Studies on the Syntheses of Heterocyclic Compounds. Part DXCVII.† Novel Formation of Benzo[5,6]cyclohept[1,2,3-*ij*]isoquinolines from Berbinium Salts

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Heating coreximine methiodide (5) with methanolic potassium hydroxide solution gave the secoberbine (13) and 1,2,3,7,12,12a-hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo[5,6]cyclohept[1,2,3-*ij*]isoquinoline (14). The latter was converted into its *OO*-dimethyl ether (16), which was also synthesised from laudanosine (18) with formalin in the presence of hydrochloric acid. Treatment of the monophenolic secoberbine (12) with acid gave the corresponding benzocycloheptisoquinoline.

PREVIOUSLY we have reported that Hofmann degradation of the 9- and 11-hydroxyberbinium salts (1) and (2) by treatment with methanolic potassium hydroxide gave the secoberbines (11) and (12) in addition to the methine bases (6) and (7), whereas the non-phenolic base (3) afforded only the methine base (8).[1] This type of abnormal Hofmann degradation of some berbinium salts possessing a phenolic hydroxy-group at other positions has been further investigated. The present paper describes the results for discretine methiodide (4) and coreximine methiodide (5), and also the formation of benzocycloheptisoquinolines from the secoberbines.

When discretine[2] methiodide (4) was refluxed with methanolic potassium hydroxide solution for 3 h, only the methine base (9) was obtained (43%); no secoberbine was observed on t.l.c. This is consistent with our suggested mechanism of formation of the secoberbine, which involves a phenolic hydroxy-group at either C-9 or C-11 in the berbine system.[1]

On the other hand, treatment of coreximine[3] methiodide (5) with hot methanolic 20% potassium hydroxide for 4 h gave no methine base (10) but afforded instead a separable mixture of the secoberbine (13) (30%) and a novel compound (14) (15%). A large amount of quaternary berbine was recovered from the aqueous solution after extraction. Treatment under the same conditions for 40 h gave the secoberbine (13) and compound (14) in yields of 17 and 60%, respectively. The same treatment for 72 h gave the product (14) in 78% yield.

Compound (14) [*m/e* 341 (M^+)], containing a phenolic 1,2,3,4-tetrahydroisoquinoline system [$\nu_{max.}$ ($CHCl_3$) 3530 cm^{-1}; $\lambda_{max.}$ (MeOH) 288 nm], was acetylated to furnish a diacetate (15) [*m/e* 425 (M^+); $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1} (ArO·COMe); δ ($CDCl_3$) 2·24 and 2·35 (each 3H, each s, 2 × COMe)] and methylated with diazomethane to afford a tetramethoxy-compound (16) [*m/e* 369 (M^+)]. The n.m.r. spectrum of the diphenolic base (14) in $CDCl_3$–$(CD_3)_2SO$ showed the presence of methylene protons between two aromatic rings [δ 4·0 (broad singlet)], three isolated aromatic protons [singlets at 6·45, 6·46, and 6·63] and an *N*-methyl (2·53) and two *O*-methyl groups (3·78). Heating the secoberbine (13) with methanolic 20% potassium hydroxide solution for 24 h gave compound (14), identical with the product obtained directly from (5).

The identification of the benzocycloheptisoquinoline (14) was confirmed by an alternative synthesis of the tetramethoxy-compound (16). Refluxing the laudanosine (18) with 37% formalin and acetic acid in the presence of hydrochloric acid for 14 h[4] gave compound (16) in 53% yield, the i.r. and n.m.r. spectra of which were identical with those of the derivative obtained from the Hofmann degradation product (14). Refluxing coreximine methiodide (5) with sodium methoxide in dry methanol for 10 h gave a mixture (1 : 1) of the secoberbine (13) and the cyclic compound (14) in 60% yield.

When the previously obtained monophenolic secoberbine (12)[1] was refluxed for 48 h with ethanolic 20% potassium hydroxide, the ethoxymethyl compound (19) [δ ($CDCl_3$) 3·45 and 1·19 (2H, and 3H, q, and t, *J* 7 Hz,

† Part DXCVI, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, **3**, 143.

