Studies on the Syntheses of Heterocyclic Compounds. Part DLXXVII.† An Abnormal Hofmann Degradation of Phenolic Berbinium Salts

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Hofmann degradation of 11-hydroxy-10-methoxy-7-methyl-2,3-methylenedioxyberbinium iodide (2) with methanolic potassium hydroxide gave 1,2,3,4-tetrahydro-1-(5-hydroxy-4-methoxy-2-methoxymethylbenzyl)-6,7-methylenedioxy-2-methylisoquinoline (14) in addition to the normal methine base (7). Abnormal Hofmann degradation was observed with schefferine methiodide (3) and nandinine methiodide (4). The mechanism of this type of reaction and the biogenesis of the protoberberine alkaloid mecambridine (22) are discussed.

HOFMANN degradation has been widely applied in determining structures of alkaloids, as illustrated by the formation of normal and abnormal methine bases [(6) and (11)] by treatment of the berbinium salt (1) [1,2] with sodium hydroxide. In some cases, this reaction is a key step in the conversion of tetrahydroprotoberberines into protopine-[3] and benzophenanthridine-type bases.[4] Since a methine base of type (11) is necessary for the synthesis of a protopine-type alkaloid, we have investigated the formation of such abnormal products by Hofmann degradation of the methiodides of the phenolic bases.

Heating 11-hydroxy-10-methoxy-7-methyl-2,3-methylenedioxyberbinium iodide (2), prepared from the corresponding berbine [5] and methyl iodide, with an excess of methanolic 20% potassium hydroxide for 3 h on a water-bath gave, after silica gel column chromatography, the normal methine base (7), in 18·8% yield [δ ($CDCl_3$) 5·15 (1H, dd, *J* 2 and 10 Hz), 5·43 (1H, dd, *J* 2 and 16 Hz), and 7·21 (1H, dd, *J* 10 and 16 Hz)] and an unexpected compound (14) in 58·8% yield, but no stilbene-type compound (12). The unexpected compound, $C_{21}H_{25}NO_5$, contained a phenolic 1,2,3,4-tetrahydroisoquinoline system, as shown by its i.r. [$\nu_{max.}$ ($CHCl_3$) 3545 cm^{-1}] and u.v. spectra [$\lambda_{max.}$ (MeOH) 289·5 nm], and supported a mass spectral fragment ion (18) (base peak) at *m/e* 188. The n.m.r. spectrum [δ ($CDCl_3$)] showed an aliphatic *O*-methyl group [3·35 (3H, s)], a methylene group [4·13 (2H, s)] between an aromatic ring and an oxygen function, and an aromatic proton [5·99 (1H, s)] resonating at abnormally high field, in addition to one *N*-methyl, one aromatic *O*-methyl, and one methylenedioxy-group and three aromatic protons. Thus, the compound could be assigned the secoberbine structure (14).

Similarly, schefferine [6] methiodide (3) gave the normal methine base (8) and the secoberbine (15), whose spectroscopic properties (see Experimental section) were similar to those of the analogue (14). Similar treatment of (3) with ethanolic 20% potassium hydroxide afforded the methine base (8) and the *O*-ethyl analogue (16).

Nandinine [5] methiodide (4) also gave the normal methine base (9) and the secoberbine (17), but not the stilbene-type methine base (13) reported by Giacopello and Deulofeu.[7]

The formation of the secoberbine (15) from the phenolic quaternary salt (3) must involve a quinonoid intermediate (20); [8] it does not take place by an S_N2-type reaction (21) (see Scheme 2), as shown by the fact that only the normal methine base (10) was formed in a Hofmann degradation of the nonphenolic quaternary base (5) under the same conditions.

The formation of the secoberbine-type base from the berbinium salt provides the evidence for a biogenetic

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[2] D. Giacopello, V. Deulofeu, and J. Comin, *Tetrahedron*, 1964, **20**, 2971; A. L. Margni, D. Giacopello, and V. Deulofeu, *J. Chem. Soc.* (*C*), 1970, 2578.

[3] R. D. Haworth and W. H. Perkin, jun., *J. Chem. Soc.*, 1926, 1769.

[4] M. Onda, K. Yonezawa, and K. Abe, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 404; 1971, **19**, 31.

