An Approach to the Synthesis of Sinomenine

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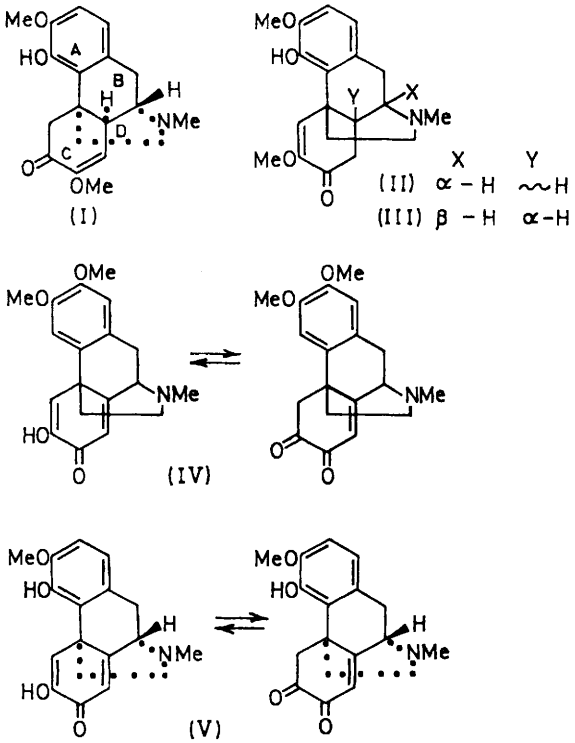
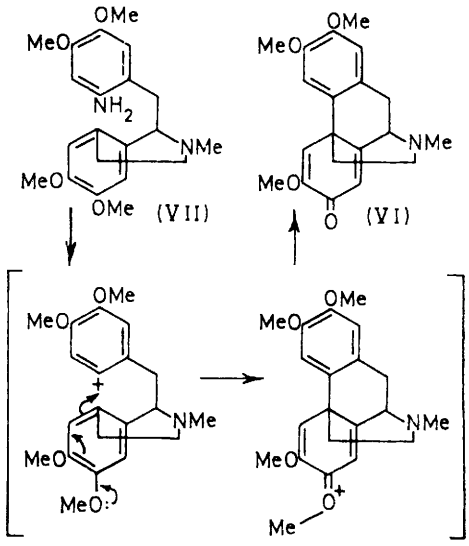
The modified Pschorr reaction of 1-(2-amino-4,5-dimethoxybenzyl)-6-benzyloxy-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (VIII) gave (±)-benzylpredicentrine (X), (±)-predicentrine (XI), and morphinandienone (XII). The (±)-predicentrine (XI) was also obtained by treatment of (X) with acid. Debenzylation of the morphinandienone (XII) afforded a diketone (IV), which had the same basic structure as a precursor (V) in the biogenesis of the sinomenine (I) proposed by Barton.

SINOMENINE, an alkaloid isolated from *Sinomenium acutum*, was studied extensively by Goto and his associates, who assigned to it the morphinan-enone structure (I).[1] Recently, Haynes and his collaborators have isolated a new alkaloid from *Croton linearis* and deduced this to be 8,14-dihydrosalutaridine (II),[2] the enantiomer of isosinomenine (III) found in *S. acutum*.[3] We are investigating the synthesis of these types of alkaloid by modified Pschorr reactions[4] and by phenolic oxidation,[5] and here report the synthesis by a modified Pschorr reaction[4a] of the sinomenine-like compound (IV), which would be useful as a model intermediate in the synthesis of sinomenine.



We have reported a general simple synthesis of the morphinandienone (VI) by the application of the Pschorr reaction to the aminoisoquinoline (VII); this method was also used in order to synthesise a model diketone for the synthesis of sinomenine.

