# Studies on Proaporphine and Aporphine Alkaloids. Part VI.[1] Synthesis of (±)-Glaziovine by Spiran Ring Construction on a Cyclopent[*ij*]isoquinoline; Stereochemistry of Reduced Proaporphines†

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The Wittig reaction of methoxymethyltriphenylphosphonium chloride (11) with 2,3,8,8a-tetrahydro-6-hydroxy-5-methoxy-1-methylcyclopent[*ij*]isoquinolin-7(1*H*)-one (4), obtained from 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1-acetic acid (6) and polyphosphoric acid, gave the *Z*-enol ether (17) and, by hydrolysis, the cyclopent[*ij*]isoquinoline-7-carbaldehyde (19); the latter afforded (±)-11,12-dihydroglaziovine (20), along with a small amount of the 8,9-dihydro-isomer (21), on ring formation with methyl vinyl ketone, catalysed by 1,5-diazabicyclo[5.4.0]undec-5-ene. Bromination of the *O*-acetate of (20), followed by dehydrobromination, yielded (±)-glaziovine (1). The relative configurations of the asymmetric centres of compounds (20) and (21), as derived from an *X*-ray crystallographic analysis of the hydrobromide of (20), provide a reference in the stereochemistry of reduced proaporphines, such as amuronine (16), to which a revised (6a*S*,7a*S*)-configuration has been assigned.

SYNTHETIC approaches to (±)-glaziovine (1) by 8,1′-ring closure of 1-benzylisoquinoline derivatives, are reported in the preceding paper;[1] a synthesis of the alkaloid (1) and of related 1-hydroxy-2-methoxy-substituted reduced

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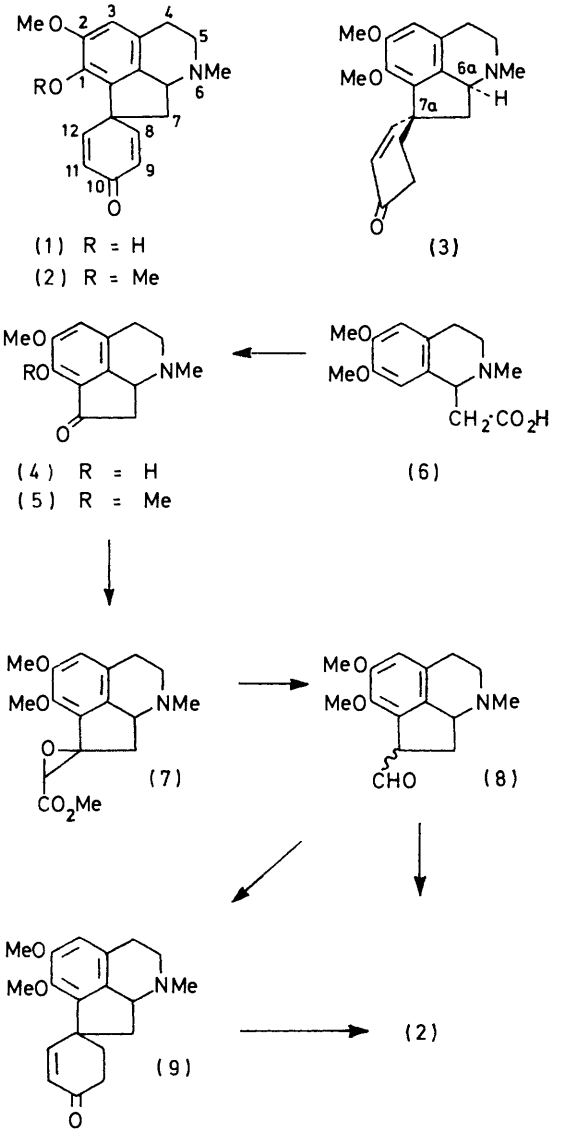
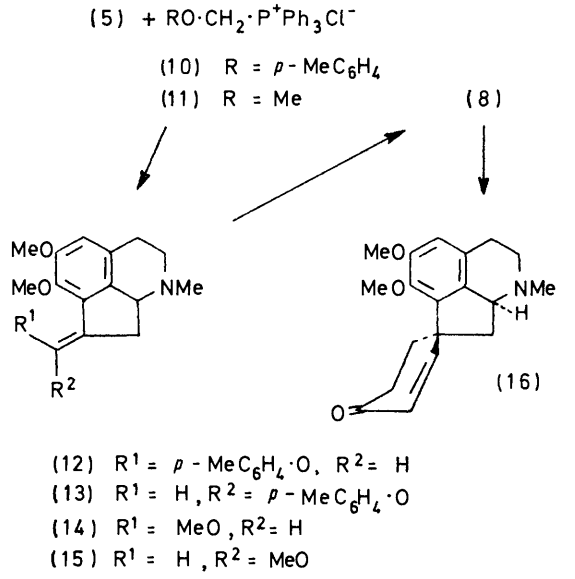
[1] Part V, C. Casagrande and L. Canonica, preceding paper.

proaporphines, from the cyclopent[*ij*]isoquinolinone (4), is now presented. Bernauer [2] synthesized (±)-pronuciferine (2) through the sequence outlined in Scheme 1, involving the conversion of the dimethoxy-ketone (5) into the aldehyde (8) by Darzens condensation, followed by Robinson annulation with methyl ethynyl ketone; as this last step proceeded in low yield, an alternative conversion of (8) into (2) was devised,[2] involving annulation




SCHEME 1

with methyl vinyl ketone to give the cyclohexenone (9) followed by oxidation with dichlorodicyanobenzoquinone or bromination–dehydrobromination; the racemic product (9) was identical, apart from optical activity, with amuronine, an alkaloid of *Papaver nudicaule* var. *amurense*, to which the absolute configuration (6a*S*,7a*R*),