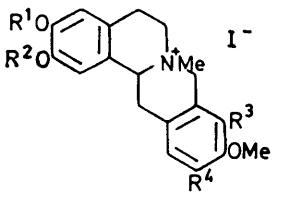
[1] T. Kametani, M. Takemura, K. Fukumoto, T. Terui, and A. Kozuka, *Heterocycles*, 1974, **2**, 433; *J.C.S. Perkin I*, 1974, 2678.

[2] T. Kametani, M. Takeshita, and S. Takano, *J.C.S. Perkin I*, 1972, 2834.

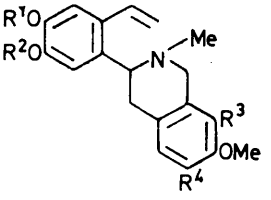
[3] T. Kametani and M. Ihara, *J. Pharm. Soc. Japan*, 1967, **87**, 174; M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan*, 1960, **80**, 1238; A. R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc.* (*C*), 1966, 1052.

[4] A. von Baeyer, *Ber.*, 1972, **5**, 280; L. H. Baekeland, *Ind. and Eng. Chem.*, 1909, **1**, 149.

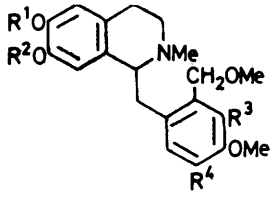
$ArCH_2O{\cdot}CH_2{\cdot}CH_3$), and 4·21 (2H, s, $ArCH_2{\cdot}OEt$)] was obtained in 95% yield, but the tetracyclic compound (17)



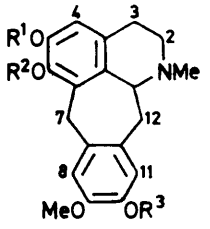
(1) $R^1R^2=CH_2, R^3=OH, R^4=H$
(2) $R^1R^2=CH_2, R^3=H, R^4=OH$
(3) $R^1=R^2=Me, R^3=OMe, R^4=H$
(4) $R^1=R^3=H, R^2=Me, R^4=OMe$
(5) $R^1=Me, R^2=R^3=H, R^4=OH$



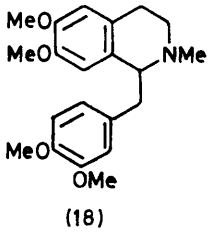
(6) $R^1R^2=CH_2, R^3=OH, R^4=H$
(7) $R^1R^2=CH_2, R^3=H\ R^4=OH$
(8) $R^1=R^2=Me, R^3=OMe, R^4=H$
(9) $R^1=R^3=H, R^2=Me, R^4=OMe$
(10) $R^1=Me, R^2=R^3=H, R^4=OH$



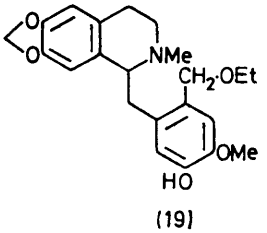
(11) $R^1R^2=CH_2, R^3=OH, R^4=H$
(12) $R^1R^2=CH_2, R^3=H, R^4=OH$
(13) $R^1=Me, R^2=R^3=H, R^4=OH$



