Studies on Proaporphine and Aporphine Alkaloids. Part V.[1] Synthesis of (±)-Glaziovine by 8,1'-Ring Closure of 1-Benzylisoquinoline Derivatives†

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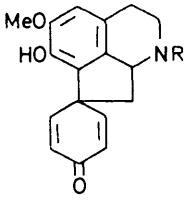
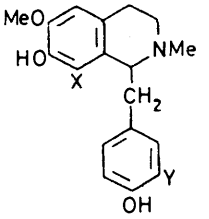
A new, convenient synthesis of (±)-glaziovine (*N*-methylcrotsparine) (1) has been devised, involving as the key steps the nitration of (±)-4'-O-benzyl-*N*-methylcoclaurine (21), followed by catalytic hydrogenation to (±)-8-amino-*N*-methylcoclaurine (23), diazotization, and irradiation of the *o*-diazo-oxide (24). The synthesis of (±)-glaziovine by irradiation of (±)-8-bromo-*N*-methylcoclaurine has been reinvestigated and improved. An attempted phenolic coupling reaction of (±)-*N*-trifluoroacetylcrotsparine (2) by vanadium oxide trichloride resulted in 8-chlorination and 4-hydroxylation [to give compounds (8) and (9)].

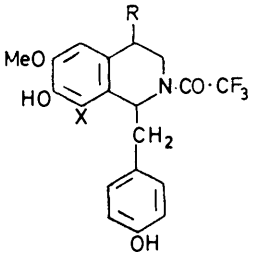
THE proaporphine alkaloid (±)-glaziovine[2] (1) is endowed with interesting psychopharmacological properties.[2,3] Since *Ocotea glaziovii* Mez, the Brazilian Lauracea



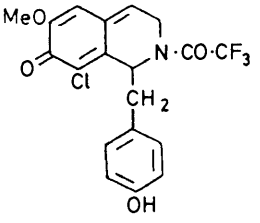
(1) R = Me
(2) R = CF_3·CO



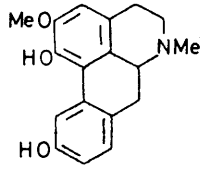
(3) X = Y = H
(4) X = Br, Y = H
(5) X = Y = Br
(6) X = H, Y = Br



(7) R = X = H
(8) R = H, X = Cl
(9) R = OH, X = Cl

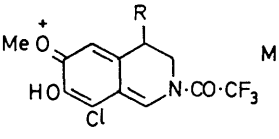


(10)

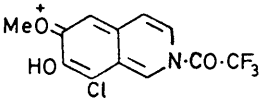


(11)

from which glaziovine has been isolated,[4] is a fairly rare tree, and no other abundant natural source of this alkaloid has been found, we became interested in developing a practical synthesis. Various synthetic approaches to the proaporphine alkaloids have been investigated,[5] but none appears satisfactory, yields being generally very low; (±)-glaziovine, in particular, has been obtained in 1% yield by a biogenetic-type synthesis,[6] involving oxidation of (±)-*N*-methylcoclaurine (3) by ferricyanide and in 7.5—10% yield by irradiation of (±)-8-bromo-*N*-methylcoclaurine (4) in alkaline solution.[7] Recently, improved yields in the synthesis of isoquinoline alkaloids by intramolecular oxidative coupling of diphenols have been achieved by using vanadium oxide trichloride;[8,9] nevertheless, when attempting the oxidation of (±)-*N*-trifluoroacetylcoclaurine (7) with this reagent in tetrahydrofuran, we were unable to detect any trace of the dienone (2), *i.e.*, (±)-*N*-trifluoroacetylcrotsparine;[1] two compounds, (8) and (9), were isolated by silica gel chromatography; their structures were disclosed by mass spectra, which showed pairs of chlorine isotopic peaks, the most relevant ions being (*a*) in the spectrum of (8) and (*b*) in that of (9), as well as (*c*) and the hydroxytropylium ion at *m/e* 107 in both spectra. Comparison of the n.m.r. spectrum of the diacetate of (8) with that of the



(*a*) R = H
(*b*) R = OH



(*c*)

diacetate of (7) enabled the chlorine atom to be located at C-8, in view of the downfield shift of the C-1 proton signal from δ 5.57 to 5.93; the shift of the C-5 proton signal to δ 6.87 in the triacetate of (9) with respect to (8) diacetate (δ 6.62) confirmed the benzylic position of the hydroxy-group. The mechanism by which the 8-chloro-substituent is introduced is not evident; an electrophilic substitution appears improbable, as there are no reports

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[1] Part IV, C. Casagrande and G. Ferrari, *Il Farmaco, ed. Sci.*, 1975, **30**, 479.

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

[3] E. Gandini-Collodel, *Boll. Soc. Med. Chir., Pisa*, 1968, **36**, 1185; B. Buffa, G. Costa, and P. Ghirardi, *Curr. Ther. Res.*, 1974, **16**, 621.

