Stereochemical Studies. Part 29.† Crystal Structure of 2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinolinium Iodide

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The structure of the title compound has been established by *X*-ray crystallography from diffractometer data. Crystals are orthorhombic, space group *Pbca*, cell dimensions *a* = 33.443(10), *b* = 9.654(4), *c* = 13.991(5) Å, *Z* = 8. The structure was solved by Patterson and Fourier techniques and refined by least-squares calculation to *R* 0.036 for 1 875 observed reflections. Ring A is in the half-chair conformation. The 1-phenyl and 2-benzyl substituents are *trans* diaxial, which has only partly corroborated the conclusion (*trans* diequatorial) inferred from ^{1}H n.m.r. studies. The nitrogen atom maintains an almost regular tetrahedron formed by four polarized C(sp^3)–N$^+$(sp^3) single bonds (mean 1.532 Å). Geometry of the molecule resembles that of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4-methylenedioxyphenyl)isoquinoline (cryptostyline *I*) methiodide.

THE selectivity of the quaternization of 1,2-disubstituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines has been studied previously by chemical methods and n.m.r. spectroscopy.[1-5] The quaternization of 1-phenyl-, 1-isopropyl-, and 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines with benzyl iodide yielded, within the limits of n.m.r. evaluation (±5%), always only one isomer (denoted by us [5] as isomer *A*). On the contrary, the quaternization of 2-benzyl bases with methyl iodide, besides *A* isomers, furnished other quaternary salts (*B* isomers), also. On the basis of an equilibration experiment [3,6] in chloroform, the *A* isomers proved to be the more stable.

^{1}H N.m.r. investigations of the quaternary salts, in accordance with the equilibrium experiments, revealed that in the predominant *A* isomers the substituents in position 1 and the benzyl group entering into the quaternization reaction are in the *trans* position. The tertiary salt 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinolinium trifluoroacetate proved to be a mixture of two isomers and the spin–spin coupling constant between C-1H and N$^+$–H protons was 6.0 and 2.5 Hz in the more and the less stable isomers, respectively.[5] Assuming that the 1,2-protons in the most stable isomer are 1-pseudo-axial and 2-axial, it followed that the 1,2-substituents had to be pseudoequatorial-equatorial. Nevertheless, we mentioned [7] that the ' stereochemistry of the quaternary salts, particularly the actual orientation of the substituents in position 1 relative to the isoquinoline moiety obviously needs further confirmation'. For this reason an *X*-ray analysis of the title compound (Figure 1) has been performed.

EXPERIMENTAL

Cell dimensions were measured from Weissenberg photographs taken with Ni-filtered Cu-$K_{\bar{\alpha}}$ (1.541 8 Å) radiation and were refined by single-crystal diffractometry.

Crystal Data.—$C_{25}H_{28}NO_2I$, M = 501.41. Orthorhombic, a = 33.443(10), b = 9.654(4), c = 13.991(5) Å, D_c = 1.474, Z = 8, D_m = 1.49 g cm^{-3} (by flotation). Space group *Pbca* (No. 61) from systematic absences. Mo-$K_{\bar{\alpha}}$ radiation, λ = 0.710 7 Å; μ(Mo-$K_{\bar{\alpha}}$) = 14.84 cm^{-1}.

Intensity data were collected on a Philips PW 1100 computer-controlled four-circle diffractometer with graphite-monochromated Mo-$K_{\bar{\alpha}}$ radiation. The crystal

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† Part 28, G. Bernáth and L. Gera, *Tetrahedron Letters*, 1976, 1615.

[1] G. Bernáth, J. Kóbor, K. Koczka, L. Radics, and M. Kajtár, *Tetrahedron Letters*, 1968, 225.

[2] G. Bernáth, K. Koczka, J. Kóbor, L. Radics, and M. Kajtár, *Acta Chim.* (*Budapest*), 1968, **55**, 331.