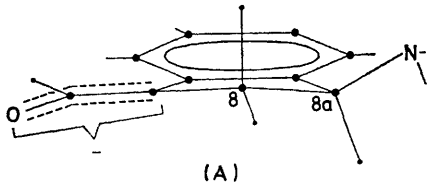

SCHEME 2

as shown in formula (3), had been ascribed; the configurational assignment of the C-6a centre rested on a chemical correlation [3–5] with (−)-(*R*)-armepavine *via* other alkaloids; that of the C-7a centre was derived from c.d. measurements.[6] In order to extend the synthesis of Bernauer to (±)-glaziovine *via* the hydroxy-ketone (4), an approach using the Wittig reaction was envisaged; experiments were initiated on the dimethoxy-ketone (5) as a model compound, since at first only low yields of (4) were obtained [by demethylation of (5) with sulphuric acid [7]]; later on, we were able to prepare (4) in 60—63% yield by simultaneous cyclization and demethylation of the isoquinolineacetic acid (6) or its methyl ester with polyphosphoric acid at 115 °C. Condensation of the ketone (5) and the ylide generated from triphenyl-(*p*-tolyloxymethyl)phosphonium chloride [8] (10) (Scheme 2) yielded a mixture of the *Z*- (12) and *E*- (13) enol ethers, which we were unable to hydrolyse to the corresponding aldehyde; in contrast, the enol ethers (14) and (15), which were obtained in 75% yield as a 30 : 70 mixture from the methoxy-methyl derivative (11),[8,9] were hydrolysed with aqueous methanesulphonic acid at 90 °C, affording the aldehyde (8), which was converted into (±)-amuronine (16); this appeared identical with a sample obtained by the method of Bernauer; furthermore its n.m.r. spectrum was identical with the spectrum of the natural product recorded by Dr. W. Döpke.

Formula (16) shows an inverted C-7a configuration

[2] K. Bernauer, *Helv. Chim. Acta*, 1968, **51**, 1119.
[3] W. Döpke, H. Flentje, and P. W. Jeffs, *Tetrahedron*, 1968, **24**, 2297.
[4] K. L. Stuart and M. P. Cava, *Chem. Rev.*, 1968, **68**, 321.
[5] M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buck, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.*, 1968, **33**, 2785.
[6] G. Snatzke and G. Wollenberg, *J. Chem. Soc.* (*C*), 1966, 1681.
[7] Belg. Pat., 665,445/1965.
[8] G. Wittig and M. Schlosser, *Chem. Ber.*, 1961, **94**, 1373; G. Wittig, W. Böll, and K.-H. Krück, *ibid.*, 1962, **95**, 2514; G. Wittig and W. Böll, *ibid.*, p. 2526.
[9] S. G. Levine, *J. Amer. Chem. Soc.*, 1958, **80**, 6150.

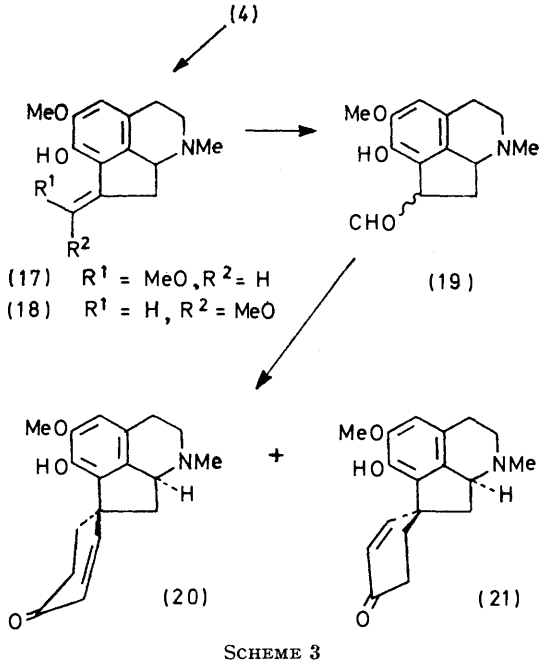
with respect to formula (3), anticipating the stereochemical conclusions which will be discussed later; from the synthetic standpoint, we note that a molecular model (A) of the enolate anion of (8) gives no indications




(A)

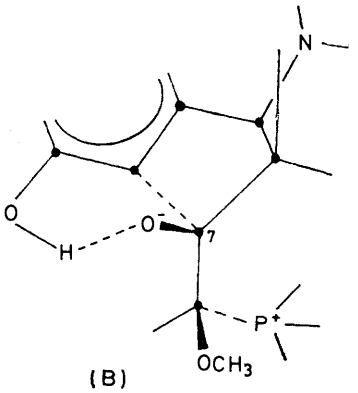
in favour of an entirely stereospecific attack from the upper side in the Michael addition, leading to compound (3) on ring closure; on the contrary, a perpendicular attack from the lower side, in a direction antiparallel to the pseudoaxial C(8)–H bond, would lead to structure (16).

The Wittig reaction with the hydroxy-ketone (4) proved more difficult than with the dimethoxy-ketone (5), and was possible only when a four molar excess of the ylide, generated with sodium methylsulphonylmethanide and kept at low temperature, was added in 10 h to the ketone in dimethyl sulphoxide at 25 °C. In this way, the *Z*-enol ether (17) (Scheme 3) was formed selectively in




SCHEME 3

70% yield; a very small amount of the *E*-isomer (18) was obtained by chromatography of the mother liquors from a large-scale run. The geometry of structures (17) and (18) was inferred from the n.m.r. spectra, in comparison with those of the other two pairs of isomers, (12)—(13), and (14)—(15), which were separated by chromatography; the differences in the chemical shifts of the olefinic protons were in reasonable agreement with the additivity rule of Pascual *et al.*;[10] furthermore, whereas compound (18) gave (15) on treatment with ethereal diazomethane, the hindered hydroxy-group of (17) resisted methylation under these conditions. The unusual selectivity with which (17) is produced may arise from the preferential formation of the betaine (B), stabilized by hydrogen bonding; the sluggishness of the irreversible elimination of triphenylphosphine oxide from (B) can




(B)

account for the excess of ylide required in the reversible, betaine-forming step to promote the formation of the end-product.[11]

Hydrolysis of compound (17) with aqueous methanesulphonic acid yielded the aldehyde (19), which could not be crystallized; annulation with methyl vinyl ketone yielded (±)-11,12-dihydroglaziovine * (20); in this case, the reaction did not appear entirely stereospecific, in contrast to that giving (±)-amuronine, the presence of *ca.* 5% of the 8,9-dihydro-isomer (21) being revealed by an extra signal in the olefinic region of the n.m.r. spectrum; indeed, a laborious chromatographic separation yielded pure (21). The main isomer (20) gave (±)-amuronine (16) on methylation with diazomethane. The relative configuration of the asymmetric centres of (20) was definitely established by an *X*-ray diffraction study[12] (Figure) of its hydrobromide, which also demonstrated that the preferred conformation of the cyclohexenone ring was, as is predictable, that having the half-chair bent away from the aromatic ring.