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

[6] T. Kametani and H. Yagi, *J. Chem. Soc.* (*C*), 1967, 2182; D. H. R. Barton, *Chem. in Brit.*, 1967, **3**, 330.

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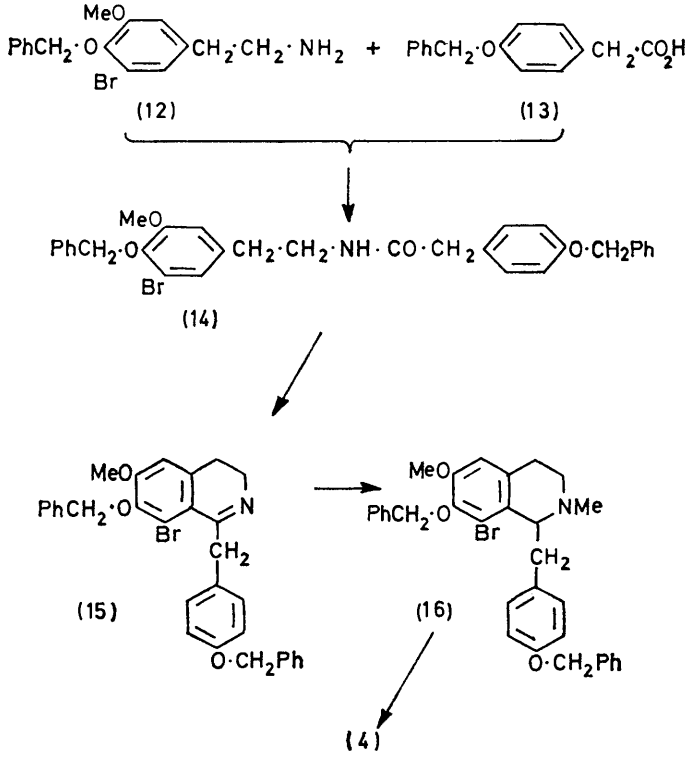
[9] W. L. Carrick, G. L. Karapinka, and G. T. Kwiatkowsky, *J. Org. Chem.*, 1969, **34**, 2388; M. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, 1970, **92**, 1090; M. A. Schwartz, *Synth. Comm.*, 1973, **3**, 33; B. Franck and V. Teetz, *Angew. Chem. Internat. Edn.*, 1971, **10**, 411; J. P. Marino and J. M. Samanen, *Tetrahedron Letters*, 1973, 4553.

of chlorination of aromatic compounds, including phenols, by vanadium oxide trichloride, even under less mild conditions [10] than those used in the present case; furthermore, the 3'-position should be preferred for electrophilic attack, as will be shown, at least for bromination, in the case of compound (6). It is conceivable that the oxidizing reagent generates a mesomeric O-7 ⟷ C-8 radical, by a mechanism similar to that proposed [8] for the coupling reaction, and that this abstracts a chlorine atom from vanadium oxide trichloride.

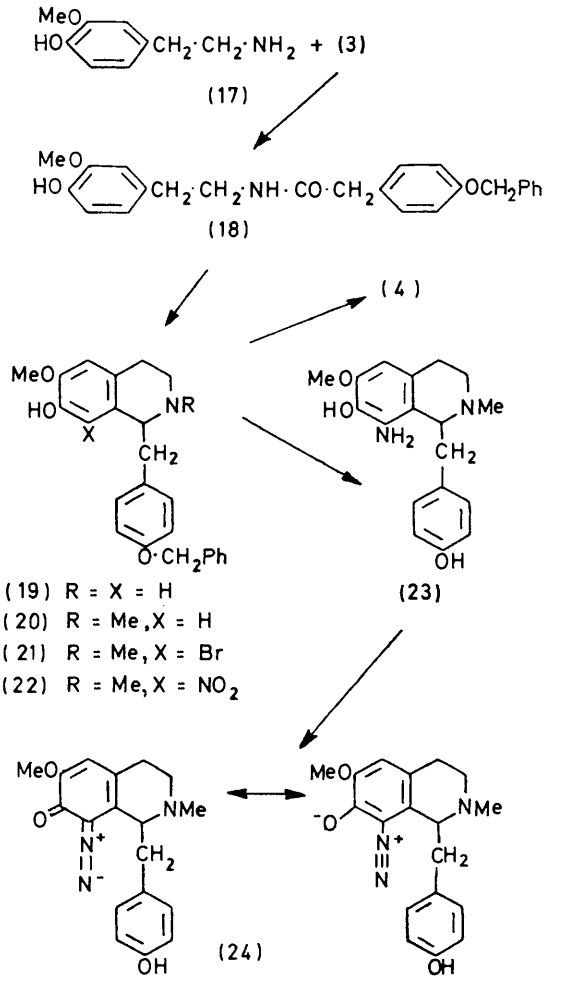
The failure of the ring closure by vanadium oxide trichloride confirms the implications of the results of the ferricyanide oxidations,[11] *i.e.* that a biogenetic-type synthesis by phenolic coupling is less rewarding with the proaporphines than with other alkaloid skeletons; we therefore abandoned this approach.