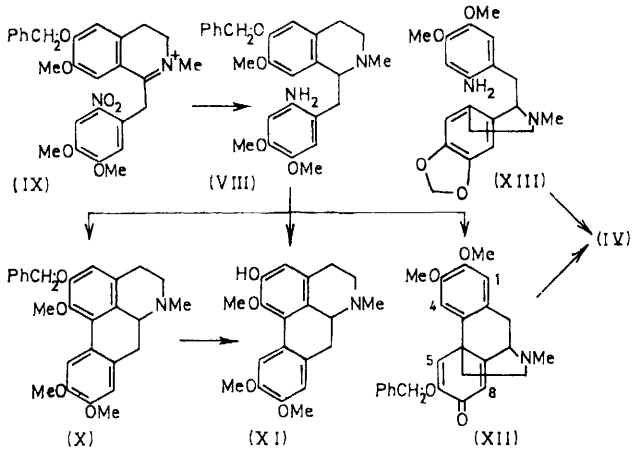


Recently, Barton and his associates suggested that an intermediate in the biogenesis of sinomenine (I) was the diketone or diosphenol (V).[3] We have used the modified Pschorr reaction of the easily available amino-compound (VIII) as a model experiment in order to obtain the diketone (IV) having the same fundamental structure as the diketone (V). The aminoisoquinoline (VIII), obtained by reduction of the nitroisoquinoline (IX)[6] with zinc and hydrochloric acid, was diazotised, and the resulting diazonium salt was decomposed thermally without metallic catalyst to give three compounds, separated and purified by column chromatography.

The first had the composition $C_{27}H_{29}NO_4$ [mass spectrum (M^+ at *m/e* 431) and microanalysis of its hydrochloride]. The u.v. and n.m.r. spectra showed the typical aporphine system [$\lambda_{max.}$ 282 and 302 mμ; τ ($CDCl_3$) 1·90 (C-11 proton)].

[1] K. Goto, 'Sinomenine,' Kitasato Institute, Tokyo, 1964; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa Inc., Tokyo, 1968, pp. 149, 251.
[2] L. J. Haynes, G. E. M. Husbands, and K. L. Stuart, *Chem. Comm.*, 1967, 15.
[3] D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1968, 929.
[4] (*a*) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1398; *J. Chem. Soc.* (*C*), 1969, 520; (*b*) T. Kametani, K. Fukumoto, and T. Sugahara, *Tetrahedron Letters*, 1968, 5459; *J. Chem. Soc.* (*C*), 1968, 801; (*c*) T. Kametani, T. Suguhara, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 1063; (*d*) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), 1969, 2030.
[5] T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *J. Chem. Soc.* (*C*), 1969, 2034, and references cited therein.
[6] R. Charubala, B. R. Pai, T. R. Govindachari, and N. Viswanathan, *Chem. Ber.*, 1968, **101**, 2665.

The second compound was characterised as its hydrochloride, m.p. 215—217° (decomp.), also obtained by the debenzylation of the first compound, and identified as (±)-predicentrine (XI)[6] from spectral evidence. The molecular formula $C_{20}H_{23}NO_4$ was indicated by the mass spectrum (M^+ at *m/e* 341), and the u.v.



spectrum showed $\lambda_{max.}$ 281 and 304 mμ (aporphine structure). The assignment was also supported by fragment ions in the mass spectrum:[7] *m/e* 340 (M — 1), 326 (M — Me), 310 (M — MeO), 298 (M — CH_2=NMe), 283 (M — CH_2=NMe — Me), and 267 (M — CH_2=NMe — OMe), and by the n.m.r. and i.r. spectra, which were identical with those of predicentrine (XI).[6] Thus, the first compound was identified as (±)-2-benzylpredicentrine (X).

The third compound, characterised as its methiodide, was identified as the morphinandienone (XII). The mass spectrum (M^+ at *m/e* 417) of the free base and microanalysis of its methiodide revealed the composition as $C_{26}H_{27}NO_4$. The i.r. spectrum showed the typical α-alkoxylated cross-conjugated cyclohexadienone system[8] ($\nu_{max.}$ 1665, 1645, and 1620 cm.$^{-1}$), also indicated by the u.v. spectrum ($\lambda_{max.}$ 236 and 283 mμ) and the mass spectrum [*m/e* 340 (M — CH_2Ph) and 312 (M — CH_2Ph — CO)]. Moreover, the n.m.r. spectrum (τ in $CDCl_3$) revealed the expected two olefinic and two aromatic (C-1 and C-4) protons as singlets at 3·41, 3·55, 3·60, and 3·70 in addition to an *N*-methyl group (7·66), two *O*-methyl groups (6·35 and 6·19), and the benzyl α-protons (4·90) and aromatic protons (2·68).