These results indicate structure (16) as the correct steric formula of amuronine; a similarly revised (6a*S*,7a*S*)-configuration should be assigned to linearisine[6,12] (2-*O*-demethylamuronine), owing to the reported[13] chemical correlation with amuronine; it also

* The numbering of the cyclohexane ring in proaporphines proposed by Stuart and Cava,[4] *i.e.* with the lower numbers (C-8 and C-9) assigned to the atoms projecting upwards from the plane of the paper, is not unequivocal, as it would lead to different numbering for enantiomeric compounds; it becomes acceptable by further specifying ' when the C-6a substituent projects downwards.'

[10] C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 164.

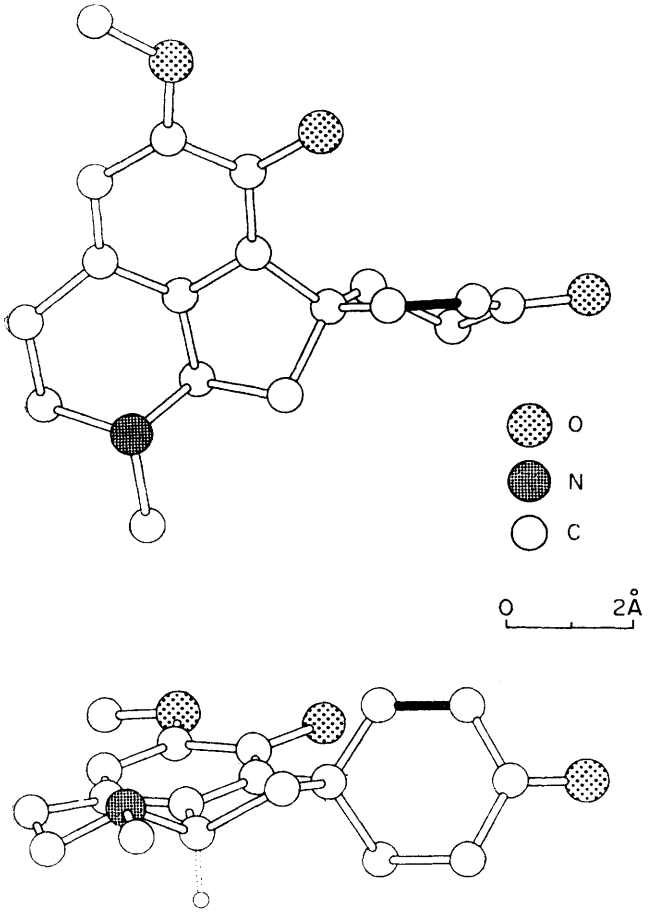
[11] For recent discussions of the mechanism and stereochemistry of the Wittig reaction see: M. Schlosser, *Topics Stereochem.*, 1970, **5**, 1; J. Reucroft and P. Sammes, *Quart Rev.*, 1971, **25**, 135.

[12] A. Colombo, in preparation.

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

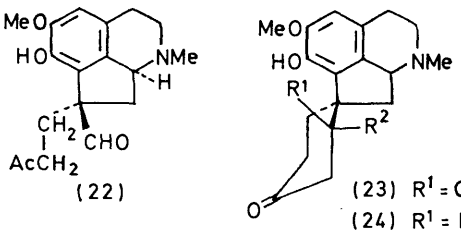
appears appropriate to reconsider the configurational assignments of the 1,2-methylenedioxy-analogue roemeronine [14] and related alkaloids, which were based on o.r.d. arguments similar to those derived from c.d. in the cases of amuronine and linearisine

A search for optimum conditions in the Robinson annulation of (19) revealed some interesting features; use of 1,5-diazabicyclo[5.4.0]undec-5-ene as catalyst (a

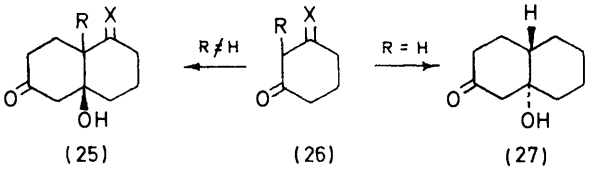



Two perspective views of the 11,12-dihydroglaziovine molecule along two orthogonal directions, as derived from the *X*-ray crystal structure refinement. All the hydrogen atoms, except those on the *N*-methyl group, have been located experimentally; only the one at C-6a is shown in the Figure (by courtesy of Dr. A. Colombo, Istituto di Chimica della Macromolicole, C.N.R., Milan)

new application of this reagent) afforded (±)-11,12-dihydroglaziovine (20) in 55% yield relative to (17), but also allowed, depending on the amount of catalyst and the temperature, the isolation of the oxo-aldehyde (22); this gave the axial β-hydroxy-ketone (23) on cyclization, whereas with sodium hydroxide or potassium t-butoxide both (23) and the thermodynamically more stable equatorial isomer (24) were formed, along with (20). The orientation of the hydroxy-group in (23) and (24) was deduced from their n.m.r. spectra, showing for the C-8 proton signal $W_{\frac{1}{2}}$ 6 Hz in (23) and $J_{ax,ax}$ 12, $J_{ax,eq}$ 6 Hz in (24); the formation of (23) is in accord with the expectation of an attack on the carbonyl group in (22) by the