Since in the report on the photoreaction [7] of the bromo-compound (4) no mention was made of either unchanged starting material or any product other than (±)-glaziovine, we decided to reinvestigate the synthesis of (±)-8-bromo-*N*-methylcoclaurine and its photoreaction. Notwithstanding some improvements in the sequence leading



SCHEME 1

to (4) (Scheme 1) (see Experimental section) the difficulties involved in the preparation of the bromo-phenethylamine (12) [12] prompted a search for an alternative based on a readily accessible intermediate. Bromination



SCHEME 2

of (−)-*N*-methylcoclaurine (3) is reported to yield the 3',8-disubstituted derivative (5); [13] by using 1 equiv. of bromine under mild conditions we obtained from the (±)-form of (3) the 3'-monosubstituted compound (6), as shown by the mass spectrum [3,4-dihydro-7-hydroxy-2-methyl-6-methoxyisoquinolium ion at *m/e* 192 and bromohydroxytropylium ion at *m/e* 185 and 187]; in contrast, in the bromination of (±)-4'-*O*-benzyl-*N*-methylcoclaurine (20) (Scheme 2), obtained from 3-methoxy-4-hydroxyphenethylamine (17) [14,15] by a sequence of high-yield steps (including Bischler–Napieralski ring closure of an unprotected phenolic amide [14,16]), the 8-bromo-derivative (21) was obtained in 90% yield; this was easily debenzylated with hydrochloric acid to give (±)-8-bromo-*N*-methylcoclaurine (4). Irradiation of alkaline solutions of compound (4) in a Pyrex vessel with a

[10] D. Cozzi and S. Cecconi, *Ricerca Sci.*, 1953, **23**, 609; S. Prasad and K. N. Upadhyaya, *J. Indian Chem. Soc.*, 1960, **37**, 543 (*Chem. Abs.*, 1961, **55**, 6231); H. Funk, W. Weiss, and M. Zeising, *Z. anorg. Chem.*, 1958, **296**, 36.

[11] For a review, see T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.

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[15] J. H. Short, D. A. Dunnigan, and C. W. Ours, *Tetrahedron*, 1973, **29**, 1931.

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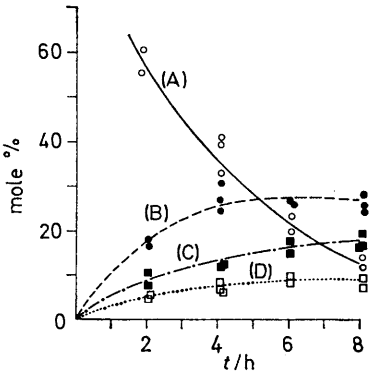
medium-pressure mercury lamp gave (±)-glaziovine, (±)-*N*-methylcoclaurine (3), and the aporphine (11), *i.e.* (±)-apoglaziovine;[1,4] the best results were obtained at controlled alkalinity (pH 12) with sodium phosphate as buffer. In a series of experiments under these conditions, the amounts of starting material and of the three products at various times were determined by densitometry on t.l.c. plates. The results (Figure 1) show that the

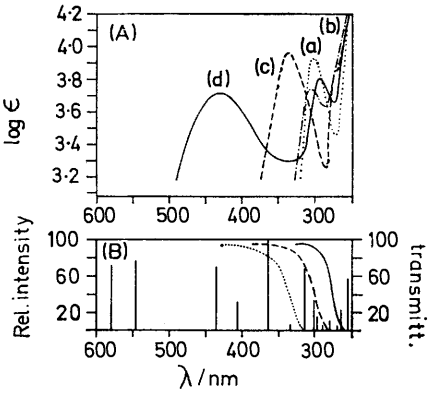


Photolysis of (A) (±)-8-bromo-*N*-methylcoclaurine (4) and the formation of (B) (±)-glaziovine (1); (C) (±)-*N*-methylcoclaurine (3); and (D) (±)-apoglaziovine (11)

photoreaction becomes progressively slower, and the amount of (±)-glaziovine reaches a plateau after 4—5 h as its yield relative to the amount of (4) consumed gradually declines. These observations may be ascribed to quenching of the useful radiation by the products, and to the increase of secondary and side reactions; indeed, only compound (3), the product formed by hydrogen abstraction from the other species present in the solution, showed a noticeable increase after the fourth hour; on the other hand, partial degradation of (±)-glaziovine (1) by irradiation under the same conditions was demonstrated in a separate experiment.

The u.v. spectra of the starting material and the products are shown in Figure 2, along with the intensities of the lines of the lamp; the Figure also shows the cut-off curves of the materials which were used to investigate the influence of the radiation wavelength on the photoreaction. Irradiation in a quartz vessel resulted in very low yields, owing to increased decomposition of (±)-glaziovine; use of quartz with 0.5% lead(II) chloride solution as a filter afforded results similar to those obtained with Pyrex, but with a six- to seven-fold increase in rate; use of common glass approximately halved the rate with respect to Pyrex. It appears from these experiments that the effective radiation mainly originates from the lines at 297, 302, and 313 nm, which are almost equally absorbed by the starting material and the products.