[3] J. Kóbor, G. Bernáth, L. Radics, and M. Kajtár, *Acta Chim.* (*Budapest*), 1969, **60**, 255.

[4] J. Volford, G. Tóth, G. Bernáth, and J. Kóbor, *Tetrahedron Letters*, 1971, 4019.

[5] L. Radics, M. Kajtár, J. Kóbor, and G. Bernáth, *Acta Chim.* (*Budapest*), 1969, **60**, 381.

[6] J. McKenna, J. M. McKenna, and J. White, *J. Chem. Soc.*, 1965, 1733.

[7] *Cf.* ref. 5, p. 393.

used was 0.08 × 0.22 × 0.27 mm. Data were not corrected for absorption. After data reduction 42 out of the 1 917 independent reflections with $F_o < 3\sigma(F_o)$ were considered unobserved.

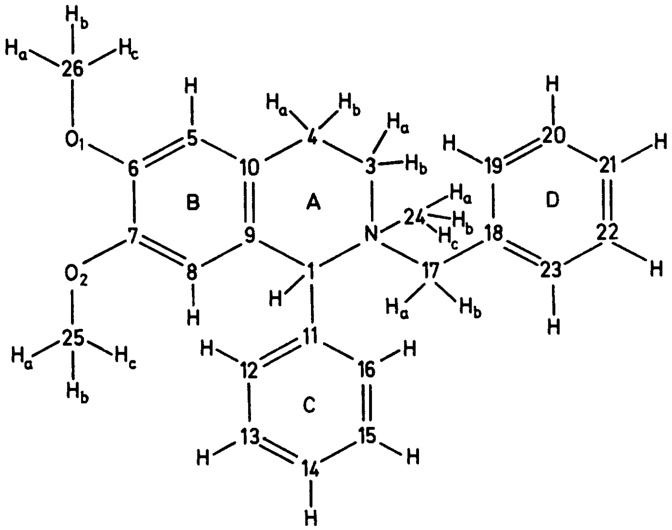

Figure 1 Atomic numbering of the title compound. Atoms are carbon unless indicated otherwise, and hydrogen atoms are numbered according to the carbon atoms to which they are linked

Solution and Refinement of the Structure.—Fractional co-ordinates of I atom were determined by Patterson method. The iodine contribution alone gave R 0.365. Two successive cycles of structure-factor and Fourier calculations revealed the positions of all non-hydrogen atoms. At this stage R was 0.260. The structure was refined by block-diagonal least-squares calculations. The function minimized was $\phi = \sum_h w(|F_o| - \frac{1}{G}\,|F_c|)^2$, with the weighting scheme[8] $w = (11.0 + F_o + 0.002F_o^2)^{-1}$. Three cycles of refinement with isotropic thermal parameters reduced R to 0.14. In order to increase the ratio between the number of reflections and the atomic parameters refined in an anisotropic cycle, atoms were arranged in two groups with fourteen and fifteen atoms in each. Three cycles of refinement with anisotropic thermal parameters for each group reduced R to 0.058. At this stage the positions of 18 hydrogen atoms were calculated geometrically, while the missing 10 hydrogen atoms were located from a difference map. Three further cycles of anisotropic refinement of the non-hydrogen atoms, with hydrogen atoms treated isotropically gave a final residual of 0.036 for the 1 875 observed reflections. Atomic scattering factors for all atoms were taken from ref. 9. All calculations were performed on a Varian 73 computer at the University of Novi Sad. Observed and calculated structure factors and anisotropic thermal parameters, and approximate hydrogen atom