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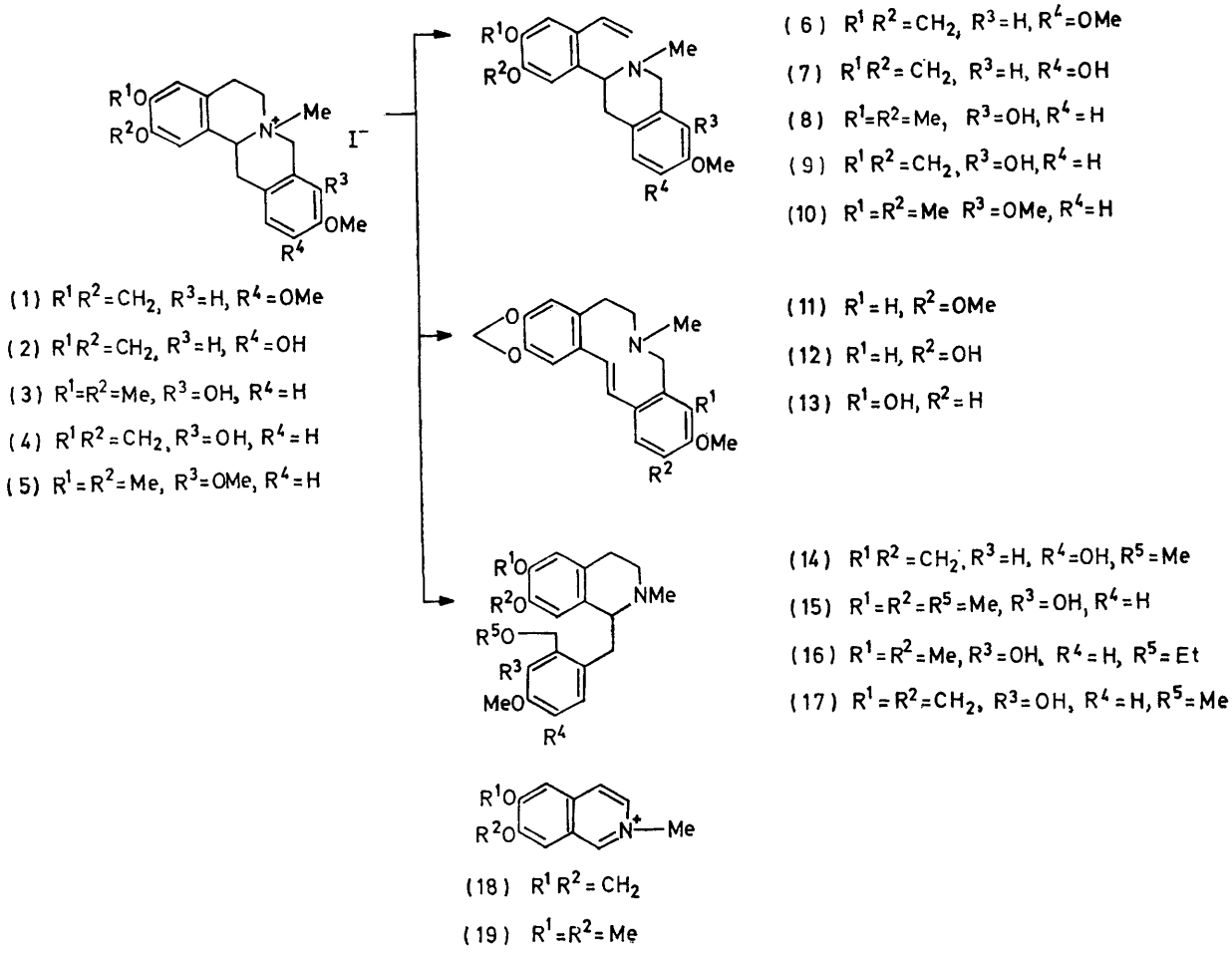
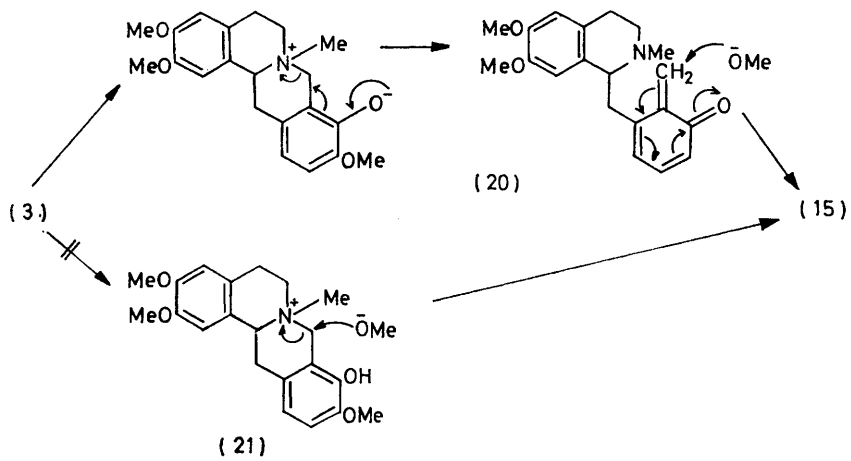
[7] D. Giacopello and V. Deulofeu, *Tetrahedron*, 1967, **23**, 3265.