(14) $R^1=Me, R^2=R^3=H$
(15) $R^1=Me, R^2=R^3=Ac$
(16) $R^1=R^2=R^3=Me$
(17) $R^1R^2=CH_2, R^3=H$

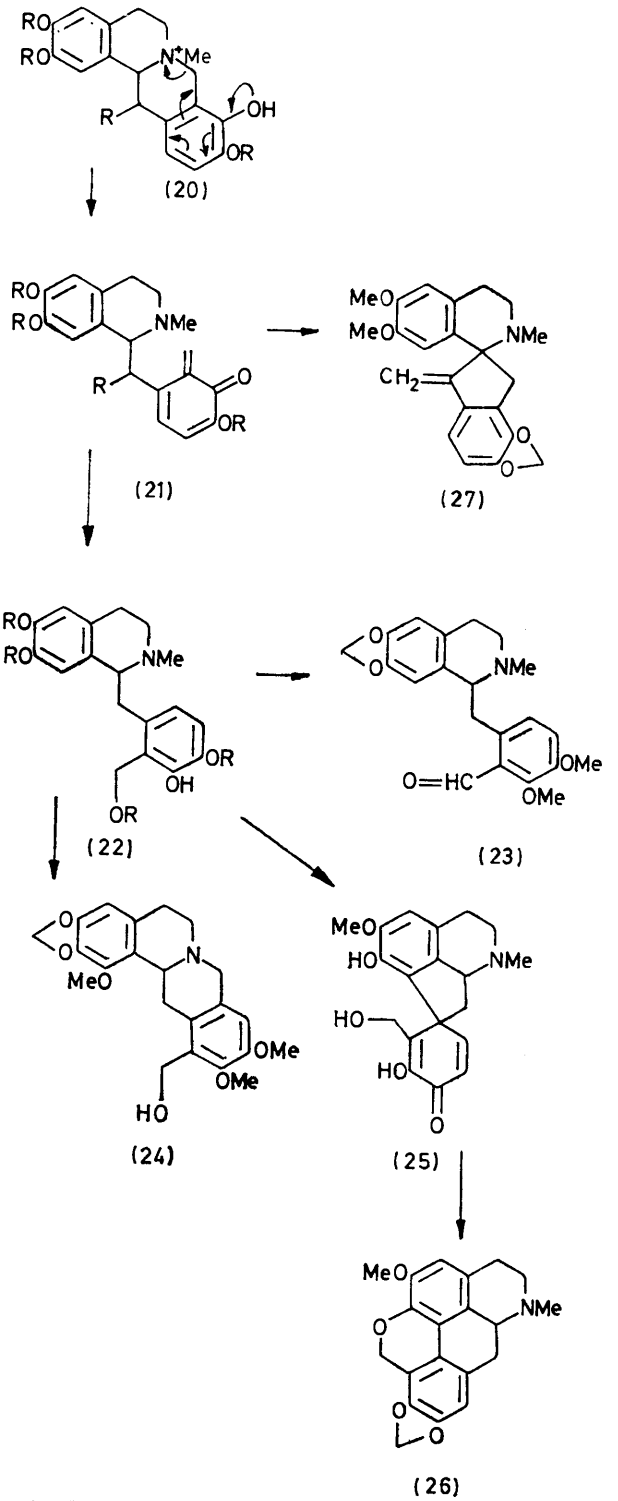


(18)



(19)

was not formed. It is therefore considered that these secoberbines are formed by a reversible reaction through the corresponding quinonoid intermediates. In order to obtain the tetracyclic compound under basic conditions, a phenolic hydroxy-group should be located at C-7, thus increasing the electron density at C-8 of the tetrahydroisoquinoline. On the other hand, heating compound (12)



(20) (21) (22) (23) (24) (25) (26) (27)

in ethanolic hydrochloric acid for 2 h gave, in 96% yield, the tetracyclic compound (17), the structure of which was confirmed by spectral analysis. This ready cyclisation under acidic conditions presumably occurs *via* a protonated quinonoid intermediate, which is a good electrophile. Heating the methiodide (2) with 30% potassium t-butoxide in t-butyl alcohol for 5 h afforded only the styrene (7), in 72% yield.

The quinonoids (21), derived from the berbinium salts (20), could play an important role in the biogenesis of certain benzylisoquinoline alkaloids. Thus nucleophilic attack on the quinonoid methylene group would generate the secoberbines (22),[1] which could then be oxidised to canadaline (23),[5] mecambridine (24),[1] or the proaporphine (25). The latter could then rearrange to *N*-demethylthalphenine (26).[6] On the other hand, coupling between the quinonoid methylene group and C-1 of the isoquinoline could give the spirobenzylisoquinoline alkaloid (27).[7]

EXPERIMENTAL

I.r. spectra were taken with a Hitachi 215 recording spectrophotometer, mass spectra with a Hitachi RMU-7 spectrophotometer, and n.m.r. spectra with a Hitachi R-20 or JNM-PMX 60 instrument.

