Crystal Structure and Relative Configuration of (±)-11,12-Dihydroglaziovine. Stereochemistry of Reduced Proaporphines

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The relative configuration of the two asymmetric centres of (±)-11,12-dihydroglaziovine (3) was established by the *X*-ray determination of the crystal and molecular structure of its hydrobromide [a = 14.607(1), b = 17.452(2), c = 13.591(1) Å, Z = 8, space group *Pbca*, orthorhombic, final R 0.036 for 1 343 reflections]. (±)-11,12-Dihydroglaziovine was found to be the 6a*S** : 7a*S** diastereoisomer. The conformations of the four atomic rings present in the molecule are also discussed, and the stereochemistry deduced of a related series of reduced proaporphines.

THE proaporphinic alkaloids (the biogenetic precursors of aporphines) comprise both compounds, such as pronuciferine (1), in which the cyclohexadienone system remains as originated in the biosynthetic procedure, and those (reduced proaporphines) in which such a system is more or less extensively reduced (saturation of one or of both double bonds, reduction of the ketonic group).[1] In the former, the absolute configuration of the sole asymmetric centre (C-6a) is definitely known, in that Cava[2] succeeded in obtaining (*R*)-armepavine (2), having a well established configuration, from pronuciferine (1). However, the configuration of the additional asymmetric centre C-7a, present in the proaporphines with one saturated double-bond in the cyclohexadienone ring, has not yet been established, although efforts have been made to deduce it from c.d.[3] or o.r.d. investigations.[4]

The racemic forms of the two diastereoisomers of dihydroglaziovine, (3) and (4) were recently synthesized.[5] Hence the possibility arose of establishing the relative configuration of the C-6a and C-7a centres in such compounds and consequently the absolute configuration of related natural products.

The crystallographic study was carried out on the hydrobromide of the diastereoisomer which is more easily synthesized. On the basis of these results we suggest the relative configuration of its asymmetric centres is as shown in (3), *i.e.* 6a*S** : 7a*S**, in agreement with the Cahn, Ingold, Prelog convention.[6,7]

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[1] For a recent survey see M. Shamma, 'The Isoquinoline Alkaloids,' Academic Press, New York, 1972, p. 182.

[2] M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buch, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.*, 1968, **33**, 2785.

[3] G. Snatzke and G. Wollenberg, *J. Chem. Soc.* (*C*), 1966, 1681.

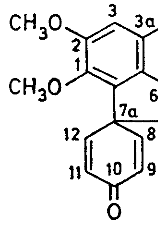
[4] J. Slavík, P. Sedmera and K. Bláha, *Coll. Czec. Chem. Comm.*, 1970, **35**, 1558.

[5] C. Casagrande, L. Canonica, and G. Severini-Ricca, *J.C.S. Perkin I*, 1975, 1652.

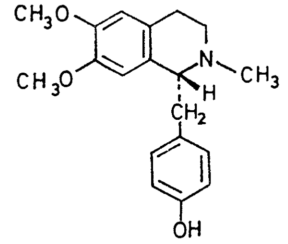
[6] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81.

[7] I.U.P.A.C. 1968, Tentative Rules, Section E, Fundamental Stereochemistry, *J. Org. Chem.*, 1970, **35**, 2849.

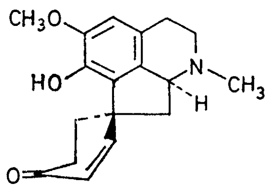
The denomination (±)-11,12-dihydroglaziovine has been suggested for this diastereoisomer.[5]



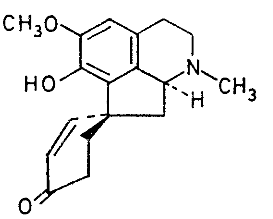
(1)



(2)



(3)



(4)

EXPERIMENTAL

Crystallographic Measurements.—The crystal used for data collection was roughly cubic with edge *ca.* 0.6 mm. Unit-cell parameters and integrated intensities were measured by use of a Philips PW 1100 single-crystal automatic diffractometer, with graphite-monochromated Mo-K_α radiation. Integrated intensities for *hkl* reflections with $h, k, l \geqslant 0$ and $3° < \theta < 22°$ were measured by the ω-scan method with scan speed of $0.03° s^{-1}$, scan width 1.4°, and background count 10 s at the start and finish of each scan. Accurate unit-cell parameters were obtained by a least-squares method from the accurate positioning of 46 strong reflections with $13° < \theta < 18°$.