[8] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 4009; 1970, **92**, 4943; M. Shamma and J. F. Nugent, *Tetrahedron Letters*, 1970, 2625; *Chem. Comm.*, 1970, 1713; *Tetrahedron*, 1973, **29**, 1265.



SCHEME 1



SCHEME 2

route to mecambridine (22) (Scheme 3) different from that previously suggested,[9] and also for the mechanism of formation of spirobenzylisoquinoline alkaloids put forward by Shamma.[8]

[9] V. Preininger, V. Simánek, and F. Šantavý, *Tetrahedron Letters*, 1969, 2109.

EXPERIMENTAL

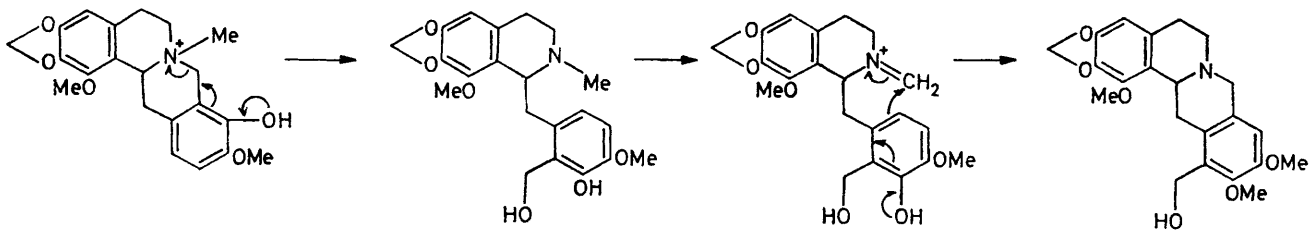
M.p.s are not corrected and were measured with a Yanagimoto micro apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 grating spectrophotometer, n.m.r. spectra with a Hitachi H-60 spectrometer with tetramethylsilane as internal standard, mass spectra with a Hitachi RMU-7

spectrometer, and u.v. spectra with a Hitachi 124 spectrometer.

Treatment of 11-*Hydroxy*-10-*methoxy*-2,3-*methylenedioxyberbine Methiodide* (2) *with Alkali*.—A suspension of the berbine [5] methiodide (2) (750 mg) in methanolic 20% potassium hydroxide (50 ml) was refluxed for 3 h. The solvent was then distilled off *in vacuo*, and to the residue was added an excess of crystalline ammonium chloride. The mixture was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated to leave a gum (550 mg), which was subjected to silica gel (10 g) column chromatography with chloroform and methanol–chloroform (1 : 99 v/v) as eluants. The chloroform eluted 1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methyl*-3-(4,5-*methylenedioxy*-2-*vinylphenyl*)*isoquinoline* (7) (100 mg, 18·4%) as yellow needles, m.p. 147—148° (from benzene) (Found: C, 71·2; H, 6·2; N, 4·3. $C_{20}H_{21}NO_4$ requires C, 70·8; H, 6·2; N, 4·1%), $\nu_{max.}$ ($CHCl_3$) 3550 cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 265 and 290 nm, δ ($CDCl_3$) 2·18 (3H, s, NMe), 3·84 (3H, s, OMe), 5·15 (1H, dd, *J* 2 and 10 Hz, *cis*-HC*H*=CH), 5·43 (1H, dd, *J* 2 and 16 Hz, *trans*-*H*CH=CH), 5·93 (2H, s, O·CH_2·O), 6·53 (1H, s, ArH), 6·58 (1H, s, ArH), 6·97 (2H, s, ArH), and 7·21 (1H, dd, *J* 10 and 16 Hz, CH_2=C*H*). Methanol–chloroform eluted 1,2,3,4-*tetrahydro*-1-(5-*hydroxy*-4-*methoxy*-2-*methoxymethylbenzyl*)-2-*methyl*-6,7-*methylenedioxyisoquinoline* (14) (350 mg, 58·8%) as prisms, m.p. 135—136° (from ethanol) (Found: C, 68·1; H, 6·9; N, 3·8. $C_{21}H_{25}NO_5$ requires C, 67·9; H, 6·8; N, 3·8%), $\nu_{max.}$ ($CHCl_3$) 3545 cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 289·5 nm, δ ($CDCl_3$) 2·43 (3H, s, NMe), 3·28 (3H, s, $ArCH_2$·O·C*H*$_3$), 3·82 (3H, s, OMe), 4·13 (2H, s, $ArCH_2$·OMe), 5·78 (2H, s, O·CH_2·O), 5·99 (1H, s, 8-H), 6·51 (1H, s, ArH), 6·69 (1H, s, ArH), and 6·78 (1H, s, ArH), *m/e* 371 (M^+), 370 ($M^+ - 1$), and 190 (base peak).