Hofmann Degradation of (±)-*Discretine Methiodide* (4).—The methiodide (4) (400 mg) of (±)-discretine, prepared from the base and methyl iodide as usual, was dissolved in methanol (100 ml) containing potassium hydroxide (30 g), and the resulting mixture was heated for 3 h under reflux. The solvent was evaporated off and the residue was treated with water (100 ml) and then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a viscous syrup, which was chromatographed on silica gel (10 g) with benzene–ether (1 : 1) as eluant to afford 1,2,3,4-tetrahydro-3-(4-hydroxy-5-methoxy-2-vinylphenyl)-6,7-dimethoxy-2-methylisoquinoline (9) as a pale yellow viscous syrup (125 mg, 43%). The *hydrochloride* formed needles, m.p. 185—187° (from methanol–ether) (Found: C, 58·8; H, 6·9; N, 2·8. $C_{21}H_{25}NO_4$,HCl,$2H_2O$ requires C, 58·7; H, 7·05; N, 3·25%), $\nu_{max.}$ ($CHCl_3$) 3600 cm^{-1} (OH), δ ($CDCl_3$) 7·11 (1H, dd, *J* 10 and 17 Hz, C*H*=CH_2), 6·96, 6·87, and 6·43 (1H, 1H, and 2H, each s, 4 × ArH), 5·37 (1H, dd, *J* 2 and 17 Hz, CH=CH*H*), 5·05 (1H, dd, *J* 2 and 10 Hz, CH=C*H*H), 3·74 and 3·70 (6H and 3H, each s, 3 × OMe), and 2·11 (3H, s, NMe).

Hofmann Degradation of Coreximine Methiodide (5).—(*a*) A solution of coreximine methiodide (5) (300 mg) in methanolic 20% potassium hydroxide solution (30 ml) was refluxed for 40 h and then diluted with water. Methanol was evaporated off, and crystalline ammonium chloride was added to the residue, which was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a powder (200 mg), which was recrystallised from chloroform to afford 1,2,3,7,12,12a-*hexahydro*-6,10-*dihydroxy*-5,9-*dimethoxybenzo*[5,6]*cyclohept*[1,2,3-ij]*isoquinoline* (14) (100 mg) as needles, m.p. 182—183°. The mother liquor was concentrated and then subjected to column chromatography on silica gel (3 g) with chloroform and methanol–chloroform (1 : 99) as eluants. The former eluate gave compound (14) (30 mg; total 60%), m.p. 182—183° (from chloroform) (Found: C, 68·6; H, 6·65; N, 3·95. $C_{20}H_{23}NO_4$,$0·5H_2O$ requires C, 68·55; H, 6·9; N, 4·0%), δ [$CDCl_3$–$(CD_3)_2SO$] 2·53 (3H, s, NMe), 3·78 (6H, s, 2 × OMe), 4·00br (2H, s, $ArCH_2Ar$), and 6·45, 6·46, and 6·63 (each 1H, each s, ArH); *m/e* 341 (M^+). The latter eluate afforded the secoberbine (13) (40 mg, 17%) as a syrup, δ ($CDCl_3$) 2·42 (3H, s, NMe), 3·25 (3H, s, $ArCH_2{\cdot}OCH_3$), 3·80 and 3·82 (each 3H, each s, 2 × OMe), 4·11 (2H, s, $ArCH_2{\cdot}$OMe), and 6·09, 6·49, 6·69, and 6·75 (each 1H, each s, ArH).

(*b*) A solution of coreximine methiodide (5) (300 mg) in methanolic 20% potassium hydroxide solution (30 ml) was refluxed for 72 h, then worked up as above to give compound (14) (170 mg, 78%), m.p. 182—183° (from chloroform), identical (spectral data) with the product obtained from (*a*).

6,10-*Diacetoxy*-1,2,3,7,12,12a-*hexahydro*-5,9-*dimethoxybenzo*[5,6]*cyclohept*[1,2,3-ij]*isoquinoline* (15).—The diphenolic base (14) (30 mg) was kept at room temperature for 16 h with a mixture of acetic anhydride (0·5 ml) and pyridine (1 ml). Evaporation of the reagents left a residue, which was treated with water and then extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give a syrup which was purified by preparative t.l.c. on silica gel [methanol–chloroform (1 : 10)] to give the diacetate (15) (28 mg) as a syrup, $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1} (ArOAc), δ ($CDCl_3$) 2·24 and 2·35 (each 3H, each s, 2 × $COCH_3$), 2·56 (3H, s, NMe), 3·84 and 3·86 (each 3H, each s, 2 × OMe), and 6·57, 6·61, and 6·67 (each 1H, each s, 3 × ArH), *m/e* 425 (M^+), 410, 383, 366, and 340. Various attempts to crystallise the product resulted in failure.