Crystal Data.—$C_{18}H_{22}BrNO_3$, $M = 308.3$. Orthorhombic, $a = 14.607$ (1), $b = 17.452(2)$, $c = 13.591(1)$ Å, $U = 3\,464.6(3)$ Å^3, $Z = 8$, $D_c = 1.46$ g cm^{-3}, $F(000) = 1\,568$. Mo-K_α radiation, $\lambda = 0.710\,69$ Å; μ(Mo-K_α) $= 25.3$ cm^{-1}. Space group *Pbca* (No. 61).

Structure Determination and Refinement.—Intensities were corrected for Lorentz and polarization effects but not for absorption in view of the crystal size.[8]

The position of the bromine atom was established by the Patterson method. From a subsequent electron-density map, all non-hydrogen atoms were located. After three cycles of block-diagonal-matrix least-squares refinement with unit weights and isotropic thermal parameters, followed by five cycles with anisotropic thermal parameters, *R* for the 1 343 observed reflections dropped to 0.055. A subsequent difference electron-density map revealed 26 peaks ranging from 0.6—0.4 eÅ^{-3}. Of these, 22 were unequivocally attributed to the 22 hydrogen atoms of the molecule, including those of the two methyl groups. Four last cycles of block-diagonal-matrix least-squares refinement, excluding hydrogen atoms from the refinement but not from the structure-factor calculation, further decreased *R* to 0.036 for the 1 343 observed reflections. The final cycle yielded a mean shift-to-error ratio of 0.3 indicating satisfactory convergence of all parameters.

TABLE 1

Non-hydrogen atom fractional co-ordinates (× 10^5 for Br, × 10^4 for others), with estimated standard deviations in parentheses

	x/a	*y/b*	*z/c*
Br	19 179(3)	−10 820(3)	20 513(4)
C(1)	4 070(4)	−1 294(3)	380(4)
C(2)	3 566(4)	−624(3)	−115(3)
C(3)	3 733(3)	146(3)	367(3)
C(4)	3 378(3)	830(3)	1(3)
C(5)	3 444(3)	1 494(3)	558(3)
C(6)	3 844(3)	1 485(3)	1 516(3)
C(7)	4 183(3)	796(3)	1 856(3)
C(8)	4 152(3)	156(2)	1 270(3)
C(9)	4 550(3)	−515(2)	1 786(3)
C(10)	4 475(3)	−283(3)	2 878(3)
C(11)	4 578(3)	596(2)	2 871(3)
C(12)	4 026(3)	933(3)	3 704(3)
C(13)	4 375(4)	1 227(3)	4 519(3)
C(14)	5 369(4)	1 290(3)	4 676(3)
C(15)	5 965(4)	831(3)	3 982(4)
C(16)	5 581(3)	855(3)	2 930(4)
C(17)	4 360(4)	−1 926(3)	1 980(4)
C(18)	2 782(3)	2 273(3)	−696(3)
N	4 029(3)	−1 220(2)	1 493(3)
O(1)	5 677(3)	1 662(3)	5 353(3)
O(2)	3 868(2)	2 124(2)	2 090(2)
O(3)	3 106(3)	2 196(2)	297(2)

TABLE 2

Fractional co-ordinates (× 10^3) for the hydrogen atoms

	x/a	*y/b*	*z/c*
H(1a)	365	−181	35
H(1b)	472	−128	6
H(2a)	370	−61	−85
H(2b)	284	−70	−4
H(4)	296	82	−70
H(9)	528	−69	160
H(10a)	377	−46	309
H(10b)	495	−59	334
H(12)	318	84	363
H(13)	390	153	506
H(15a)	662	113	404
H(15b)	604	27	439
H(16a)	561	140	268
H(16b)	597	46	260
H(17a)	423	−245	186
H(17b)	439	−188	268
H(17c)	500	−219	182
H(18a)	261	283	−79
H(18b)	206	199	−80
H(18c)	329	210	−133
H(19)	365	264	182
H(20)	331	−115	166

The Fourier syntheses were performed with the program of Immirzi based on the Cooley–Tukey algorithm.[9] For the structure-factor calculations scattering factors were taken from ref. 10. In the Tables and in the structural discussion, reference is made to the arbitrary crystallographic atom numbering shown in the Figure. Systematic numbering for the proaporphinic system is indicated in the pronuciferine formula (1).

Table 1 reports the final positional parameters of the non-hydrogen atoms, together with their estimated standard

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[8] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1969.

