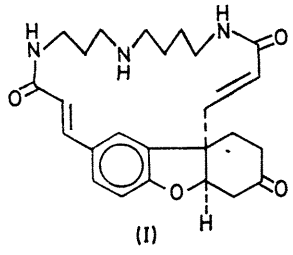
Codonocarpine, a New Lunaria-Type Alkaloid from *Codonocarpus australis* A. Cunn.

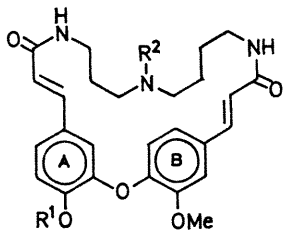
By RAYMOND W. DOSKOTCH,* A. B. RAY, and JACK L. BEAL
(*Division of Natural Products Chemistry, College of Pharmacy, Ohio State University, Columbus, Ohio* 43210)

Summary The structure of a new lunaria-type alkaloid, codonocarpine, has been established by physical and chemical methods.

To date seven alkaloids have been reported from the seeds of *Lunaria* sp. (family Cruciferae).[1] The structure of lunarine (I), the major alkaloid, was recently determined by *X*-ray crystallography[2] and three others were related to it by chemical means. Examination of the bark of *Codonocarpus australis* A. Cunn. (family Phytolaccaceae) for medicinal constituents showed a number of alkaloids.[3] One of these, codonocarpine, has been shown to have structure (II).

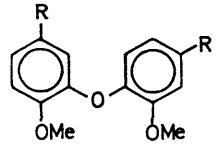


(I)

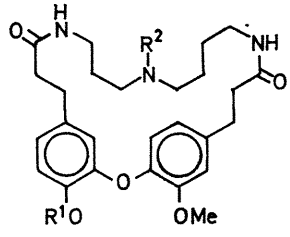


(II; R^1=R^2=H)
(IV; R^1=R^2=Ac)

$H_2N(CH_2)_3NH(CH_2)_4NH_2$
(III)



(V; R=COOMe)
(VII; R=CH_2CH_2COOMe)
(VIII; R=$CH_2CH_2CONH_2$)



(VI; R^1=R^2=Ac)
(IX; R^1=H, R^2=Ac)

Codonocarpine (II) was isolated from the quaternary alkaloid fraction, crystallizing as pale yellow rosettes of needles (from methanol), m.p. 187° (decomp.) $[\alpha]_D$ (methanol) 0°, mass spectrum† M^+ 465·2259 ($C_{26}H_{31}H_3O_5$ requires 465·2264). Strong-acid hydrolysis gave a triamine, $C_7H_{19}N_3$, M^+ 145, identified as spermidine (III), the picrate and hydrochloride salts being identical (mixed m.p. and i.r. spectra) with authentic samples. This suggested the lunaria alkaloids, the u.v. spectra of which are in accord with that of codonocarpine (II), λ_{max} (MeOH) 312 nm (log ϵ 4·33), 283 (4·44) and 218 (4·42), and support a *trans*-cinnamamide structure ν_{max} (KBr) ν 1650 (C=O), 990, and 980 cm^{-1} (*trans*-C=C)]. The bathochromic shift in strong alkali, λ_{max} 363 nm (log ϵ 4·33) and 309 (4·32) suggested a phenolic group(s) and the three-proton singlet in the n.m.r. spectrum‡ (CD_3·OD) at δ 3·84 was assigned to a methoxy-group.

Formation of a neutral diacetate (IV), m.p. 169—171°, M^+ 549·2458 (18%) (calc. for $C_{30}H_{35}N_3O_7$ *m/e* 549·2475); i.r. (KBr) ν 1770 and 1630 cm^{-1} (C=O); n.m.r. ($CDCl_3$–CD_3·OD) δ 2·40 (O–Ac) and 2·08 (N–Ac) p.p.m. supported the presence of one phenolic group and an acylable amino-group in codonocarpine. Since two *trans*-cinnamamide units are required by the molecular formula, one additional oxygen atom needed characterization. Its nature and the mode of coupling of the cinnamamide units were clarified by the product of $KMnO_4$ oxidation of the amorphous permethylated (Me_2SO_4–NaOH) codonocarpine. The isolated diacid, m.p. 272—273°, gave a dimethyl ester (diazomethane) m.p. 96° that was identical (i.r., n.m.r., and mixed m.p.) with 2,2′-dimethoxy-4,5′-dimethoxycarbonyldiphenyl ether (V) synthesised in four steps from methyl vanillate and 3,3′-diformyl-6,6′-dimethoxydiphenyliodonium sulphate. The latter substance was made from anisaldehyde and iodyl sulphate.[4]

