Conversion of Protopine into the Secoberbines Corydalisol and Hypecorine

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Pyrolysis of protopine *N*-oxide (6) leads to the dibenzoxazacycloundecine (7) whose reduction with palladium catalyst affords (±)-corydalisol (2). Alternatively, zinc in acetic acid treatment of (7) leads to (±)-hypecorine (3) and (±)-corydalisol (2).

Protopine (1) is one of the more commonly available alkaloids, being widely distributed among members of the plant families Berberidaceae, Fumariaceae, and Papaveraceae.† Since we had on hand a supply of this alkaloid, it was decided to explore possibilities for its conversion into members of less commonly occurring groups of natural isoquinoline bases. In particular, we became interested in the transformation of protopine into members of the secoberine class as exemplified by the alkaloids corydalisol (2) [2,‡] and hypecorine (3).[3,§]

It was initially envisioned that such a change could be brought about by selective oxidative fission of the N-7 to C-8 bond of protopine [see formula (6) for numbering], immediately followed by nucleophilic attack of the basic nitrogen atom at the electron poor C-14 carbonyl centre to form after reduction either corydalisol (2) or hypecorine (3).

A model reaction that was relevant to our purpose was the pyrolytic Meisenheimer rearrangement of the tetrahydroisoquinoline *N*-oxide (4) to produce the benzoxazepine (5), as established by Bremner and co-workers.[4] Their significant finding was that ring insertion of the oxygen atom occurred at the carbon to nitrogen benzylic bond. It was, therefore, possible to conceive of a similar sequence on protopine *N*-oxide (6), to generate the dibenzoxazacycloundecine (7). Selective fission of the nitrogen to oxygen bond of (7), succeeded by reductive cyclization could then supply the required secoberbines (2) and (3).

m-Chloroperbenzoic acid oxidation of protopine (1) supplied the crystalline *N*-oxide (6) in 93% yield. Pyrolysis of this material near 180 °C *in vacuo* generated two compounds giving Dragendorff positive spots on t.l.c. The first, obtained in 35% yield was suspected of being the required compound (7) while the second which was produced in only 12% yield was the styrene (8).

The ^{1}H n.m.r. spectrum of the dibenzoxazacycloundecine (7), as summarized around formula (7), did not allow for a clear cut structural differentiation from the isomeric dibenzoxazacycloundecine (9), although we were confident, on the basis of the Bremner results, that we had on hand species (7) rather than (9). The mass spectrum of (7) showed the correct molecular weight, indicating facile loss of 59 mass units, corresponding to a $CH_2N(CH_3)O$ fragment, as indicated in formula (7), to form base peak *m/z* 310. The fragment of 59 mass units, however, could equally well have originated from the alternative species (9).

Fortunately, the ^{13}C n.m.r. spectrum of (7), when compared to that of protopine [see formulae (7a) and (1)] furnished sufficient direct evidence in favour of the expected structure (7) to allow us to continue with the sequence. In particular, C-8 in protopine, which is found at 50.86 p.p.m., is shifted downfield to 62.19 p.p.m. in the dibenzoxazacycloundecine (7) since it is now flanked by an aromatic ring and an oxygen atom.

In a first attempt to convert (7) into a secoberbine, the compound was hydrogenated in ethanol using 5% palladium on carbon. The product, obtained in 30% yield, proved to be the desired secoberbine (±)-corydalisol (2), identical with an authentic sample in our possession. Alternatively, reduction of (7) with zinc in glacial acetic acid furnished (±)-corydalisol (2) in 15% yield, while the main product, obtained in 31% yield was (±)-hypecorine (3), characterized through its ^{1}H n.m.r. spectrum summarized in formula (3), which is similar to the spectrum reported for the alkaloid in carbon tetrachloride.[3] Additionally, the u.v. and mass spectra are, in general, in accord with the structural assignment

Finally, since catalytic as well as zinc in acetic acid reduction had been tried on the dibenzoxacycloundecine (7), the compound was also subjected to sodium borohydride reduction in ethanol. The product, obtained in nearly quantitative yield, was the alcohol (10) which furnished the acetate (11) upon acetylation with acetic anhydride in pyridine.

The above simple sequence, involving formation of the protopine *N*-oxide, followed by pyrolysis and reduction, may be adapted to the synthesis of other secoberbine alkaloids, provided that adequate supplies of the corresponding protopine bases are available.¶

Experimental

All n.m.r. spectra were recorded for solutions in deuteriochloroform unless indicated otherwise. ^{1}H N.m.r. spectra were recorded on a Bruker WM-360 or a Bruker WP-200 instrument, and a Bruker WP-200 machine operating at 50.32 MHz was used to record the ^{13}C spectra. I.r. spectra were obtained in chloroform solution, and u.v. spectra in methanol. All t.l.c. was on Merck Silica Gel F-254 glass plates. Elemental analyses were confirmed by means of high-resolution mass spectroscopy.