Debenzylation of the morphinandienone (XII) with 48% hydrobromic acid under mild conditions afforded the diketone (IV), identical (spectral data and t.l.c. R_F value in two systems) with the sample prepared from the aminoisoquinoline (XIII).[9] We are now attempting the total synthesis of sinomenine by a similar method.

EXPERIMENTAL

N.m.r. spectra were obtained with a Hitachi H-60 spectrometer for solutions in deuteriochloroform, with tetramethylsilane as internal reference. I.r. spectra were taken for solutions in chloroform with a Hitachi EPI-S_2 spectrophotometer, and u.v. spectra for solutions in methanol with a Hitachi EPS-3 recording spectrophotometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer.

1-(2-*Amino*-4,5-*dimethoxybenzyl*)-6-*benzyloxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline* (VIII).—To a solution of 6-benzyloxy-1-(4,5-dimethoxy-2-nitrobenzyl)-3,4-dihydro-7-methoxyisoquinoline methiodide[6] (IX) (4·5 g.) in acetic acid (200 ml.), concentrated hydrochloric acid (70 ml.), and water (40 ml.), was added zinc powder (43 g.) in small portions during 1 hr. at 5—10° with stirring. Stirring was continued for 5 hr. at 5—10°. The mixture was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to leave the aminobenzyl compound (VIII) (2·0 g.), m.p. 96—97° (from benzene–hexane), as colourless needles,[6] $\nu_{max.}$ ($CHCl_3$) 3310—3375 cm.$^{-1}$ (NH_2).

Modified Pschorr Reaction of the Aminobenzylisoquinoline (VIII).—A solution of the aminobenzylisoquinoline (VIII) (3·0 g.) in 5% sulphuric acid (95 ml.) and acetic acid (20 ml.) was diazotised with 10% sodium nitrite (7 ml.) at 0—5° with stirring for 90 min.; stirring was continued for 1 hr. at 5°. The mixture was gradually warmed to 70° and then stirred for a further 2 hr. The cooled mixture was then basified with 10% ammonia and extracted with methylene dichloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown gum (3·0 g.), which was chromatographed on silica gel (80 g.), with methylene dichloride [fractions (100 ml.) 1—13, monitored by i.r. and u.v. spectra] and methylene dichloride–methanol (99 : 1 v/v; fractions 14—23] as eluants. Fractions 7—9 gave the benzylpredicentrine (X) as a yellowish-brown viscous syrup. The *hydrochloride* (250 mg.) gave colourless needles, m.p. 230—232° (from methanol–ether) (Found: C, 67·25; H, 7·0. $C_{27}H_{29}NO_4$,HCl,H_2O requires C, 66·75; H, 6·65%), $\nu_{max.}$ ($CHCl_3$) (free base) 1088 and 1105 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) (free base) 282 and 302 mμ (log ε 4·13 and 4·155), τ ($CDCl_3$) (free base) 7·41 (3H, s, NMe), 6·30 (3H, s, OMe), 6·09 (6H, s, 2 × OMe), 4·89 (2H, s, O·C*H*$_2$Ph), 3·37 (1H, s, 8-H or 3-H), 3·24 (1H, s, 3-H or 8-H), 1·90 (1H, s, 11-H), and 2·60br (5H, s, O·CH$_2$*Ph*), *m/e* 431 (M), 430 (M — 1), 416 (M — Me), 400 (M — OMe), 388 (M — CH_2=NMe), 340 (M — CH_2Ph), 297 (M — CH_2Ph — CH_2=NMe). Fractions 11 and 12 gave (±)-predicentrine (XI) as a green viscous syrup, which was characterised as its hydrochloride (150 mg.), m.p. 215—217° (decomp.),[6] $\nu_{max.}$ ($CHCl_3$) (free base) 3480 (OH) and 1085 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) (free base) 281 and 304 mμ (log ε 4·14 and 4·14), τ ($CDCl_3$) (free base) 7·46 (3H, s, NMe), 6·42 (3H, s, OMe), 6·14 (3H, s, OMe), 6·11 (3H, s, OMe), 3·46 (1H, s, 3-H or 8-H), 3·24 (1H, s, 8-H or 3-H), and 2·07 (1H, s, 11-H), *m/e* 341 (M), 340, 326, 310, 298, 283, and 267.