[9] A. Immirzi, *J. Appl. Cryst.*, 1973, **6**, 246.

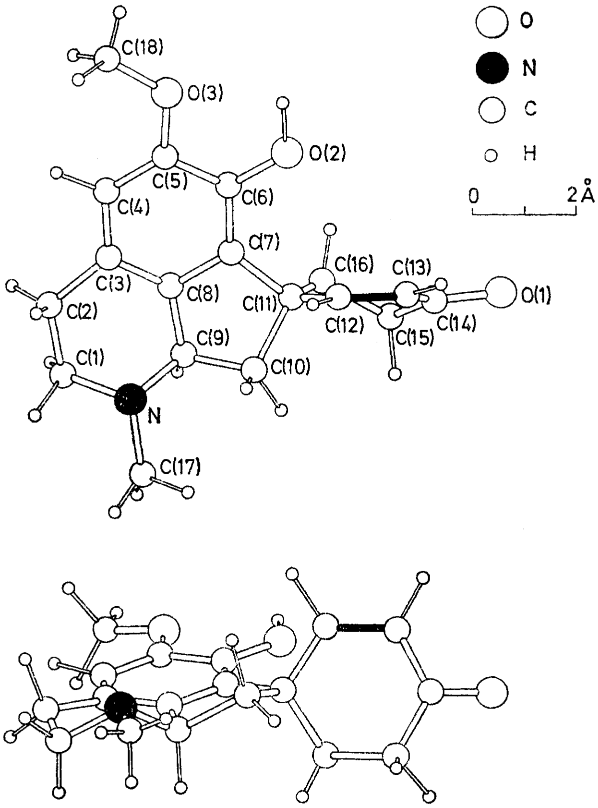
[10] D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **A24**, 321.

deviations. Corresponding anisotropic thermal parameters and final observed and calculated structure factors are deposited in Supplementary Publication No. SUP 21765 (17 pp., 1 microfiche).*

Isotropic thermal factors, equal to the means of the atoms to which they were bonded, were assigned to hydrogen atoms. Hydrogen atom co-ordinates (Table 2) do not considerably differ from those calculated on geometrical grounds. The greatest deviation between experimental and calculated values (0.3 Å) is for a hydrogen atom of a methyl group.

DISCUSSION

The Figure shows one of the two enantiomers (*R* : *R*) of (±)-11,12-dihydroglaziovine obtained from the structural refinement of its hydrobromide. The molecule is shown from two different viewpoints (along two orthogonal non-crystallographic axes), which show the relative configuration of the two asymmetric centres C(9) and C(11); *i.e.* $S^*:S^*$ according to the Cahn, Ingold, Prelog convention.[6,7] In configuration the double bond between C(12) and C(13) of the cyclohexenone ring lies on the opposite side of the hydrogen atom bound to C(9), with respect to the five-membered ring (see also Table 3).



The *R* : *R* enantiomer of (±)-11,12-dihydroglaziovine represented along two mutually orthogonal, non-crystallographic axes. The positional parameters are those resulting from the structural refinement. Arbitrary crystallographic numbering is shown; hydrogen atoms are numbered according to the atom to which they are bonded

TABLE 3

Deviations (Å) of relevant atoms from least-squares planes

Plane (I): Cyclohexenone ring, C(11)—(14), O(1)

[C(11) −0.011, C(12) −0.034, C(13) 0.035, C(14) 0.075, C(15) 0.377, C(16) −0.334, O(1) −0.065]

Plane (II): Cyclopentane ring, C(7)—9, C(11)

[C(7) −0.014, C(8) 0.014, C(9) −0.008, C(10) 0.503, C(11) 0.008, C(12) 0.992, C(13) 0.784, C(15) −1.422, C(16) −1.405, H(9) −1.000]

Plane (III): Piperidine ring, C(1)—(3), C(8), C(9)

[C(1) −0.050, C(2) 0.072, C(3) −0.050, C(8) 0.001, C(9) 0.027, N 0.700]

Plane (IV): Benzene ring, C(3)—(8)

[C(2) 0.253, C(3) 0·014, C(4) 0.009, C(5) −0.017, C(6) 0.004, C(7) 0.018, C(8) −0.028, C(9) 0.001, C(11) 0.150, O(2) 0.052, O(3) 0.007, H(19) −0.013]

The methyl group on the nitrogen atom is equatorial, as predicted for a *N*-substituted piperidine ring.[11,12]