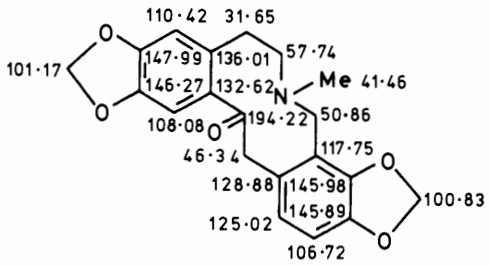
Protopine N-*Oxide* (6).—A solution of *m*-chloroperbenzoic acid (204 mg, 1.18 mmol) in chloroform (10 ml) was placed in ice. Protopine (1) (376 mg, 1.06 mmol) was dissolved in chloroform (10 ml), and added dropwise with stirring. The mixture was placed in a refrigerator overnight. The solution was thoroughly washed with 5% aqueous sodium carbonate (40 ml). The aqueous phase, when allowed to stand overnight at room temperature, deposited pure (6) (332 mg), and the organic layer, after drying and evaporation of the solvent,

† For a recent listing of the protopine alkaloids, together with their physical and spectral properties see ref. 1.

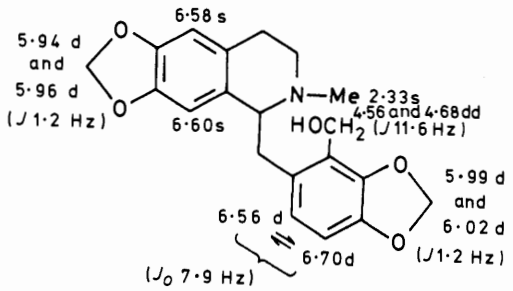
‡ (±)-Corydalisol has previously been prepared from synthetic coptisine iodide by a four step sequence, see M. Shamma, A. S. Rothenberg, and S. F. Hussain, *Heterocycles*, 1977, **6**, 707.

§ For a review of the chemistry of the secoberbines, see M. Shamma and J. L. Moniot, ' Isoquinoline Alkaloids Research,' 1972—1977, Plenum Press, N.Y. (1978), pp. 261—270.

¶ For example, 1-methoxyallocryptopine could supply the secoberbine macrantaline.



(1)



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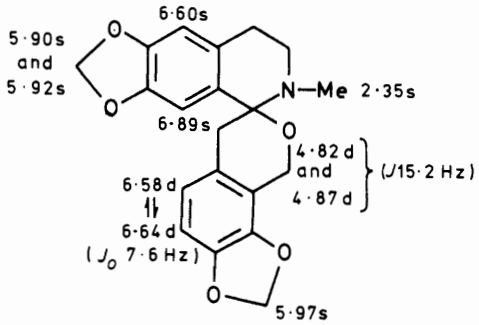

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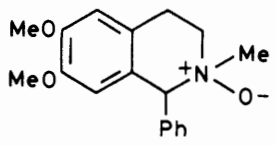

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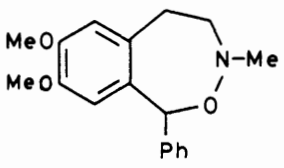

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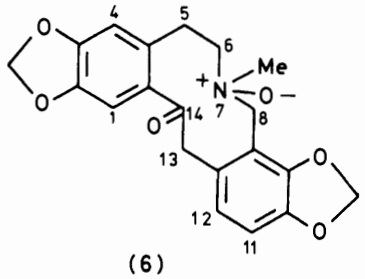


(6)

yielded further (6) (18 mg); total yield 93%. The product recrystallized from chloroform as fine needles, m.p. 156—157 °C, $\lambda_{max.}$ 209, 228, 283sh, and 302 nm (log ε 4.56, 4.42, 3.85, and 3.97); $\nu_{max.}$ 1 670 cm^{-1}; *m/z* 369 (M^+, 16%), 353 (6), 352 (24), 334 (8), 323 (16), 322 (66), 311 (15), 310 (78), 293 (8), 281 (17), 267 (32), 252 (14), 237 (7), 206 (21), 176 (33), 175 (100), 163 (25), 162 (19), 149 (20), 148 (66), and 134 (34); δ (200 MHz, CD_3OD) 2.99 (s, 3 H, NCH_3), 5.90 and 5.92 (2 × d, 4 H, *J* 0.9 Hz, 2 × OCH_2O), 6.74 (s, 1 H, ArH), 6.87 (d, 1 H, *J* 8.2 Hz, ArH), 6.94 (s, 1 H, ArH), and 7.08 (d, 1 H, *J* 8.2 Hz, ArH) (Found: C, 65.05; H, 5.0; $C_{20}H_{19}NO_6$ requires C, 65.03; H, 5.19%).

