: J. Mol. Struct., Theocchem. 104, 451 (1983).
12. Remko M., Čižmárik J.: Acta Fac. Pharm. Univ. Comenianae, in press.
13. Remko M., van Duijnen P. Th., Sekerka I., Čižmárik J.: Proceedings of Symposium *Pharmacological Stabilization of Excitable Membranes*, p. 55. Smolenice, Czechoslovakia 1984.
14. Remko M., Sekerka I., Čižmárik J.: Unpublished results.
15. Sheldrick G. M.: Program SHELX76. Cambridge University, England 1978.
16. *International Tables for X-ray Crystallography*, Vol. IV. Kynoch Press, Birmingham 1974.
17. Kettmann V., Majer J., Csöllei J.: Farm. Obzor 52, 539 (1983).
18. Dexter D. D.: Acta Crystallogr. B 28, 77 (1972).
19. Sutton L. E., Ed.: *Configuration in Molecules and Ions*, Spcc. Publ. No 18. The Chemical Society, London 1965.

Translated by Z. Votický.