These results, allowing (±)-glaziovine to be obtained in 26% yield, were not entirely satisfactory with respect to the yield and the large amount of energy required. It was then considered that a coloured diazo-oxide, such as (24), being more sensitive to light than (4) and absorbing (Figure 2) in a region different from (±)-glaziovine and including the strong visible lines of the mercury arc, would be most suitable for the photoreaction. In order to synthesize compound (24), the 4′-*O*-benzyl ether (20) (Scheme 2) was nitrated in 83—85% yield by shaking a solution in chloroform with very dilute nitric acid and a catalytic[17] amount of sodium nitrite; hydrogenation of the nitro-compound (22) over palladium–carbon brought about simultaneous reduction and debenzylation, affording (23) in 92% yield; this was diazotized and the resulting deep yellow solution of (24) was made alkaline with sodium hydroxide and irradiated in a Pyrex vessel. A fast photoreaction, leading to complete disappearance of (24) in one fiftieth of the time required for 65% photoreaction of the bromo-compound (4), produced (±)-glaziovine in 45% yield; the minor products were the same as in the photoreaction of (4), but they were formed in a different ratio, the amount of (±)-*N*-methylcoclaurine (3) being very small; this difference invites speculation as to differences in mechanism between the photoreactions of (4) and (24), involving long-debated topics such as the modes of



(A) U.v. spectra of (a) (±)-8-bromo-*N*-methylcoclaurine (4), (*b*) (±)-glaziovine (1), (c) (±)-apoglaziovine (11), and (d) the diazo-oxide (24) in ethanolic 0.1N-NaOH; the spectrum of (±)-*N*-methylcoclaurine (3) (not shown) was similar to that of (4). (B) Relative intensity of the main lines of the medium-pressure mercury lamp and transmittance of common glass (1 mm; · · · ·), Pyrex (2 mm; – – – –), and aqueous 0.5% lead(II) chloride (1 cm; ——)

photochemical and thermal decomposition of diazo-oxides[18] and diazonium salts,[19] as well as the mechanism of the Pschorr and related ring closures;[20] this is at present precluded by the paucity of the experimental evidence.

The present synthesis of (±)-glaziovine, involving a

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[18] O. Süs, K. Möller, and H. Heiss, *Annalen*, 1956, **598**, 123; M. J. S. Dewar and A. N. James, *J. Chem. Soc.*, 1958, **917**, 4265; R. Huisgen, G. Birsch, and H. König, *Chem. Ber.*, 1964, **97**, 2868, 2884; H. Böttcher, R. Werner, and H. G. O. Becker, *Z. Chem.*, 1973, **13**, 374.

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straightforward approach to the key intermediate (23) and an improved yield in the final step, compares favourably with previous syntheses of alkaloidal cyclohexa-2,5-dienones from diazonium salts; these originated from the observation [21] of the anomalous course of the Pschorr cyclization of 2-amino-*N*-ethyl-4'-methoxybenzanilide (25), resulting in 2-ethylisoindoline-1-spiro-1'-cyclohexadiene-3,4'-dione and were used in the construction of the morphinandienone,[22] homomorphinandienone,[23] and proaporphine [24] skeletons; the proaporphine synthesis of Ishiwata and Itakura,[24] starting from phenethylamines containing a protected amino-group in the aromatic ring, afforded (±)-pronuciferine, (±)-homolinearisine, and (±)-*O*-methylorientalinone with yields in the final step ranging from 10 to 20%. The extension of methods based on the photolysis of *ortho*- and *para*-diazo-oxides to the synthesis of other proaporphines as well as alkaloids with different skeletons is being investigated.

EXPERIMENTAL

M.p.s were taken for samples in capillaries. Silica gel (0.05—0.2 mm) and neutral alumina (both Merck) were used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thick, were used both for qualitative t.l.c. and for densitometric experiments; they were observed in u.v. light or sprayed with iodine solution. Spectral data were obtained with the following instruments: u.v., Beckmann DB-GT spectrophotometer; i.r., Perkin-Elmer 257 spectrophotometer; n.m.r., Varian NV-14 spectrometer (60 MHz) (solutions in $CDCl_3$ with Me_4Si as internal standard); mass spectra, Varian MAT CH-7 spectrometer (70 eV).