Table 1

Final fractional co-ordinates (× 10^4) for non-hydrogen atoms, with estimated standard deviations in parentheses

	x	*y*	*z*
I	8 947(1)	9 619(1)	9 824(1)
O(1)	2 573(2)	4 269(6)	2 031(4)
O(2)	2 458(2)	2 612(6)	3 469(4)
N	4 201(2)	4 003(6)	4 427(4)
C(1)	3 778(2)	3 618(8)	4 826(5)
C(3)	4 201(2)	5 463(8)	4 030(6)
C(4)	3 906(2)	5 630(8)	3 221(7)
C(5)	3 231(2)	4 924(7)	2 596(6)
C(6)	2 880(3)	4 176(8)	2 674(6)
C(7)	2 818(2)	3 291(8)	3 435(6)
C(8)	3 121(2)	3 100(8)	4 117(5)
C(9)	3 479(2)	3 860(8)	4 036(5)
C(10)	3 531(2)	4 770(8)	3 292(6)
C(11)	3 671(2)	4 369(7)	5 721(5)
C(12)	3 540(2)	5 745(8)	5 727(5)
C(13)	3 414(2)	6 338(8)	6 574(6)
C(14)	3 420(2)	5 623(8)	7 419(6)
C(15)	3 552(2)	4 249(9)	7 407(5)
C(16)	3 675(2)	3 645(7)	6 579(5)
C(17)	4 313(2)	2 901(7)	3 682(5)
C(18)	4 717(2)	3 156(7)	3 185(5)
C(19)	5 071(2)	2 685(7)	3 589(6)
C(20)	5 435(2)	2 926(8)	3 117(6)
C(21)	5 445(2)	3 577(8)	2 262(7)
C(22)	5 091(2)	3 999(9)	1 828(6)
C(23)	4 731(2)	3 778(8)	2 297(5)
C(24)	4 497(2)	3 921(8)	5 240(5)
C(25)	2 383(3)	1 747(11)	4 260(6)
C(26)	2 574(3)	5 393(10)	1 373(7)

Table 2

Bond lengths (Å) with estimated standard deviations in parentheses

C(1)–N	1.565(10)	C(7)–O(2)	1.372(10)
C(1)–C(9)	1.508(10)	O(2)–C(25)	1.409(11)
C(1)–C(11)	1.491(10)	C(11)–C(12)	1.399(10)
N–C(3)	1.515(10)	C(12)–C(13)	1.380(10)
N–C(17)	1.536(9)	C(13)–C(14)	1.370(11)
N–C(24)	1.511(10)	C(14)–C(15)	1.398(11)
C(3)–C(4)	1.510(11)	C(15)–C(16)	1.360(11)
C(4)–C(10)	1.508(11)	C(11)–C(16)	1.390(10)
C(5)–C(10)	1.406(11)	C(17)–C(18)	1.538(10)
C(5)–C(6)	1.381(11)	C(18)–C(19)	1.389(10)
C(6)–C(7)	1.381(11)	C(19)–C(20)	1.403(11)
C(7)–C(8)	1.405(11)	C(20)–C(21)	1.352(12)
C(8)–C(9)	1.408(10)	C(21)–C(22)	1.393(12)
C(9)–C(10)	1.373(10)	C(22)–C(23)	1.386(11)
C(6)–O(1)	1.369(10)	C(23)–C(18)	1.381(10)
O(1)–C(26)	1.423(11)		