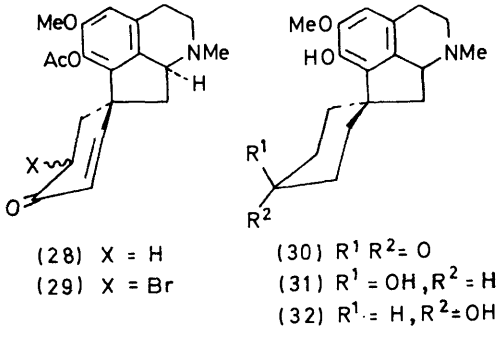

terminal carbanion of the four-atom chain on the less hindered side, *i.e.* the one opposite to the aromatic ring. This result parallels those observed with cyclohexanones (Scheme 4), where a *cis*-fused ketol (25) was formed in the presence of a C-2 substituent (26; R = Me, X = $H_2$ or




SCHEME 4

R = AcO, X = O), whereas the *trans*-ketol (27) was obtained from unsubstituted cyclohexanone.[15]

Bromination of (±)-11,12-dihydroglaziovine (20) gave a mixture of products in low yield, as observed with (±) amuronine, but an 85% yield of the monobromo-compound (29) was obtained from the acetate (28); (29) was shown to be a mixture of pseudoaxial and pseudo-equatorial isomers by its n.m.r. spectrum. Among various reagents tested in the dehydrobromination of (29), 1,5-diazabicyclo[5.4.0]undec-5-ene proved the most useful, and was also effective in removing the acetyl group, affording (±)-glaziovine (1) in 60—64% yield. The same yields in the final steps of the synthesis were achieved by using pure (20) or the 95 : 5 mixture of (20)




and (21), since the minor isomer also was usefully converted into (±)-glaziovine.

Catalytic hydrogenation of (±)-glaziovine over 10%

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

[15] T. A. Spencer, K. K. Schniegel, and K. L. Williamson. *J. Amer. Chem. Soc.*, 1963, **85**, 3785; J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, 1964, **29**, 2501.

palladium–carbon gave the tetrahydro-ketone (30); use of platinum oxide afforded the axial alcohol (31), which yielded a diacetate showing in the n.m.r. spectrum the C-10 proton signal at δ 5.1 with $W_{\frac{1}{2}}$ 7 Hz; (31) was also formed by reduction of (30) with sodium borohydride, along with the equatorial alcohol (32) (δ 4.73, $J_{ax,ax}$ 10.5, $J_{ax,eq}$ 5 Hz for the diacetate); these results are similar to those reported by Bernauer [2] for the 1,2-dimethoxy-series. Compound (31) has the same structure as (*S*)-*N*-methyloreoline [16] (*N*-methyloridine [17]), an alkaloid of *Papaver oreophilum* Rupr., which was thus synthesized in the racemic form; hydrogenation of (−)-(*S*)-glaziovine [18] yielded the laevorotatory alkaloid.

## EXPERIMENTAL

For general methods see preceding paper; in addition a Varian XL-100 spectrometer was used to obtain 100 MHz n.m.r. spectra.

(Z)- *and* (E)-1,2,3,7,8,8a-*Hexahydro*-5,6-*dimethoxy*-1-*methyl*-7-p-*tolyloxymethylenecyclopent*[ij]*isoquinoline* [(12) *and* (13)].—An ethereal solution of phenyl-lithium (40 ml; 1.09% w/v as lithium; 0.062 mol) was added under nitrogen to a suspension of triphenyl-(*p*-tolyloxymethyl)-phosphonium chloride [8] (10) (25.1 g, 0.060 mol) in dry ether (160 ml); the mixture was stirred for 2 h, then 2,3,8,8a-tetrahydro-5,6-dimethoxy-1-methylcyclopent[*ij*]isoquinolin-7(1*H*)-one [2] (5) (11.5 g, 0.0465 mol) in dry tetrahydrofuran (30 ml) was added during 15 min and stirring was continued for 30 min. The mixture was diluted with ether (200 ml) and filtered, and the filtrate was washed with water, dried ($Na_2SO_4$), and evaporated, thus giving a crude product (18.4 g) which was shown by t.l.c. ($CH_2Cl_2$–$CH_3OH$–$H_2O$ 89 : 10.2 : 0.8) to contain (12) and (13) in the ratio *ca.* 1 : 2, along with *ca.* 15% of unchanged (5). The mixture was chromatographed on silica gel (1 200 g) [eluants $CHCl_3$ and $CHCl_3$–$CH_3OH$ (98 : 2)]. The E-*isomer* (13) was eluted first and crystallized as the *hydrochloride* (5.5 g), m.p. 198—200° (from methanol–ether) (Found: Cl, 9.0; N, 3.6. $C_{22}H_{25}NO_3$,HCl requires Cl, 9.1; N, 3.6%). The base had m.p. 74—75° (from ether–light petroleum); $\nu_{max.}$ (KBr) 1 670, 1 605, and 1 490 cm$^{-1}$; δ ($CDCl_3$; 60 MHz) 2.31 (3H, s, $ArCH_3$), 2.39 (3H, s, $NCH_3$), 3.78 (6H, s, 2 × $OCH_3$), 6.5 (1H, s, 4-H), 7.00 (4H, m, aromatic), and 7.38 (1H, dd, *J* 1 and 3 Hz, C=CH–O). Further elution gave the *Z-isomer* (12), crystallized as the *perchlorate* (2.3 g), m.p. 186—188° (from ethanol) (Found: Cl, 8.3; N, 3.0. $C_{22}H_{25}NO_3$,$HClO_4$ requires Cl, 7.9; N, 3.1%). The base had m.p. 114—116° (from ether); $\nu_{max.}$ (KBr) 1 670, 1 605, and 1 500 cm$^{-1}$; δ ($CDCl_3$; 60 MHz) 2.28 (3H, s, $ArCH_3$), 2.35 (3H, s, $NCH_3$), 3.70 (3H, s, $OCH_3$), 3.77 (3H, s, $OCH_3$), 6.55 (1H, s, 4-H), 6.60 (1H, dd, *J* 0.5 and 2 Hz, C=CH–O), and 7.02 (4H, m, aromatic).