(±)-N-*Trifluoroacetylcoclaurine* (7).—(±)-Coclaurine [25] (10 g) in pyridine (50 ml) was treated at 0 °C with trifluoroacetic anhydride (14 ml); the mixture was kept at 20 °C for 2 h, then diluted with water and acidified (HCl). The precipitate was filtered off, yielding the *product* (7) (8.8 g, 65%), m.p. 240—242° (from ethanol) (Found: F, 14.8; N, 3.7. $C_{19}H_{18}F_3NO_4$ requires F, 14.9; N, 3.7%); $\nu_{max.}$ (KBr) 3 450, 3 365, and 1 675 cm^{-1}. The *diacetate*, prepared by treatment with acetic anhydride–pyridine for 48 h at room temperature, had m.p. 152—154° (from ethanol) (Found: C, 60.0; H, 5.0; N, 2.9. $C_{23}H_{22}F_3NO_6$ requires C, 59.4; H, 4.8; N, 3.0%); $\nu_{max.}$ (KBr) 1 773, 1 750, and 1 687 cm^{-1}, δ ($CDCl_3$) 2.23 (6H, s, 7- and 4'-AcO), 3.77 (3H, s, CH_3O), 5.57 (1H, m, 1-H), 6.55 (1H, s, 5-H), 6.65 (1H, s, 8-H), and 6.99 (4H, aromatic).

Oxidation of Compound (7) *with Vanadium Oxide Trichloride*.—Vanadium oxide trichloride (12 ml) was added at −60 °C under nitrogen to a solution of compound (7) (9.2 g) in dry tetrahydrofuran (THF) (3.6 l); the solution was stirred at −60 °C for 2 h, then gradually brought to room temperature and stirred for 70 h. After the addition of water (200 ml), sodium dithionite was added in small portions until the violet colour was discharged. Previous experiments had shown that the addition of sodium dithionite did not modify the composition of the mixture, while making easier the purification of the products. Ammonium hydroxide was added (to pH 4) and the solvent was evaporated off under reduced pressure. The dark residue was washed with water, dried *in vacuo*, taken up in THF (100 ml) and chromatographed on alumina (100 g; activity II), with THF (700 ml) as eluant; most of the colour was left on the column; the product (8.14 g), containing neither *N*-trifluoroacetylcrotsparine [2] (2) nor any other ketonic compound [t.l.c., benzene–ethyl acetate (1 : 1), 2,4-dinitrophenylhydrazine spray], was chromatographed on silica gel (300 g) with benzene–ethyl acetate (8 : 2, then 1 : 1). The latter eluant gave 8-*chloro*-1,2,3,4-*tetrahydro*-7-*hydroxy*-1-(4-*hydroxybenzyl*)-6-*methoxy*-2-*trifluoroacetylisoquinoline* (8) (2.6 g, 26%) and thereafter 8-*chloro*-1,2,3,4-*tetrahydro*-4,7-*dihydroxy*-1-(4-*hydroxybenzyl*)-6-*methoxy*-2-*trifluoroacetylisoquinoline* (9) (2.08 g, 20%). Compound (8) showed m.p. 209—211° (from ethanol–water) (Found: C, 55.1; H, 4.1; Cl, 8.7; N, 3.6. $C_{19}H_{17}ClF_3NO_4$ requires C, 54.9; H, 4.1; Cl, 8.5; N, 3.4%); *m/e* 417/415 (0.5%), 310/308 (100), 306 (12), 295/293 (6.5), 213/211 (3), 209 (2.5), 198/196 (7), and 107 (12). It gave a *diacetate* with acetic anhydride–pyridine, m.p. 177—179° (from absolute ethanol) (Found: C, 55.3; H, 4.6; N, 2.4. $C_{23}H_{21}ClF_3NO_6$ requires C, 55.3; H, 4.2; N, 2.8%); $\nu_{max.}$ (KBr) 1 770, 1 755, and 1 700 cm^{-1}; δ 2.23 and 2.33 (3H each, s, 4'- and 7-OAc), 3.80 (3H, s, CH_3O), 5.93 (1H, m, 1-H), 6.62 (1H, s, 5-H), and 7.00 (4H, aromatic).

Compound (9) showed m.p. 184—185° (from ethanol–water) (Found: C, 53.5; H, 4.5; N, 2.9. $C_{19}H_{17}ClF_3NO_5$ requires C, 53.0; H, 4.0; N, 3.2%); *m/e* 433/431 (0.5%), 415/413 (1), 326/324 (38), 308/306 (100), 211/209 (15), and 107 (9). A *triacetate*, obtained with acetic anhydride–pyridine, had m.p. 180—182° (from ethanol) (Found: C, 54.2; H, 4.3; N, 2.4. $C_{25}H_{23}ClF_3NO_8$ requires C, 53.9; H, 4.2; N, 2.5%); $\nu_{max.}$ (KBr) 1 770, 1 740, and 1 700 cm^{-1}; δ 2.00 (3H, s, 4-OAc), 2.23 and 2.33 (3H each, s, 4'- and 7-OAc), 3.80 (3H, s, CH_3O), 5.82 (1H, m, 4-H), 6.10 (1H, m, 1-H), 6.87 (1H, s, 5-H), and 7.06 (4H, aromatic). The n.m.r. spectrum did not allow a definite assignment of the relative configuration of the C-1 and C-4 substituents in (9).