Table 3

Bond angles (°) with estimated standard deviations in parentheses

C(1)–N–C(3)	110.6(5)	C(8)–C(9)–C(1)	115.1(6)
C(1)–N–C(17)	107.4(5)	C(1)–C(9)–C(10)	124.8(7)
C(1)–N–C(24)	108.2(5)	C(9)–C(1)–N	107.5(6)
C(3)–N–C(17)	113.3(5)	C(9)–C(1)–C(11)	112.4(6)
C(3)–N–C(24)	108.9(5)	N–C(1)–C(11)	113.7(6)
C(17)–N–C(24)	108.3(5)	C(1)–C(11)–C(12)	122.9(6)
N–C(3)–C(4)	112.0(6)	C(1)–C(11)–C(16)	118.7(5)
C(3)–C(4)–C(10)	115.8(7)	C(12)–C(11)–C(16)	118.3(6)
C(4)–C(10)–C(5)	119.4(7)	C(11)–C(12)–C(13)	119.7(7)
C(4)–C(10)–C(9)	120.5(7)	C(12)–C(13)–C(14)	121.8(7)
C(5)–C(10)–C(9)	120.2(7)	C(13)–C(14)–C(15)	118.2(7)
C(10)–C(5)–C(6)	119.7(7)	C(14)–C(15)–C(16)	120.8(7)
C(5)–C(6)–C(7)	120.8(8)	C(15)–C(16)–C(17)	121.2(7)
C(5)–C(6)–O(1)	123.5(7)	N–C(17)–C(18)	114.2(6)
C(7)–C(6)–O(1)	115.7(7)	C(17)–C(18)–C(19)	120.8(6)
C(6)–O(1)–C(26)	118.2(6)	C(17)–C(18)–C(23)	120.4(6)
C(6)–C(7)–C(8)	119.7(7)	C(19)–C(18)–C(23)	118.6(7)
C(6)–C(7)–O(2)	117.1(7)	C(18)–C(19)–C(20)	119.6(7)
C(8)–C(7)–O(2)	123.2(7)	C(19)–C(20)–C(21)	121.1(7)
C(7)–O(2)–C(25)	117.8(6)	C(20)–C(21)–C(22)	119.9(8)
C(7)–C(8)–C(9)	119.4(7)	C(21)–C(22)–C(23)	119.2(8)
C(8)–C(9)–C(10)	120.1(7)	C(22)–C(23)–C(18)	121.5(7)

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[8] D. W. J. Cruickshank, D. E. Pilling, A. Bujosa, F. M. Lowell, and M. R. Truther, in 'Computing Methods and the Phase Problem in X-Ray Crystal Analysis,' Pergamon, Oxford, 1961.

[9] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

positions are listed in Supplementary Publication No. SUP 21950 (13 pp., 1 microfiche).* Final fractional co-ordinates are given in Table 1, and bond distances and angles in Tables 2 and 3.

DISCUSSION

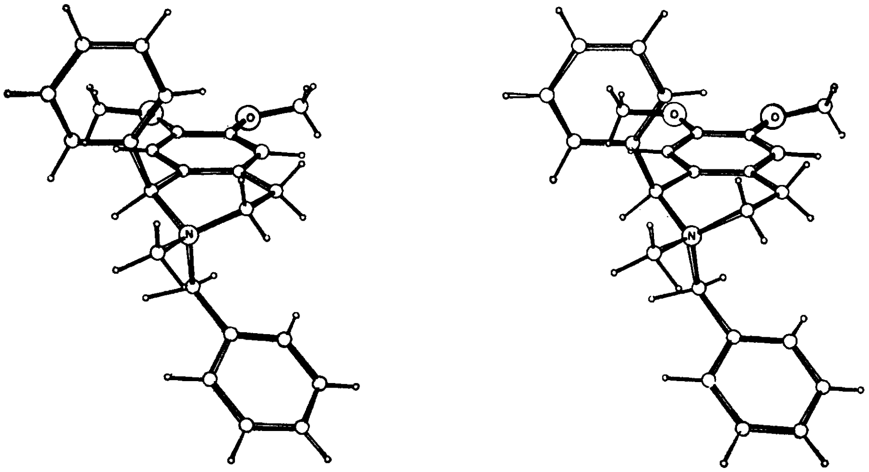

FIGURE 2 An ORTEP stereodrawing with labelled heteroatoms

TABLE 4

Torsion angles (°) in ring A

C(9)–C(1)–N–C(3)	−54.5	C(3)–C(4)–C(10)–C(9)	2.5
C(1)–N–C(3)–C(4)	60.3	C(4)–C(10)–C(9)–C(1)	0.6
N–C(3)–C(4)–C(10)	−33.0	C(10)–C(9)–C(1)–N	25.3