Acidic hydrolysis of (12) and (13) under various conditions did not lead to any identifiable aldehydic product.

(Z)- *and* (E)-1,2,3,7,8,8a-*Hexahydro*-5,6-*dimethoxy*-7-*methoxymethylene*-1-*methylcyclopent*[ij]*isoquinoline* [(14) *and* (15)].—The Wittig reaction leading to (14) and (15) was performed either with potassium t-butoxide in t-butyl alcohol or, preferably, with sodium methylsulphinylmethanide in dimethyl sulphoxide (DMSO), as follows: methoxymethyl-(triphenyl)phosphonium chloride [8,9] (11) (68.4 g, 0.2 mol) in DMSO (200 ml) was added under nitrogen at room temperature to a solution of sodium methylsulphinylmethanide [from 5.25 g (0.22 mol) of sodium hydride] in DMSO (100 ml). After stirring for 15 min at room temperature, the ketone (5) (24.7 g, 0.1 mol) in DMSO (200 ml) was added and the mixture was stirred for 14 h at room temperature, then diluted with water, and extracted with ether. The extracts were dried ($Na_2SO_4$) and evaporated and the residue was taken up in cyclohexane and filtered from insoluble triphenylphosphine oxide. The solution was then evaporated, leaving a crude mixture (20.6 g, 75%) of *Z*- and *E*-isomers, (14) and (15), in the ratio 3 : 7 (t.l.c., $CH_2Cl_2$–$CH_3OH$–$H_2O$ 94.5 : 5 : 0.5), which was used without further purification for the preparation of the aldehyde (8).

Pure samples of the isomers were obtained by chromatographing the mixture (4.4 g) on alumina (440 g; activity II) with chloroform. The E-*isomer* (15) was eluted first (2.5 g), m.p. 84—85° [from light petroleum (b.p. 80—120°)] (Found: N, 5.1. $C_{16}H_{21}NO_3$ requires N, 5.1%); $\nu_{max.}$ (KBr) 1 665, 1 610, and 1 595 cm$^{-1}$; δ ($CDCl_3$; 60 MHz) 2.35 (3H, s, $NCH_3$), 3.70 (3H, s, $OCH_3$), 3.76 (6H, s, 2 × $OCH_3$), 6.43 (1H, s, 4-H), and 6.95 (1H, dd, *J* 1.2 and 2.7 Hz, C=CH–O). The *perchlorate* showed m.p. 184—186° (from methanol–ether) (Found, Cl, 9.2. $C_{16}H_{21}NO_3$,$HClO_4$ requires Cl, 9.4%). Further elution gave the *Z-isomer* (14), crystallized as the *perchlorate* (1.5 g), m.p. 189—190° (from methanol–ether) (Found: Cl, 9.3%); $\nu_{max.}$ (KBr) 1 665, 1 612, and 1 585 cm$^{-1}$. The free base, obtained from the perchlorate but not characterized, showed δ ($CDCl_3$; 60 MHz) 2.33 (3H, s, $NCH_3$), 3.69, 3.75, and 3.78 (3H each, s, 3 × $OCH_3$), 6.18 (1H, dd, *J* 0.5 and 2 Hz, C=CH–O), and 6.53 (1H, s, 4-H).

(±)-*Amuronine* (16).—A solution of the crude mixture (15 g) of enol ethers (14) and (15) obtained from (5) was heated at 90 °C under nitrogen in aqueous methanesulphonic acid (3.5%; 700 ml) for 40 min, then cooled, washed with chloroform, saturated with sodium chloride and potassium hydrogen carbonate, and extracted with chloroform. The extract was dried ($Na_2SO_4$) and evaporated under reduced pressure on a bath kept at 35 °C. The residue, $\nu_{max.}$ (neat) 1 725 cm$^{-1}$, in t-butyl alcohol (90 ml) was treated under nitrogen with methyl vinyl ketone (5.4 g) and Triton B (50%; 8.4 g). The mixture, which warmed spontaneously to 50 °C, was left for 1 h at room temperature, then diluted with water and extracted with ether. The extracts were washed with water and evaporated and the crude (±)-amuronine (16) was chromatographed on alumina (100 g; activity II) and eluted with ether, yielding the product (9.05 g, 53%), m.p. 120—122° [from light petroleum (b.p. 60—80°)] (lit.,[2] 121—123°), *m/e* 313 ($M^+$), δ ($CDCl_3$; 60 MHz) 2.37 (3H, s, $NCH_3$), 3.73 and 3.80 (each 3H, s, $OCH_3$), 6.04 (1H, d, *J* 10 Hz, 9-H), 6.60 (1H, s, 3-H), and 6.77 (1H, d, *J* 10 Hz, 8-H); the n.m.r. spectrum was identical with that of the natural product.

(±)-Amuronine (16) was also prepared (*a*) as above, but with potassium t-butoxide in the annulation as indicated by Bernauer,[2] in 34.5% yield; (*b*) by Darzens condensation with the ketone (4) and further transformations according to Bernauer; [2] and (*c*) by methylation of (±)-11,12-dihydroglaziovine (20) (see below) with diazomethane; all samples were identical (mixed m.p., t.l.c., i.r.).

2,3,8,8a-*Tetrahydro*-6-*hydroxy*-5-*methoxy*-1-*methylcyclopent*[ij]*isoquinolin*-7(1H)-*one* (4).—The hydrochloride of

[16] J. Mann and S. Pfeifer, *Die Pharmazie*, 1967, **22**, 124; S. Pfeifer and J. Mann, *ibid.*, 1968, **23**, 82.

[17] F. Šantavý and M. Maturová, *Planta Med.*, 1967, **16**, 311.

[18] G. Ferrari and C. Casagrande, *Il Farmaco, ed. Sci.*, 1970, **25**, 449.