7-*Benzyloxy*-1-(4-*benzyloxybenzyl*)-8-*bromo*-3,4-*dihydro*-6-*methoxy*-*isoquinoline* (15).—*N*-(4-Benzyloxy-5-bromo-3-methoxyphenethyl)-*p*-benzyloxyphenylacetamide[5] (14) (70 g) in dry acetonitrile (1 l) was treated with phosphoryl chloride (105 ml) and refluxed under nitrogen for 1 h; the solvent was evaporated off and the excess of reagent was removed *in vacuo*. The residue was triturated in dry ethyl acetate–ether (1 : 3), yielding a crystalline *salt* (74 g, 85%), m.p. 136—138° [Found: total halogen as Br, 35.0; P, 4.7. $C_{31}H_{28}BrNO_3,HOP(O)Cl_2$ requires total halogen as Br, 35.4; P, 4.6%]. A *picrate* obtained from benzene–ethanol and recrystallized from acetone had m.p. 161—162° (Found: Br, 10.5; N, 7.3. $C_{31}H_{28}BrNO_3,C_6H_3N_3O_7$ requires Br, 10.4; N, 7.3%).

7-*Benzyloxy*-1-(4-*benzyloxybenzyl*)-8-*bromo*-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinoline* (16).—A solution of the dichlorophosphate of (15) (45 g) in chloroform was rapidly washed (N-NaOH and water), dried (Na_2SO_4), and evaporated under reduced pressure. The base in acetonitrile (450 ml) and methyl iodide (180 ml) was refluxed

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[23] T. Kametani and K. Fukumoto, *J. Heterocyclic Chem.*, 1971, **8**, 341; *Accounts Chem. Res.*, 1972, **5**, 212.

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under nitrogen for 3 h. Evaporation gave the crude methiodide, which was reduced in chloroform (200 ml) and methanol (1 200 ml) by adding sodium borohydride (30 g) in portions and then stirring for 30 min at room temperature. The solvent was evaporated off, and water and chloroform were added; the organic phase was dried (Na_2SO_4) and evaporated and the residue was dissolved in benzene and acidified with aqueous 70% perchloric acid in ethanol, thus precipitating the *product* (16) *perchlorate* (29.5 g, 68%), m.p. 172—173° (from acetone) (Found: total halogen as Br, 24.0; N, 2.3. $C_{32}H_{32}BrNO_3,HClO_4$ requires total halogen as Br, 24.2; N, 2.1%). The free *base* showed m.p. 92—94° (from ether) (Found: Br, 14.4; N, 2.7. $C_{32}H_{32}BrNO_3$ requires Br, 14.3; N, 2.5%).

(±)-3′-*Bromo*-N-*methylcoclaurine* (6).—A solution of bromine in acetic acid (27 ml; 16% w/v) was added in 40 min at 15 °C to a stirred solution of (±)-*N*-methylcoclaurine [26] (3) (8 g); stirring was continued for 20 min, then the solvent was evaporated off and the residue was taken up in ice–water, made basic (pH 8.5 with NH_4OH), extracted into chloroform, and chromatographed on silica gel (400 g) with chloroform and then chloroform–ethanol (9 : 1). The latter eluate afforded *compound* (6), crystallized as its *hydrogen oxalate* (6.3 g, 51%), m.p. 162—163° (from ethanol) (Found: Br, 17.2; N, 3.0. $C_{18}H_{20}BrNO_3,C_2H_2O_4$ requires Br, 17.0; N, 3.0%). The base showed *m/e* 378 (0.2%), 376 (0.2), 192 (100), 187 (0.6), 185 (0.6), 177 (41), 163 (*m**), 162 (2.5), 149 (6), and 148 (8). T.l.c. (CH_2Cl_2–CH_3OH–H_2O 89 : 10.2 : 0.8) of the reaction mixture revealed unchanged (±)-*N*-methylcoclaurine and the 3′,8-dibromo-derivative (5) [12] as minor components.

p-*Benzyloxyphenyl*-N-(4-*hydroxy*-3-*methoxyphenethyl*)*acetamide* (18).—A mixture of *p*-benzyloxyphenylacetic acid (13) (430 g), 4-hydroxy-3-methoxyphenethylamine (17) (297 g), and decalin (1.4 l) was heated with stirring at 175—180 °C under a slow stream of nitrogen. The decalin was then evaporated off under reduced pressure and the residue was dissolved in chloroform and washed (dilute HCl and aqueous $NaHCO_3$). Evaporation, and trituration of the residue with light petroleum (b.p. 80—120°) gave the amide (18) (630 g, 91%), m.p. 124—126° (lit.,[27] 111—113°) (Found: N, 3.5. Calc. for $C_{25}H_{25}NO_4$: N, 3.6%).