The geometry of the molecule (Figure 2) can best be described in terms of the torsion angles (Table 4), Newman projections (Figure 3) calculated for the atoms of ring A (Figure 1) and the least-squares planes obtained for the atomic moieties as given in Table 5. The characteristic parameters of the molecular geometry are summarized in Figure 4(a). Comparison of these parameters with the corresponding values found in two related compounds [Figures 4(b) and 4(c): 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4-methylenedioxyphenyl)isoquinoline (cryptostyline *I*) methiodide [10] and 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (cryptostyline *II*) hydrobromide [11,12]] shows that the conformation of ring A is quite similar to that of the quaternary salt, Cryptostyline *I* methiodide [Figure 4(b)] but visibly differs from the corresponding one in the tertiary salt, Cryptostyline *II* hydrobromide [Figure 4(c)]. Ring A has a half-chair conformation to which the 1-phenyl and 2-benzyl groups are linked in *trans*-positions as was predicted,[5] but their actual orientations are axial (pseudo-axial and axial, respectively). This contradicts, however, the conclusion inferred from ^1H n.m.r. studies on the corresponding tertiary salts when extended to the quaternized salt pairs concerning the pseudo-equatorial conformation of the 1-phenyl ring and the equatorial one of the 2-benzyl moiety. A ^{13}C n.m.r. study of the quaternary salt pairs in solution and an *X*-ray structure determination of further derivatives *e.g.* of 2-benzyl-1,2,3,4-tetrahydro-1-isopropyl-6,7-dimethoxy-2-methylisoquinolinium iodide might perhaps throw further light upon this contradiction.

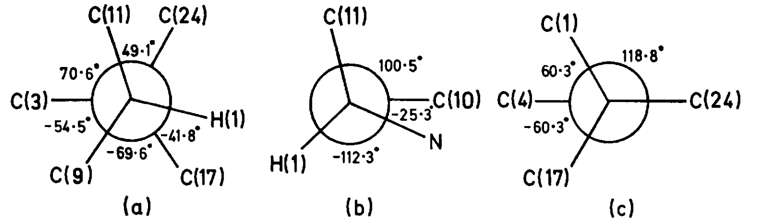

FIGURE 3 Newman projections down the bonds (a) C(1)–N, (b) C(1)–C(9), and (c) N–C(3) in ring A, showing the conformation angles

The aromatic rings B and C are nearly perpendicular to each other (the angle between their normals is 87.2°) while the dihedral angle between the best planes of rings B and D is 30.1° (Table 4). The oxygen atoms of

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* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin II*, 1976, Index issue.

[10] L. Westin, *Acta Chem. Scand.*, 1972, **26**, 2305.

[11] A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1971, **54**, 1564.

[12] J. F. Blount, V. Toome, S. Teitel, and A. Brossi, *Tetrahedron*, 1973, **29**, 31.

the methoxy-groups are displaced only slightly above and below plane (2) while the displacements of C(25) and C(26) from this plane are 0.163 and 0.287 Å. The C(sp^3)–O and C(sp^2)–O mean bond lengths (1.416 and 1.371 Å) are significantly different but agree well with literature data; *cf. e.g.* 1-cyano-6,7-dihydro-9,10-dimethoxy-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline.[13,14]