1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1-acetic acid [19] (6) (100 g) was added in portions during 20 min to polyphosphoric acid (1 kg) stirred under nitrogen at 90—100 °C. The mixture was stirred at 115—120 °C for 2.5 h, then poured on ice, adjusted to pH 8.5 (40% NaOH) and extracted with chloroform. The extracts were dried ($Na_2SO_4$) and evaporated and the hydroxy-ketone (4) was crystallized from methanol; yield 48.5 g (62.5%), m.p. 176—178°. A sample twice crystallized from methanol had m.p. 185—187° (lit.,[7] 177—180°) (Found: C, 66.6; H, 6.7; N, 5.9. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); $\nu_{max.}$ ($CHCl_3$) 1 683 $cm^{-1}$.

(Z)-1,2,3,7,8,8a-*Hexahydro-6-hydroxy-5-methoxy-7-methoxymethylene-1-methylcyclopent*[ij]*isoquinoline* (17).—The ylide from methoxymethyl(triphenyl)phosphonium chloride (0.7 mol) was prepared in DMSO as indicated for the dimethoxy-enol ethers (14) and (15). Portions of the red ylide solution, which was kept in an ice-bath, were periodically unfrozen and added during 10 h at 20—25 °C to a stirred solution of the hydroxy-ketone (4) (40 g, 0.175 mol) in DMSO (400 ml); the mixture was kept for 5—12 h at room temperature, diluted with water, and extracted with chloroform. The extracts were evaporated and the residue was washed with water and dissolved in aqueous tartaric acid. The solution was washed with chloroform, made basic with ammonia, and extracted with ethyl acetate; the extracts were evaporated and the *enol ether* (17) was triturated in ether; yield 31.4 g (70%), m.p. 102—104°. A sample recrystallized from ethyl acetate had m.p. 107—108° (Found: C, 69.3; H, 7.3; N, 5.3. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.3%), $\nu_{max.}$ (KBr) 3 330, 1 670, 1 630, and 1 600 $cm^{-1}$; δ ($CDCl_3$; 60 MHz) 2.33 (3H, s, $NCH_3$), 3.72 and 3.80 (3H each, s, 2 × $OCH_3$), 6.05 (1H, dd, *J* 0.5 and 2 Hz, C=CH–O), and 6.53 (1H, s, 4-H). Compound (17) was unaffected by ethereal diazomethane.

The ethereal mother liquors from a large scale (1.75 mol) preparation of the *Z*-isomer (17) were chromatographed with chloroform on alumina (activity III; 30 : 1 ratio). After a further amount of (17), the E-*isomer* (18) was eluted; m.p. 155—156° (from ethyl acetate) (Found: N, 5.2%); $\nu_{max.}$ (KBr) 1 665, 1 610, and 1 490 $cm^{-1}$; δ ($CDCl_3$; 60 MHz) 2.35 (3H, s, $NCH_3$), 3.66 and 3.75 (2 × 3H, each s, 2 × $OCH_3$), 6.35 (1H, s, 4-H), and 6.88 (1H, dd, *J* 1 and 2.7 Hz, C=CH–O). With diazomethane in ether compound (18) gave the dimethoxy-*E*-enol ether (15), identical with the material obtained from (5) (mixed m.p., i.r.).

The following δ values for olefinic protons were calculated according to Pascual *et al.*: [10] compound (12), 6.06; (13), 6.50; (14) and (17), 6.10; (15) and (18), 6.54.

(±)-11,12-*and* 8,9-*Dihydroglaziovine* [(20) *and* (21)].—The enol ether (17) (40 g) was hydrolysed by heating at 90 °C in aqueous methanesulphonic acid (8%; 400 ml) under nitrogen for 45 min. The solution was made basic ($KHCO_3$) and extracted with chloroform. The crude aldehyde (19) left after evaporation of the extract was unstable and could not be crystallized; it was kept under nitrogen at −18 °C or, preferably, directly dissolved in benzene (400 ml) and treated at 20—25 °C with methyl vinyl ketone (35 ml) and 1,5-diazabicyclo[5.4.0]undec-5-ene (2.3 g). The mixture was kept for 2 h at room temperature; t.l.c. ($CH_2Cl_2$–$CH_3OH$–$H_2O$ 89 : 10.5 : 0.5) showed the intermediate oxo-aldehyde (22) and axial β-hydroxy-ketone (23) as the main components, along with a small amount of (±)-11,12-dihydroglaziovine. The excess of methyl vinyl ketone and most of the solvent were removed *in vacuo* on a bath kept at 25 °C, the solution was made up to the original volume with benzene and was heated at 70 °C under nitrogen for 18 h. Water and acetic acid (pH 8.5) were added, the benzene layer was separated, and the aqueous layer was extracted with chloroform. The extracts were combined and evaporated and the residue was chromatographed on alumina (450 g; activity III) (eluant $CHCl_3$), giving (±)-11,12-dihydroglaziovine (20) (25.2 g, 55%), m.p. 192—193° (from ethyl acetate); this product was found to contain about 5% of the 8,9-dihydro-isomer by t.l.c. ($CH_2Cl_2$–$CH_3OH$–28% $NH_4OH$ aq. 94 : 5.6 : 0.4; two runs) and by observing the olefinic proton n.m.r. signals.

The isomers were separated by chromatography on alumina (activity III; 200 : 1 ratio; $CHCl_3$); the 8,9-dihydro-compound was eluted first. Pure (±)-11,12-*dihydroglaziovine* (20) had m.p. 199—200° (from ethyl acetate) (Found: C, 72.0; H, 7.2; N, 5.0. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.1; N, 4.7%); $\nu_{max.}$ (KBr) 3 200br, 1 672, and 1 610 $cm^{-1}$; δ ($CDCl_3$; 100 MHz) 2.37 (3H, s, $NCH_3$), 3.80 (3H, s, $OCH_3$), 5.99 (1H, d, *J* 10 Hz, 9-H), 6.52 (1H,s, 3-H), and 6.75 (1H, dd, *J* 10 and 1 Hz, 8-H); *m/e* 299 ($M^+$, 100%), 298 (81), 257 (16), and 256 (90). The hydrobromide, which was used in *X*-ray diffraction, had m.p. 240° (decomp.) (from ethanol). The 8,9-*dihydro-isomer* (21) had m.p. 176—177° (from ethyl acetate) (Found: N, 4.8%); $\nu_{max.}$ (KBr) 1 660 $cm^{-1}$; δ ($CDCl_3$; 100 MHz) 2.36 (3H, s, $NCH_3$), 3.82 (3H, s, $OCH_3$), 5.94 (1H, d, *J* 10 Hz, 11-H), 6.54 (1H, s, 3-H), and 6.85 (1H, dd, *J* 10 and 1 Hz, 12-H); *m/e* 299 ($M^+$, 100%), 298 (89), 257 (16), and 256 (83).