Pyrolysis of the N-*Oxide* (6).—The *N*-oxide (6) (171 mg) was pyrolysed in a microsublimation apparatus for 2 h at 180 °C and 0.3 mmHg. The product was dissolved in chloroform and separated by t.l.c. using benzene–chloroform–acetone (20 : 15 : 5). The less polar band (R_F 0.47) gave (7) (59 mg, 35%), while the slower band (R_F 0.35) supplied (8) (20 mg, 12%).

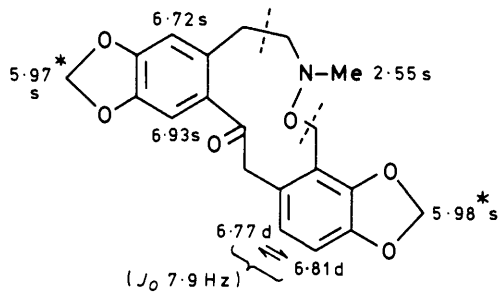
Compound (7) crystallized from methanol as colourless rods, m.p. 164—166 °C, $\lambda_{max.}$ 208, 223sh, and 297 nm (log ε 4.48, 4.29, and 3.87); $\nu_{max.}$ 1 690 cm^{-1}; *m/z* 369 (M^+, 10%), 352 (25), 322 (6), 310 (100), 281 (26), 267 (56), 252 (30), 237 (14), 224 (11), 206 (30), 176 (10), 175 (14), 163 (24), 162 (18), 149 (16), 148 (40), 147 (19), 135 (23), 134 (56), and 60 (33) (Found: C, 65.15; H, 5.2. $C_{20}H_{19}NO_6$ requires C, 65.03; H, 5.19%).

Compound (8), amorphous, $\lambda_{max.}$ 208, 239, 292, and 322sh (log ε 4.56, 4.41, 4.00, and 3.75); $\nu_{max.}$ 1 600, 1 620, and 1 675 cm^{-1}; *m/z* 369 (M^+, 1%) 353 (3), 352 (10), 335 (15), 334 (20), 322 (16), 321 (18), 320 (21), and 175 (100) (Found: C, 65.2; H, 5.2. $C_{20}H_{19}NO_6$ requires C, 65.03; H, 5.19%).

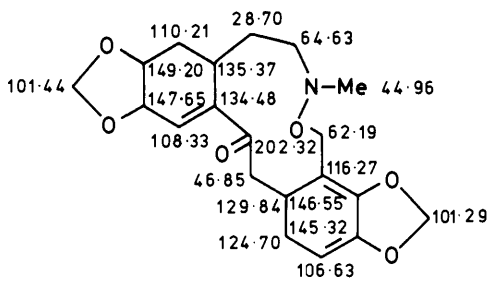
Hydrogen–Palladium Reduction of (7).—Compound (7) (7.1 mg) was dissolved in ethanol (10 ml) and 5% Pd/C (3 mg) added. Hydrogenation with stirring was continued until no more hydrogen uptake was observed (5 h). Work-up and purification by t.l.c. using benzene–chloroform–methanol (21 : 15 : 5) supplied starting (7) (2.3 g, 32%), R_F 0.67, together with amorphous (±)-corydalisol (2) (2.1 mg, 30%), R_F 0.37.

(±)-Corydalisol (2), $C_{20}H_{21}NO_5$: $\lambda_{max.}$ 210, 239sh, and 293 nm (log ε 4.51, 3.87, and 3.91); $\nu_{max.}$ 1 450, 1 480, 1 500, 1 600, and 3 340 cm^{-1}; *m/z* 355 (0.4%), 344 (3), 353 (12), 338 (9), 322 (8), 191 (11), 190 (83), and 148 (100).

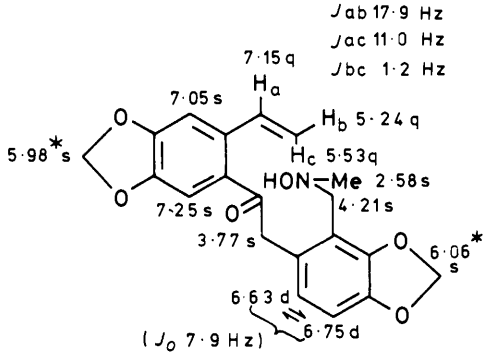
Zinc in Acetic Acid Reduction of (7).—Compound (7) (11.2 mg) was dissolved in glacial acetic acid (5 ml) and zinc dust (53 mg) added. The mixture was stirred for 2.5 h, after which