1-(4-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* (19).—Phosphoryl chloride (173 ml) was added to a boiling solution of the amide (18) (200 g) in acetonitrile (2 l); refluxing was continued for 1.5 h, then most of the solvent was evaporated off and the residue was poured on ice–water and stirred for 30 min. The water was decanted and the pasty mass was dissolved in ethanol (850 ml); the solution was made basic in the cold (NH_4OH) and diluted with water, thus precipitating 1-(4-benzyloxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (m.p. 165—167°), which was filtered off and immediately dissolved in methanol (3.3 l). Sodium borohydride (46 g) was added in 30 min and the mixture was stirred for 1 h; the solvent was evaporated off, water and chloroform were added, and the organic phase was dried (Na_2SO_4) and evaporated giving *compound* (19) (151 g, 78%), m.p. 155—157° (from ethyl acetate) (Found: C, 77.0; H, 6.8; N, 3.5. $C_{24}H_{25}NO_3$ requires C, 76.8; H, 6.7; N, 3.7%).

1-(4-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (20).—A mixture of the secondary base (19) (100 g), 85% formic acid (240 ml), and aqueous 34% formaldehyde (300 ml) was heated at 100 °C for 2 h. The residue obtained by evaporation under reduced pressure, addition of water, and re-evaporation was taken up in water and made basic (NH_4OH) at 20 °C; the precipitate was collected and triturated in boiling ethanol, giving compound (20) (94 g, 91%), m.p. 137—138° (lit.,[28] 135—136°) (Found: N, 3.4. Calc. for $C_{25}H_{27}NO_3$: N, 3.6%).

1-(4-*Benzyloxybenzyl*)-8-*bromo*-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (21).—A solution of bromine in acetic acid (560 ml; 6.3% w/v) was added with stirring at 15—18 °C to the 7-hydroxyisoquinoline (20) (80 g) and anhydrous sodium acetate (28.5 g) in acetic acid (1 l); stirring was continued for 1 h, then the mixture was cooled to near its freezing point and the precipitate was filtered off, yielding the acetate (85 g, 80%) of the 8-bromo-derivative (21). A further amount of (21) (total yield 90.5%) was obtained by evaporating the mother liquors, taking up the residue in ethanol, and adding ammonia to pH 8.5. The free *base* had m.p. 155—156° (from ethyl acetate) (Found: Br, 17.3; N, 3.0. $C_{25}H_{26}BrNO_3$ requires Br, 17.1; N, 3.0%).

(±)-8-*Bromo*-N-*methylcoclaurine* (4).—(*a*) This was obtained [5] from the perchlorate of the bisbenzyloxy-derivative (16) in 95% yield; m.p. 175—176° (lit.,[5] 182—183°).

(*b*) The 4′-benzyloxy-7-hydroxy-compound (21) (80 g) was debenzylated in a similar way by refluxing with concentrated hydrochloric acid (800 ml), methanol (800 ml), and water (160 ml) for 75 min; yield 96%.

Irradiation of (±)-8-*Bromo*-N-*methylcoclaurine* (4).—(a) *Preliminary experiments.* A solution of the bromo-compound (4 g) and trisodium phosphate dodecahydrate (24 g) in water (1 l) was irradiated at 15—18 °C for 8 h with a 700 W medium-pressure mercury-vapour lamp, through a Pyrex immersion well with cooling jacket. Acetic acid was added (pH 8.5), and the solution was extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated and the residue was chromatographed on silica gel (200 g) [elution with chloroform, and then chloroform–methanol (96 : 4)], affording (±)-glaziovine (1), m.p. 222—224° (from ethyl acetate), identical (t.l.c., i.r.) with the natural product.[2] Further elution with chloroform–methanol (9 : 1) afforded some starting material (4), followed by (±)-apoglaziovine (11), precipitated from ethanol as the picrate, which was reconverted into the base with aqueous 2,2′-iminodiethanol; this showed m.p. 231—233° and was identical [t.l.c., n.m.r. spectrum in $(CD_3)_2SO$] with a sample obtained [1] from *Ocotea glaziovii*. Further elution of the column with chloroform–methanol (9 : 1) gave (±)-*N*-methylcoclaurine (3), m.p. 154—156° (from toluene), identical (t.l.c., i.r.) with an authentic sample.[26]

Experiments in which sodium sulphite or sodium dithionite (700 mg l^{-1}) was added gave similar results, but the products were more easily purified; no apparent advantage was shown under these conditions by the addition of sodium iodide.