(±)-11,12-Dihydroglaziovine (20) in methanol was treated during 24 h with small portions of ethereal diazomethane; the product was chromatographed on alumina (activity III), giving (±)-amuronine (16), m.p. 121—123°, identical, as previously shown, with the synthetic product obtained from (5) and with the natural alkaloid.

1,2,3,7,8,8a-*Hexahydro-6-hydroxy-5-methoxy-1-methylcyclopent-7-*(3-*oxobutyl*)[ij]*isoquinoline-7-carbaldehyde* (22).—Methyl vinyl ketone (20 ml) and 1,5-diazabicyclo[5.4.0]-undec-5-ene (1 g) were added to the crude aldehyde (19) [obtained from 20 g of enol ether (17)] in ethyl acetate; the solution was kept at 25 °C under nitrogen for 5 h. The composition of the reaction mixture was the same as in the case of the reaction in benzene, but in this instance the oxo-aldehyde (22) crystallized on cooling; it was collected (8.15 g, 33.6; m.p. 162—164°) and twice recrystallized from acetone; m.p. 173—175° (Found: C, 68.3; H, 7.5; N, 4.2. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.3; N, 4.4%); $\nu_{max.}$ ($CHCl_3$) 3 570 and 1 718br $cm^{-1}$; $\nu_{max.}$ (KBr) 1 725 and 1 710 $cm^{-1}$; δ ($CDCl_3$; 60 MHz) 2.08 (3H, s, $COCH_3$), 2.36 (3H, s, $NCH_3$), 3.81 (3H, s, $OCH_3$), 6.55 (1H, s, 4-H), and 9.46 (1H, s, CHO).

Pure (±)-11,12-dihydroglaziovine (20) (2 g, 80%) was obtained by heating at 50 °C for 5 h the oxo-aldehyde (25) (2.65 g) in ethanol (250 ml) with an equal amount of 1,5-diazabicyclo[5.4.0]undec-5-ene.

(±)-8,9,11,12-*Tetrahydro-8-hydroxyglaziovine* [*Axial and Equatorial Isomers*, (23) *and* (24)].—A solution of the oxo-aldehyde (22) (3.7 g) and sodium hydroxide (1.3 g) in absolute ethanol (340 ml) was kept at room temperature for 2 h, neutralized with acetic acid, and evaporated. Water and chloroform were added, the organic layer was evaporated, and the residue (2.9 g) was chromatographed on alumina (activity II; 90 g); elution with chloroform gave

[19] J. R. Carson, U.S.P. 3,247,210/1966.

compound (20) (0.6 g), and thereafter elution with chloroform–ethanol (9 : 1) gave a mixture (1.3 g) of the axial (23) and equatorial (24) alcohol isomers. The latter crystallized from acetone; the mother liquors were evaporated and the residue was taken up in benzene, from which crystalline (23) was separated.

The *axial isomer* (23) had m.p. 135—137° (Found: C, 72.4; H, 7.5; N, 3.5. $C_{18}H_{23}NO_4,C_6H_6$ requires C, 72.9; H, 7.4; N, 3.5%); $\nu_{max.}$ (KBr) 3 400—2 500br and 1 712 $cm^{-1}$; δ ($CDCl_3$; 100 MHz) 2.40 (3H, s, $NCH_3$), 3.78 (3H, s, $OCH_3$), 3.90 (1H, m, $W_{\frac{1}{2}}$ 6 Hz, 8-H), 6.55 (1H, s, 3-H), and 7.28 (6H, s, $C_6H_6$). Compound (23) was partially converted into (20) when heated *in vacuo* in order to remove the crystallization solvent.

The *equatorial isomer* (24) had m.p. 190—192° (Found: C, 68.0; H, 7.4; N, 4.3. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.3; N, 4.4%); $\nu_{max.}$ (KBr) 3 400br and 1 708 $cm^{-1}$; δ ($CDCl_3$; 60 MHz) 2.45 (3H, s, $NCH_3$), 3.88 (3H, s, $OCH_3$), 4.26 (1H, dd, $J_{ax,ax}$ 12, $J_{ax,eq}$ 6 Hz, 8-H), and 6.40 (1H, s, 3-H).

When the axial isomer (23) (20 mg) and 1,5-diazabicyclo-[5.4.0]undec-5-ene (0.1 ml of 10% ethanolic solution) in benzene (0.5 ml) were heated at 70 °C for 15 h, complete conversion into (±)-11,12-dihydroglaziovine (20) was observed (t.l.c.; $CH_2Cl_2$–$CH_3OH$—$H_2O$ 83 : 16 : 1); the conversion of the equatorial isomer (24) under the same conditions was *ca.* 50%.

When compound (20), (22), (23), or (24) was kept at room temperature in aqueous ethanolic 20% sodium hydroxide, the formation of an equilibrium mixture of (20) and (23) was observed by t.l.c. in all instances.

(±)-1-O-*Acetyl*-11,12-*dihydroglaziovine* (28).—Acetylation of (20) (13 g) with acetic anhydride (20 ml) in pyridine (65 ml) for 24 h at room temperature gave the *acetate* (28) (14 g, 94%), m.p. 178—179° (from ether) (Found: N, 4.2. $C_{20}H_{23}NO_4$ requires N, 4.1%); $\nu_{max.}$ (KBr) 1 760 and 1 675 $cm^{-1}$.