(7)



(7a)



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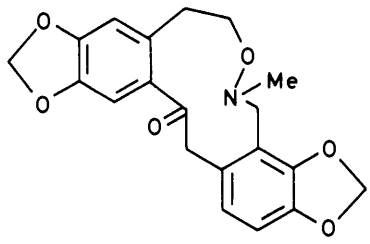

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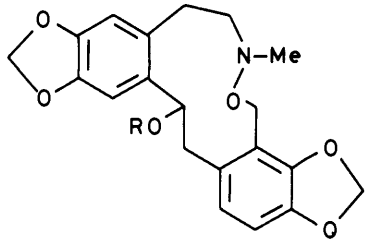

(10) R = H
(11) R = Ac

In the diagrams above, chemical shift values with identical superscripts are interchangeable

the reaction mixture remained the same. The pH was adjusted to *ca.* 5 by addition of aqueous sodium hydroxide. Aqueous sodium carbonate was then added, and the solution extracted with chloroform. The crude product was subjected to t.l.c. using chloroform–methanol–ammonia (80 : 20 : 1). The least polar band (R_F 0.74) consisted of starting material (7) (3.2 mg, 25%). (±)-Corydalisol (2) formed the band with next higher R_F (0.66) (1.6 mg, 15%), while the lowest R_F band (0.54) consisted of (±)-hypecorine (3) (3.4 mg, 31%). (±)-Hypecorine (3), $C_{20}H_{19}NO_5$; $\lambda_{max.}$ (MeOH or MeOH, H^+) 208, 248, 294, and 369 nm (log ε 4.55, 4.15, 3.85, and 3.89); $\lambda_{max.}$ (MeOH, OH^-) 212, 236sh, and 288 nm (log ε 4.67, 3.96, and 3.88); $\nu_{max.}$ 1 455, 1 480, 1 495, and 1 600 cm^{-1}; *m/z* 353 (M^+, 1%), 338 (2), 322 (1), 191 (19), 190 (100), 188 (3), and 148 (5).

The Alcohol (10).—Reduction of (7) with sodium borohydride in ethanol overnight led to a nearly quantitative yield of amorphous (10), $\lambda_{max.}$ 208, 237sh, and 293 nm (log ε 4.64, 3.86, and 3.88); *m/z* 354 $(M - 17)^+$ (1%), 353 $(M - 18)^+$ (2), 281 (3), 267 (5), 209 (6), 190 (9), 165 (8), 163 (18), 149 (12), 148 (100), and 134 (19); δ (360 MHz) 2.73 (s, 3 H, NCH_3), 4.45 and 4.97 (dd, 2 H, *J* 9.8 Hz, OCH_2Ar), 5.31 (d, 1 H, *J* 8.9 Hz, H *gem* to OH), 5.92, 5.94, and 5.97, 5.98 (2 × dd, 4 H, J_{gem} 1.5 Hz, 2 × OCH_2O), 6.59 (s, 1 H, ArH), 6.77 and 6.92 (dd, 2 H, J_o 7.9 Hz, ArH), and 7.14 (s, 1 H, ArH) (Found: C, 64.4; H, 5.6. $C_{20}H_{21}NO_6$ requires C, 64.68; H, 5.70%).

The Acetate (11).—This was obtained from (10) by acetylation with acetic anhydride in at room temperature, overnight; $\lambda_{max.}$ 210, 238sh, and 293 nm (log ε 4.43, 3.83, and 3.83); $\nu_{max.}$ 1 600 and 1 735 cm^{-1}; *m/z* 354 $(M - OAc)^+$ (7%), 353 (6), 338 (5), 336 (7), 295 (11), 294 (55), 293 (9), 191 (9), 190 (61), 188 (6), 177 (7), 176 (6), 164 (6), 163 (15), 149 (18), 148 (20), 135 (10), 102 (29), 60 (100), and 43 (32); δ (200 MHz) 1.99 (s, 3 H, OAc), 2.75 (s, 3 H, NCH_3), 4.48 and 4.98 (dd, 2 H, *J* 10.1 Hz, OCH_2Ar), 5.94 (s, 2 H, OCH_2O), 5.97 and 5.99 (dd, 2 H, J_{gem} 1.5 Hz, OCH_2O), 6.26 (q, 1 H, J_A 2.1 Hz, J_B 8.7 Hz, H *gem* to OAc), 6.60 (s, 1 H, ArH), 6.73 and 6.81 (dd, 2 H, J_o 7.9 Hz, ArH), and 6.93 (s, 1 H, ArH) (Found: C, 63.95; H, 5.55. $C_{22}H_{23}NO_7$ requires C, 63.91; H, 5.61%).

Acknowledgements

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