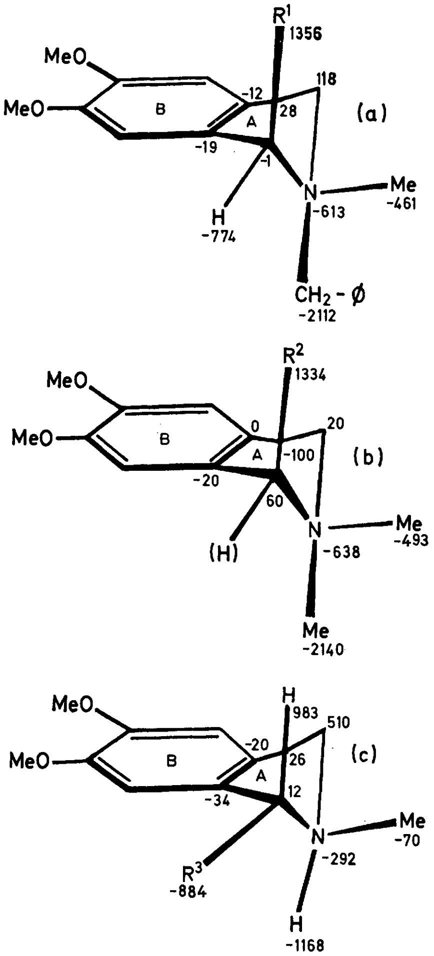

FIGURE 4 Perspective drawing of the geometry of ring A in (a) the title compound, (b) cryptostyline *I* methiodide, and (c) cryptostyline *II* hydrobromide; R^1 = phenyl, R^2 = 3,4-methylenedioxyphenyl, and R^3 = 3,4-dimethoxyphenyl. Values ($10^3 \times$ Å) of atom deviations from the best plane of ring B are given. C(4) atoms are hidden by the vertical bonds from position 1

The nitrogen atom sits in the centre of an almost regular tetrahedron (root-mean-square value for mean bond angle of 109.45° is 0.62°) formed by four polarized C(sp^3)–N$^+$(sp^3) single bonds (mean bond length 1.532 Å). The bond lengths and angles for the isoquinoline moiety are as expected.[15,16] Mean bond lengths in the aromatic rings (B, C, and D) are 1.392, 1.382, and 1.384 Å.

TABLE 5

Equations of best least-squares planes in the form: $lX + mY + nZ = p$, where X, Y, and Z are orthogonal ($10^3 \times$ Å) co-ordinates, and in square brackets deviations (Å) of atoms from the planes

Plane (1): Ring B

$-0.399\,6X + 0.739\,9Y + 0.541\,1Z = 1.168\,6$

[C(5) −4, C(6) −11, C(7) 17, C(8) −9, C(9) −6, C(10) 12, C(1) 20, N −572, C(3) 170, C(4) 71]

Plane (2): C(1), C(4)—(10)

$-0.410\,9X + 0.732\,6Y + 0.542\,6Z = 1.031\,4$

[C(1) −1, C(4) 28, C(5) −18, C(6) −7, C(7) 32, C(8) −3, C(9) −19, C(10) −12, O(1) −5, O(2) 72, N −613, C(3) 118, C(11) 1 356, C(17) −2 112, C(24) −461, C(25) 163, C(26) 287, H(1) −774]

Plane (3): Ring C

$0.934\,3X + 0.312\,0Y + 0.172\,4Z = 14.167\,4$

[C(11) −2, C(12) 4, C(13) −5, C(14) 3, C(15) −1, C(16) 0, C(1) −109]

Plane (4): Ring D

$0.090\,6X + 0.885\,8Y + 0.455\,2Z = 6.134\,9$

[C(18) 21, C(19) −16, C(20) −1, C(21) 14, C(22) −9, C(23) −9, C(17) −3]

Dihedral angles (°) between planes: (1)–(2) 1.0, (1)–(3) 87.2, (1)–(4) 30.1, (2)–(3) 86.4, (2)–(4) 30.8, (3)–(4) 63.9

We thank Gy. Argay for his help in preparing the ORTEP stereodrawing, and the Research Foundation of the Socialist Autonomous Province of Vojvodina (Yugoslavia) for financial support of this work.

[6/1497 *Received, 2nd August*, 1976]

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[14] K. Simon, K. Harsányi, L. Párkányi, and A. Kálmán, to be published.

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[16] R. F. Baggio and S. Baggio, *Cryst. Struct. Comm.*, 1973, **2**, 251.