(b) *Kinetic measurements.* A solution of the bromo-compound (4 g), trisodium phosphate dodecahydrate (24 g), and sodium sulphite (0.7 g) in water (1 l) was used; this solution, in a 1 cm cell, showed 10 and 20% transmittance, respectively, at 340 and 350 nm; it was irradiated as in (a) under nitrogen at 16—17 °C. Samples were taken at various times, buffered with ammonium chloride, and diluted with

[26] D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 1954, 669.
[27] L. V. Volkova, O. N. Tolkachev, and N. A. Preobrashenskii, *Doklady Akad. Nauk. S.S.S.R.*, 1955, **102**, 521 (*Chem. Abs.*, 1956, **50**, 4491).
[28] Y.-Y. Hsie, P.-C. Pan, W.-C. Chen, and Y.-S. Kao, *Sci. Sinica* 1964, **12**, 2020 (*Chem. Abs.*, 1965, **62**, 9184).

ethanol; the amounts of starting material and compounds (1), (3), and (11) were determined on t.l.c. by fluorescence quenching on a Vitatron densitometer [development with CH_2Cl_2–CH_3OH–H_2O (89 : 10.2 : 0.8)] (Figure 1). A 6- to 7-fold increase in rate, with overall similar results, was obtained when a quartz immersion well was used and a refrigerated aqueous solution of lead(II) chloride (0.5%) was circulated in the jacket; interposition of a thin (1 mm) sleeve of common glass approximately halved the rate with respect to Pyrex.

Irradiating a solution of (±)-glaziovine (1) (3 g l^{-1}) in aqueous sodium phosphate through Pyrex for 4 h resulted in 18% decomposition, as estimated by densitometry on t.l.c.; neither (3) nor (11) was formed under these conditions.

(c) *Preparation of* (±)-*glaziovine* (1). A solution of compound (4) was prepared and irradiated through the lead chloride solution as described in (b) for 40 min, thus forming (1) in 27—30% yield while leaving about 40% of unchanged (3); products from three 1 l runs were combined and extracted with chloroform (3 × 1.5 l). The extracts were evaporated and the residue was chromatographed on alumina (200 g; activity IV); elution with chloroform afforded (±)-glaziovine (1) (2.46 g, 26%), m.p. 220—222°. Unchanged (4) and minor products (3) and (11) were left in the aqueous phase, from which they were recovered by adding hydrochloric acid (pH 8.5) and extracting with chloroform–methanol (4 : 1).

1-(4-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methyl*-8-*nitroisoquinoline* (22).—A solution of nitric acid (65%; 26.6 ml) in water (85 ml) was added at 25 °C to a stirred solution of the isoquinoline (20) (60 g) in chloroform (300 ml), Thereafter, sodium nitrite (0.3 g) was added and the mixture was stirred at 30 °C for 90 min; crystallization of the nitrate of (22) started within a few minutes. The mixture was cooled and the nitrate was filtered off and washed with cold chloroform, water, and ethyl acetate. A *sample* recrystallized from ethanol had m.p. 135—137° (decomp.) (Found: N, 8.6. $C_{25}H_{26}N_2O_5,HNO_3$ requires N, 8.4%); the salt was dissolved in methanol (150 ml) and ammonia was added (pH 8.5), thus precipitating the *base* (55.5 g, 83%), m.p. 183—185°. A recrystallized sample had m.p. 190—191° (from acetonitrile) (Found: C, 68.9; H, 6.1; N, 6.4. $C_{25}H_{26}N_2O_5$ requires C, 69.1; H, 6.0; N, 6.4%).

8-*Amino*-1,2,3,4-*tetrahydro*-7-*hydroxy*-1-(4-*hydroxybenzyl*)-6-*methoxy*-2-*methylisoquinoline* (23).—The nitro-compound (22) (50 g) in acetic acid (250 ml) was hydrogenated over 5% palladium–charcoal (10 g) under 3—4 atm for 12 h; the catalyst was filtered off, the solvent evaporated off under reduced pressure, and the residue taken up in ice–water. The solution was made basic (pH 8.5) with ammonia and the precipitated *base* (23) was filtered off and dried at room temperature under nitrogen (33.2 g, 92%; m.p. 206—208°). A recrystallized sample had m.p. 213—214° (from methanol) (Found: N, 8.8. $C_{18}H_{22}N_2O_3$ requires N, 8.9%).

Irradiation of the Diazo-oxide (24).—Sodium nitrite (2.1 g) was added at 0—5 °C to a solution of the amine (23) (9.42 g) in N-sulphuric acid (300 ml); thereafter, cold 2N-sodium hydroxide (250 ml) (the yellow diazo-oxide was at first precipitated and then redissolved) and water (450 ml) were added. The solution which showed 10 and 20% transmittance at 625 and 655 nm, respectively, was irradiated in a Pyrex vessel under nitrogen at 15 °C under the conditions indicated for (±)-8-bromo-*N*-methylcoclaurine. In this case, the starting material had completely reacted in 15 min; the yields of compounds (1), (3), and (11) were estimated as 48, 4, and 28%, respectively, by densitometry on t.l.c. Hydrochloric acid was added to the solution (pH 8.5), then chloroform (150 ml); the mixture was stirred and filtered, the chloroform layer was separated, and the aqueous phase was extracted with chloroform (4 × 150 ml). The extracts were dried (Na_2SO_4) and evaporated and the residue was chromatographed on alumina (120 g); elution with chloroform afforded (±)-glaziovine (1) (4.02 g, 45%), m.p. 220—222° (from ethyl acetate).

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