(±)-*Schefferine* α- *and* β-*Methiodides* (3).*—To a solution of (±)-schefferine [6] (3 g) in methanol (50 ml) was added methyl iodide (5 ml), and the mixture was set aside at room temperature overnight. The precipitate was collected and recrystallised from methanol to give the β-*methiodide* (3β) (1·8 g) as pale yellowish prisms, m.p. 275—277° (decomp.) (Found: C, 50·6; H, 5·85; N, 2·7. $C_{21}H_{26}INO_4,H_2O$ requires C, 50·3; H, 5·6; N, 2·8%). The mother liquor was evaporated to dryness and the residue was recrystallised from methanol to afford the α-*methiodide* (3α) as prisms, m.p. 284—288° (decomp.) (Found: C, 51·9; H, 5·65; N, 2·8. $C_{21}H_{26}INO_4$ requires C, 52·2; H, 5·4; N, 2·9%).

Reaction of (±)-*Schefferine Methiodides* (3) *with Methanolic Potassium Hydroxide*.—A suspension of the methiodides (3) (750 mg) in methanolic 20% potassium hydroxide (50 ml) was refluxed for 1 h, and the product worked up as above to give a gum which was chromatographed on silica gel (20 g). Elution with chloroform–methanol (99·5 : 0·5 v/v) gave 3-(4,5-*dimethoxy*-2-*vinylphenyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methylisoquinoline* (8) (260 mg, 47·2%) as prisms, m.p. 128—130° (from hexane) (Found: C, 70·8; H, 7·1; N, 3·6. $C_{21}H_{25}NO_4$ requires C, 71·0; H, 7·1; N, 3·9%), $\nu_{max.}$ ($CHCl_3$) 3590 cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 263 and 288 nm, δ ($CDCl_3$) 2·20 (3H, s, NMe), 3·80 (3H, s, OMe), 3·82 (3H, s, OMe), 3·88 (3H, s, OMe), 5·12 (1H, dd, *J* 2 and 9 Hz, *cis*-HC*H*=CH), 5·44 (1H, dd, *J* 2 and 17 Hz, *trans*-*H*CH=CH), 5·78br (1H, s, OH), 6·46 (1H, d, *J* 9 Hz, ArH), 6·67 (1H, d, *J* 9 Hz, ArH), 6·92 (1H, s, ArH), 6·95 (1H, s, ArH), and 7·18 (1H, dd, *J* 9 and 17 Hz, C*H*=CH_2), *m/e* 355 (M^+), 354, 340, 324, 218, and 206. Elution with chloroform–methanol (98 : 2 v/v) afforded the secoberbine (15) (45 mg, 7·5%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3580 cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 287 nm, δ ($CDCl_3$) 2·52 (3H, s, NMe), 3·82 (6H, s, 2 × OMe), 3·35 (3H, s, $ArCH_2$·O·C*H*$_3$), 3·48 (3H, s, OMe), 4·27 and 4·52 (each 1H, each d, *J* 11 Hz, $ArCH_2$·OMe), 5·80 (1H, s, ArH), 6·47 (1H, d, *J* 8 Hz, ArH), 6·55 (1H, s, ArH), and 6·72 (1H, d, *J* 8 Hz, ArH).