Fractions 14—18 afforded the crude dienone (290 mg.), which was rechromatographed on alumina (16 g.) and eluted with benzene [fractions (50 ml.) 1—3], benzene–chloroform (9 : 1 v/v; fractions 4—15), and benzene–chloroform (7 : 3 v/v; fractions 16—60). Fractions 33—38 gave the dienone (XII) (220 mg.) as a yellow viscous syrup, $\nu_{max.}$ ($CHCl_3$) 1655, 1645, and 1620 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 236 and 283 mμ

[7] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Determination of Natural Products by Mass Spectrometry,' vol. I. 'Alkaloids,' Holden-Day, San Francisco, p. 175.

[8] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, 1968, **33**, 690.

[9] T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. and Ind.*, 1969, 833.

(log ε 4·13 and 3·79), τ ($CDCl_3$) 7·66 (3H, s, NMe), 6·35 (3H, s, OMe), 6·19 (3H, s, OMe), 4·90 (2H, s, O·CH_2Ph), 3·70 (1H, s, 8-H), 3·60 (1H, s, 4-H), 3·55 (1H, s, 5-H), 3·41 (1H, s, 1-H), and 2·68br (5H, s, O·CH_2Ph), *m/e* 417, 340, and 312. The *methiodide* formed pale yellow prisms, m.p. 225—227° (decomp.), insoluble in all solvents tried (Found: C, 57·7; H, 5·7. $C_{27}H_{40}INO_4$ requires C, 57·95; H, 5·40%).

Debenzylation of Benzylpredicentrine (X).—A mixture of benzylpredicentrine (X) (200 mg.), concentrated hydrochloric acid (5 ml.), and ethanol (5 ml.) was refluxed for 5 hr. and the solvent was distilled off to leave a brown gum, which was washed with ether. The residue was dissolved in chloroform; the solution was washed successively with 10% ammonia and water, dried (Na_2SO_4), and evaporated to leave a brown syrup, which was chromatographed on silica gel (10 g.) with chloroform as eluant. The appropriate fraction (monitored by i.r. spectrum and t.l.c.) gave the predicentrine (XI) as a green viscous syrup, identical (i.r. spectrum) with the sample obtained before.

Debenzylation of Morphinandienone (XII).—A mixture of morphinandienone (XII) (194 mg.), 48% hydrobromic acid (25 ml.), and methanol (30 ml.) was refluxed for 10 min. and then evaporated *in vacuo*. The residue was extracted with chloroform and the extract was washed with 10% ammonia and water, dried (Na_2SO_4), and evaporated to leave a brown gum, which was chromatographed on silica gel (5·5 g.) with chloroform [fractions (10 ml.) 1—10] as eluant. Fractions 5 and 6 (monitored by i.r. and t.l.c.) gave the dienone (IV) as a pale brown syrup, *m/e* 327 (M^+), identical [$\nu_{max.}$ ($CHCl_3$) 3400 (OH in diosphenol) 1652 and 1626 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 236 and 286 mμ, τ ($CDCl_3$) 7·55 (3H, s, NMe), 6·17 (3H, s, OMe), 6·13 (3H, s, OMe), 4·14, 3·62, 3·30, and 3·21 (each 1H, s, C-1, C-4, C-5, and C-8 protons)] with the sample prepared by another route,[9] R_F 0·785 [Wakogel (0·2 mm.); $CHCl_3$–MeOH (5 : 1)] or 0·845 [Wakogel (0·2 mm.); $CHCl_3$–Me_2CO–MeOH (5 : 4 : 1)].

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