(±)-1-O-*Acetyl*-11-*bromo*-11,12-*dihydroglaziovine* (29).—A solution of bromine in acetic acid (4% w/v; 240 ml) was added in 30 min with stirring to a solution of compound (28) (20 g) in acetic acid (650 ml) containing dry hydrogen bromide (25 g). Potassium acetate was added and most of the acetic acid was removed under reduced pressure. The residue was taken up in water, adjusted to pH 8 ($KHCO_3$), and extracted with chloroform. The extract was dried ($Na_2SO_4$) and evaporated; the *bromo-ketone* (29) was triturated in ether; yield 21 g (85%); m.p. 180° (decomp.) (Found: Br, 20.5; N, 3.5. $C_{20}H_{22}BrNO_4$ requires Br, 19.0; N, 3.3%). The product was shown to be a mixture of axial and equatorial isomers by t.l.c. (benzene–ethyl acetate–methanol 3 : 6 : 1; two runs) and by the n.m.r. signals at δ 4.7—5.2.

(±)-*Glaziovine* (1).—The bromo-ketone (29) (20 g) and 1,5-diazabicyclo[5.4.0]undec-5-ene (45 g) were stirred for 3.5 h at 25 °C; water (150 ml) was added and the mixture was kept at 25 °C for 1.5 h, then adjusted to pH 8.5 (HCl) and extracted with chloroform. The extract was evaporated and the residue was chromatographed on alumina (activity IV; 400 g); elution with chloroform yielded (±)-glaziovine (1) (9.05 g, 64%), m.p. 220—222° (from ethyl acetate), identical (t.l.c., i.r.) with the natural compound.[18]

Acetylation, bromination, and dehydrobromination of the 95 : 5 mixture of isomers (20) and (21) afforded (±)-glaziovine in yields substantially identical with those given by pure (20).

(±)-8,9,11,12-*Tetrahydroglaziovine* (30).—(±)-Glaziovine (1) (5 g) in absolute ethanol (250 ml) was hydrogenated over 10% palladium–charcoal (1 g) at 3—4 atm for 30 min; the catalyst was filtered off, the solvent was removed, and the residue was chromatographed on silica gel (280 g). Elution with chloroform–methanol (98 : 2) gave *tetrahydroglaziovine* (30) (3.5 g, 69%), m.p. 160—162° (from ethyl acetate) (Found: C, 71.7; H, 7.7; N, 4.6. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7; N, 4.6%); $\nu_{max.}$ (EtOH) 286 nm (log ε 3.51); $\nu_{max.}$ (KBr) 1 715 $cm^{-1}$.

(±)-N-*Methyloreoline* (31).—(±)-Glaziovine (1) (2 g) in acetic acid (200 ml) was hydrogenated over platinum oxide (1 g) at 3—4 atm for 30 min; work-up and chromatography on silica gel (120 g) with chloroform–methanol (95 : 5) as eluant gave N-*methyloreoline* (31) (1.2 g, 59%), m.p. 187—189° (from ethyl acetate) (Found: C, 70.6; H, 8.2; N, 4.6. $C_{18}H_{25}NO_3$ requires C, 71.3; H, 8.3; N, 4.6%); $\lambda_{max.}$ (EtOH) 286 nm (log ε 3.36); $\nu_{max.}$ ($CHCl_3$) 3 565 $cm^{-1}$; δ ($C_5D_5N$; 60 MHz) 2.36 (3H, s, N-$CH_3$), 3.63 (3H, s, $OCH_3$), 4.30 (1H, m, $W_{\frac{1}{2}}$ 7 Hz, 10-H), and 6.53 (1H, s, 3-H). A *diacetate*, obtained with acetic anhydride–pyridine at room temperature, had m.p. 170—171° (from ether); δ ($CDCl_3$; 60 MHz) 2.02 (3H, s, 10-OAc), 2.26 (3H, s, 1-OAc), 2.31 (3H, s, $NCH_3$), 3.70 (3H, s, $OCH_3$), 5.10 (1H, m, $W_{\frac{1}{2}}$ 7 Hz, 10-H), and 6.55 (1H, s, 3-H).

(−)-(S)-N-*Methyloreoline* (31; 6aα-H).—This was obtained by hydrogenation over platinum of (−)-(*S*)-glaziovine;[18] m.p. 186—188° (from ethyl acetate), $[\alpha]_D$ −59.7° (*c* 1 in $CHCl_3$) (lit.,[17] m.p. 192—193°).

*Reduction of* (±)-*Tetrahydroglaziovine* (30) *with Sodium Borohydride*.—The hydride (10.5 g) was added in 30 min to compound (30) (7 g) in methanol (200 ml); the solution was left at room temperature during the night, and evaporated. Water and hydrochloric acid (to pH 8.5) were added and the mixture was extracted with chloroform. The extracts were evaporated and the residue was chromatographed on silica gel (700 g); elution with chloroform and with chloroform–methanol (98 : 2 to 90 : 10) gave in the following order: compound (31) (1.2 g, 17%), m.p. 186—188°; a mixture (2.5 g) of (31) and (32); and compound (32) (2.7 g, 38%); the equatorial (±)-*hexahydroglaziovine* (32) had m.p. 178—180° (from ethyl acetate) (Found: N, 4.8. $C_{18}H_{25}NO_3$ requires N, 4.6%); $\nu_{max.}$ ($CHCl_3$) 3 565 $cm^{-1}$; δ ($CDCl_3$; 60 MHz) 2.36 (3H, s, $NCH_3$), 3.65 (partly masked m, 10-H), and 6.46 (1H, s, 3-H). A *diacetate* obtained with acetic anhydride–pyridine at room temperature had m.p. 171—172° (from ether); δ ($CDCl_3$; 60 MHz) 2.00 (3H, s, 10-OAc), 2.26 (3H, s, 1-OAc), 2.31 (3H, s, $NCH_3$), 3.73 (3H, s, $OCH_3$), 4.73 (1H, m, $J_{ax,ax}$ 10.5, $J_{ax,eq}$ 5 Hz, 10-H), and 6.53 (1H, s, 3-H).

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