On the basis of these results and from chemical correlations already existing or specially established for the absolute configuration of C-6a [C(9)], the complete steric structures of the following reduced proaporphines may also be determined: amuronine [5,13] (6a*S* : 7a*S*) and the corresponding pseudo-equatorial alcohol amuroline [13] (6a*S* : 7a*S* : 10*R*); linearisine [5,14] (6a*S* : 7a*S*); crotsparinine and its *N*-methyl-derivative [15-17] (6a*R* : 7a*S*); isocrotsparinine and its *N*-methyl-derivative [17] (6a*S* : 7a*S*); jacularine [15,18] (6a*R* : 7a*R*); and Base E [17,19] (6a*R* : 7a*R* : 10*R*). The configurations suggested for amuronine and linearisine (both 6a*S* : 7a*R*) by c.d. studies [3] do not agree with our results. This is the reason why the absolute configurations of roemeronine and roemeramine,[4] analogously determined by means of o.r.d., must be re-examined. Table 4 reports bond lengths, relative valency angles and the most significant torsion angles, together with their estimated standard deviations. Bond distances and valency angles are as expected.[20]

Table 3 shows the deviations of the most relevant atoms from the best least-squares planes through the co-planar atoms of the four rings. The conformation of the cyclohexenone ring is a half-chair bent away from O(2). The geometry of the cyclopentane ring is very

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* See Notice to Authors, No. 7, in *J.C.S. Perkin II*, 1975, Index issue.

[11] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ' Conformational Analysis,' Interscience, New York, 1965.

[12] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493.

[13] W. Döpke, H. Flentje, and P. W. Jeffs, *Tetrahedron*, 1968, **24**, 2297.

[14] L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1966, 1676.

[15] D. S. Bhakuni and M. M. Dhar, *Experientia*, 1969, **25**, 354.

[16] D. S. Bhakuni, S. Satish, and M. M. Dhar, *Phytochemistry*, 1970. **9**, 2573.

[17] C. Casagrande, L. Canonica, and G. Severini-Ricca, *J.C.S. Perkin I*, 1975, 1659.

[18] K. L. Stuart, L. J. Haynes, M. Barret, and G. E. M. Husbands, *Tetrahedron Letters*, 1968, 4473.

[19] L. J. Haynes, G. E. M. Husbands, and K. L. Stuart, *J. Chem. Soc.* (*C*), 1966, 1680.

[20] ' Molecular Structures and Dimensions,' Vol. A1, Internat. Union Crystallography, 1972.

close to the so called C_s or ' envelope ' form, which is one of the preferred conformations assumed by substituted cyclopentanes among the various possible puckered forms[11,21] [C(10) deviates from Plane (II) by 0.50 Å (Table 3)]. Owing to the constraint of the two adjacent rings, an evident envelope conformation at the nitrogen atom is also assumed by the piperidine ring instead of the more usual chair form.[11,12] The benzene ring is completely planar. The two methyl groups have a conformation very close to the staggered one (see torsion angles, Table 4); furthermore the conformation of the methoxy-group is such that methyl is bent away from the adjacent hydroxy-group.

TABLE 4

Molecular dimensions,* with estimated standard deviations in parentheses

(*a*) Bond distances (Å)

C(1)–C(2)	1.537(7)	C(11)–C(12)	1.510(6)
C(2)–C(3)	1.515(7)	C(12)–C(13)	1.323(7)
C(3)–C(8)	1.372(6)	C(13)–C(14)	1.472(8)
C(8)–C(9)	1.484(6)	C(14)–C(15)	1.513(7)
C(9)–N	1.502(6)	C(15)–C(16)	1.538(7)
N–C(1)	1.519(6)	C(16)–C(11)	1.535(6)
C(3)–C(4)	1.393(7)	C(14)–O(1)	1.213(7)
C(4)–C(5)	1.388(7)	C(6)–O(2)	1.361(6)
C(5)–C(6)	1.428(6)	C(5)–O(3)	1.368(6)
C(6)–C(7)	1.379(6)	O(3)–C(18)	1.436(6)
C(7)–C(8)	1.372(6)	N–C(17)	1.481(7)
C(9)–C(10)	1.543(6)	N–H(20)	1.080(4)
C(10)–C(11)	1.542(6)	Br–H(20)	2.107(1)
C(11)–C(7)	1.535(6)	Br–N	3.184(4)

(*b*) Valency angles (°)