(22)

Scheme 3

Reaction of (±)-*Schefferine Methiodides* (3) *with Ethanolic Potassium Hydroxide*.—A suspension of the methiodide (3) (500 mg) in ethanolic 20% potassium hydroxide (50 ml) was refluxed for 1 h, and the product worked up as before to give a gum, which was chromatographed on silica gel (15 g). Elution with chloroform–methanol (99·5 : 0·5 v/v) gave the methine base (8) (160 mg, 43·6%), identical with the sample prepared by treatment of (3) with methanolic potassium hydroxide. Elution with chloroform–methanol (98 : 2 v/v) afforded the secoberbine (16) (35 mg, 8·4%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3580 cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 258 and 286 nm, δ ($CDCl_3$) 1·20 (3H, t, *J* 7 Hz, O·CH_2·C*H*$_3$), 2·54 (3H, s, NMe), 3·47 (3H, s, OMe), 3·84 (3H, s, 2 × OMe), 4·35 and 4·55 (each 1H, each d, *J* 11 Hz, $ArCH_2$·OEt), 5·82 (1H, s, ArH), 6·44 (1H, d, *J* 8 Hz, ArH), 6·56 (1H, s, ArH), and 6·72 (1H, d, *J* 8 Hz, ArH).

Reaction of (±)-*Nandinine Methiodides* (4) *with Methanolic Potassium Hydroxide*.—A suspension of the methiodides (4) [5] (750 mg) in methanolic 20% potassium hydroxide (50 ml) was refluxed for 1 h, and the product worked up as before to give a gum, which was chromatographed on silica gel (15 g). Elution with chloroform–methanol (99·5 : 0·5 v/v) gave the methine base (9) (210 mg, 38·6%) as an oil, $\lambda_{max.}$ (MeOH) 264 and 303 nm, δ ($CDCl_3$) 2·21 (3H, s, NMe), 3·83 (3H, s, OMe), 5·12 (1H, dd, *J* 2 and 10 Hz, *cis*-HC*H*=CH), 5·42 (1H, dd, *J* 2 and 17 Hz, *trans*-*H*CH=CH), 5·92 (2H, s, O·CH_2·O), 6·50 (1H, d, *J* 8 Hz, ArH), 6·69 (1H, d, *J* 8 Hz, ArH), 6·94 (1H, s, ArH), 6·96 (1H, s, ArH), and 7·17 (1H, dd, *J* 10 and 17 Hz, C*H*=CH_2). Elution with chloroform–methanol (98 : 2 v/v) afforded the secoberbine (17)

* The α- and β-methiodides are so described according to the nomenclature of ref. 10.

[10] H. A. D. Jowett and F. L. Pyman, *J. Chem. Soc.*, 1913, **103**, 2908.

(30 mg, 5%) as an oil, $\lambda_{max.}$ (MeOH) 291 nm, δ ($CDCl_3$) 2·50 (3H, s, NMe), 3·38 (3H, s, $ArCH_2{\cdot}O{\cdot}CH_3$), 3·76 (3H, s, OMe), 4·38 and 4·59 (each 1H, each d, *J* 11·5 Hz, $ArCH_2{\cdot}$OMe), 5·82 (2H, s, $O{\cdot}CH_2{\cdot}O$), 5·98 (1H, s, 8-H), 6·51 (1H, d, *J* 9 Hz, ArH), 6·54 (1H, s, ArH), and 6·74 (1H, d, *J* 9 Hz, ArH).

Reaction of Canadine Methiodide (5) *with Methanolic Potassium Hydroxide*.—A suspension of the methiodide (5) (500 mg) in methanolic 20% potassium hydroxide (50 ml) was refluxed for 1 h, and the product worked up as before to give a gum, which was chromatographed on silica gel (15 g). Elution with chloroform–methanol (99·5 : 0·5 v/v) gave the *methine base* (10) (85 mg, 22·4%) as prisms, m.p. 114—115° (from hexane) (Found: N, 3·75. $C_{21}H_{23}NO_4$ requires N, 3·95%), δ ($CDCl_3$) 2·22 (3H, s, NMe), 3·84 (6H, s, OMe), 5·18 (1H, dd, *J* 2 and 11 Hz, *cis*-HC*H*=CH), 5·46 (1H, dd, *J* 2 and 17 Hz, *trans*-*H*CH=CH), 5·94 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·77 (2H, s, ArH), and 7·19 (1H, dd, *J* 11 and 17 Hz, C*H*=CH_2).

We thank Mrs. H. Hori, Mrs. A. Sato, Mrs. C. Koyanagi, Miss A. Ujie, Miss R. Kato, Miss C. Sato, Miss R. Suenaga, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements.

[4/1602 *Received*, 31*st July*, 1974]