1,2,3,7,12,12a-*Hexahydro*-5,6,9,10-*tetramethoxybenzo*[5,6]*cyclohept*[1,2,3-ij]*isoquinoline* (16).—(a) *From compound* (14). To a solution of the diphenolic base (14) (30 mg) in ethanol (5 ml) was added an excess of ethereal diazomethane (from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide). The mixture was set aside at room temperature for 24 h. Evaporation left the *tetramethoxy-compound* (30 mg) (16) as needles, m.p. 116—118° (from ether) (Found: C, 71·4; H, 7·25; N, 3·9. $C_{22}H_{27}NO_4$ requires C, 71·5; H, 7·35; N, 3·8%), δ ($CDCl_3$) 2·59 (3H, s, NMe), 3·75, 3·80, and 3·85 (3H, 6H, and 3H, each s, 4 × OMe), 4·05br (2H, s, $ArCH_2Ar$), and 6·53 and 6·72 (2H, and 1H, each s, 3 × ArH), *m/e* 369 (M^+), 354, 338, and 204, $\lambda_{max.}$ (MeOH) 285 nm.

(b) *From laudanosine* (18). A mixture of laundanosine (18) (2 g), 37% formalin (30 ml), concentrated hydrochloric acid (2 ml), and glacial acetic acid (30 ml) was refluxed for 14 h, cooled, basified with sodium hydrogen carbonate, and then extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to afford a pale yellow viscous syrup, which was treated with ether to give the base (16) as prisms (1·1 g, 53%), m.p. 116—118° (from ether), identical with the above compound.

1-(2-*Ethoxymethyl*-5-*hydroxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*methylenedioxyisoquinoline* (19).—A mixture of the secoberbine (12) (100 mg) in ethanolic 20% potassium hydroxide solution (25 ml) was refluxed for 48 h, then treated with water, and the ethanol was evaporated off. Ammonium chloride was added to the residue and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a brown syrup, which was recrystallised from ethanol to afford the ethoxymethyl compound (19) as *needles* (100 mg, 95%), m.p. 115—117° (Found: C, 68·55; H, 6·95; N, 3·7.

[5] J. Gleye, A. Ahond, and E. Stainslas, *Phytochemistry*, 1974, **13**, 675.

[6] M. Shamma and D.-Y. Hwang, *Heterocycles*, 1973, **1**, 31.

[7] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 4009; 1970, **92**, 4943.

$C_{22}H_{27}NO_5$ requires C, 68·55; H, 7·05; N, 3·65%), δ ($CDCl_3$) 1·19 (3H, t, *J* 7 Hz, O·CH_2·CH_3), 2·44 (3H, s, NMe), 3·45 (2H, q, *J* 7 Hz, O·CH_2·CH_3), 3·85 (3H, s, OMe), 4·21 (2H, s, ArCH_2·OEt), 5·80 (2H, s, O·CH_2·O), and 6·03, 6·51, 6·71, and 6·80 (each 1H, each s, 4 × ArH).

1,2,3,7,12,12a-*Hexahydro*-10-*hydroxy*-9-*methoxy*-5,6-*methylenedioxybenzo*[5,6]*cyclohept*[1,2,3-ij]*isoquinoline* (17). —A solution of the secoberbine (12) (100 mg) in ethanolic 10% hydrochloric acid (15 ml) was refluxed for 2 h, diluted with water, and then evaporated. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give compound (17) as *needles* (90 mg, 96%), m.p. 230—231° (from chloroform) (Found: C, 68·65; H, 6·6; N, 3·6. $C_{20}H_{21}NO_4$,0·5H_2O requires C, 68·95; H, 6·35; N, 4·0%), δ (CF_3·CO_2H) 3·98 (3H, s, OMe), 4·09 (2H, s, ArCH_2Ar), 6·03 (2H, s, O·CH_2·O), and 6·69, 6·81, and 6·92 (each 1H, each s, 3 × ArH).

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