C(1)–C(2)–C(3)	114.1(2)	C(14)–C(15)–C(16)	110.8(2)
C(2)–C(3)–C(8)	118.1(2)	C(15)–C(16)–C(11)	112.9(2)
C(3)–C(8)–C(9)	125.9(2)	C(16)–C(11)–C(12)	110.9(2)
C(8)–C(9)–N	108.9(2)	C(2)–C(3)–C(4)	123.1(2)
C(9)–N–C(1)	108.3(2)	C(6)–C(7)–C(11)	129.3(2)
N–C(1)–C(2)	110.6(2)	C(7)–C(11)–C(16)	109.9(2)
C(3)–C(4)–C(5)	119.6(2)	C(10)–C(11)–C(12)	109.3(2)
C(4)–C(5)–C(6)	121.1(2)	C(10)–C(9)–N	115.7(2)
C(5)–C(6)–C(7)	117.5(2)	C(13)–C(14)–O(1)	121.1(3)
C(6)–C(7)–C(8)	120.2(2)	C(15)–C(14)–O(1)	122.9(3)
C(7)–C(8)–C(3)	123.0(2)	C(5)–C(6)–O(2)	121.6(2)
C(8)–C(3)–C(4)	118.3(2)	C(7)–C(6)–O(2)	120.8(2)
C(7)–C(8)–C(9)	110.8(2)	C(4)–C(5)–O(3)	125.6(2)
C(8)–C(9)–C(10)	102.7(2)	C(6)–C(5)–O(3)	113.2(2)
C(9)–C(10)–C(11)	104.3(2)	C(5)–O(3)–C(18)	116.6(2)
C(10)–C(11)–C(7)	101.3(2)	C(1)–N–C(17)	111.2(2)
C(11)–C(7)–C(8)	110.4(2)	C(9)–N–C(17)	113.4(2)
C(11)–C(12)–C(13)	124.9(3)	C(6)–O(2)–H(19)	120.5(1)
C(12)–C(13)–C(14)	122.1(2)	C(1)–N–H(20)	105.0(2)
C(13)–C(14)–C(15)	115.9(2)	C(9)–N–H(20)	109.8(2)
		C(17)–N–H(20)	108.8(2)

TABLE 4 (*Continued*)

(*c*) Selected torsion angles (°)

(i) Piperidine ring	
C(1)–C(2)–C(3)–C(8)	−12.0
C(2)–C(3)–C(8)–C(9)	6.7
C(3)–C(8)–C(9)–N	−29.8
C(8)–C(9)–N–C(1)	57.1
C(9)–N–C(1)–C(2)	−65.1
N–C(1)–C(2)–C(3)	41.1
(ii) Benzene ring	
C(3)–C(4)–C(5)–C(6)	− 2.0
C(4)–C(5)–C(6)–C(7)	1.5
C(5)–C(6)–C(7)–C(8)	1.9
C(6)–C(7)–C(8)–C(3)	−5.1
C(7)–C(8)–C(3)–C(4)	4.6
C(8)–C(3)–C(4)–C(5)	−1.0
(iii) Cyclopentane ring	
C(7)–C(8)–C(9)–C(10)	21.6
C(8)–C(9)–C(10)–C(11)	−31.6
C(9)–C(10)–C(11)–C(7)	29.6
C(10)–C(11)–C(7)–C(8)	−17.4
C(11)–C(7)–C(8)–C(9)	−2.6
(iv) Cyclohexenone ring	
C(11)–C(12)–C(13)–C(14)	3.2
C(12)–C(13)–C(14)–C(15)	−14.6
C(13)–C(14)–C(15)–C(16)	39.5
C(14)–C(15)–C(16)–C(11)	−54.6
C(15)–C(16)–C(11)–C(12)	42.9
C(16)–C(11)–C(12)–C(13)	−17.6
(v) Methyl groups	
C(1)–N–C(17)–H(17a)	−46.3
C(1)–N–C(17)–H(17b)	174.8
C(1)–N–C(17)–H(17c)	52.1
C(5)–O(3)–C(18)–H(18a)	174.7
C(5)–O(3)–C(18)–H(18b)	76.6
C(5)–O(3)–C(18)–H(18c)	−53.2

* For simplicity only few meaningful bond distances and angles involving hydrogen atoms are reported.

In the crystal short intermolecular contacts between the bromine anions and the O(2) and N atoms (3.34 and 3.18 Å respectively) in addition to the favourable positions of the hydrogen atoms suggest the formation of hydrogen bonds; there are no strong interactions among the cations.

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[6/188 *Received*, 28*th January*, 1976]

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