The n.m.r. spectrum of the diacetate (IV) showed two AB quartets centred at δ 7·58, 7·42, 6·50, and 5·90 (1H each) p.p.m. (J 15 Hz). The large coupling constant established the *trans*-nature of the olefinic protons. These assignments were confirmed by the hydrogenation of *ON*-diacetylcodonocarpine (IV) (PtO_2 in ethanol) to the amorphous tetrahydro-derivative (VI), M^+ 553·2791 ($C_{30}H_{39}N_3O_7$ requires 553·2788) which lacks the olefin peaks in the n.m.r. spectrum but instead shows two 4H absorptions each between δ 2·3—2·7 and δ 2·7—3·5 p.p.m.

Strong-acid hydrolysis of compound (VI) gave a phenolic acid fraction that after treatment with diazomethane yielded an amorphous diester (VII), $C_{22}H_{26}O_7$, i.r. ($CHCl_3$) ν 1735 cm^{-1} (C=O), M^+ 402 (100%), n.m.r. ($CDCl_3$) four methoxy groups at δ 3·84, 3·82, 3·68, and 3·62 p.p.m., eight methylene protons between δ 2·4 and 3·2 p.p.m. and six aromatic protons between δ 6·4 and 6·9. The diester (VII) was converted into the diamide (VIII), $C_{20}H_{24}N_2O_5$, i.r. ($CHCl_3$) ν 1680 cm^{-1} (C=O), M^+ 372·1687 (100%) (requires 372·1685) and n.m.r. ($CDCl_3$) δ 3·82 and 3·72 (methoxy-groups) p.p.m. These derivatives demonstrated the dimeric phenylpropide nature of the dicarboxylic portion of codonocarpine and provided intact the carbon skeleton of that unit.

Placement of the phenolic groups in ring A resulted from the negative Gibbs test[5] (for phenols with an unsubstituted *para*-position) obtained with *N*-acetyltetrahydrocodonocarpine (IX); the i.r. spectrum ($CHCl_3$) lacked the ester band at 1760 cm^{-1}, and the u.v. spectrum showed λ_{max} (MeOH) 282 nm (log ϵ 3·60) with a bathochromic shift in alkali to λ_{max} 298 nm (log ϵ 3·55) and 286 (3·54). The

† Mass spectra were obtained by the direct inlet method on an A.E.I. MS-9 double-focussing instrument.
‡ Taken at 60 MHz with Me_4Si as internal standard.

Gibbs test on codonocarpine itself gave anomalous results because, apparently, of the $\alpha\beta$-unsaturated amide group. The structure (II) for codonocarpine is one of two supported experimentally. The other involves the reversal in the spermidine portion and the present data will not differentiate between the two.

The lunaria-type alkaloids, characterised by a diamide structure based on a polybasic 'animal-type' amine (*e.g.* spermidine) and a dicarboxylic acid formed by phenol coupling[6] of two phenylpropide units, are thus not restricted to the seeds of a single genus, being found in at least one member of an unrelated family.

This study was supported by a grant from the U.S. Public Health Service. We thank Mr. R. Weisenberger of the Chemistry Department and Dr. R. L. Foltz of Battelle Memorial Institute for the mass spectra.

(*Received, December 7th*, 1970; *Com.* 2100.)

[1] R. H. E. Manske, "The Alkaloids," vol. X, Academic Press, New York, 1968, p. 572; C. Poupat, B. Rodriguez, H.-P. Husson, P. Potier, and M.-M. Janot, *Compt. rend.*, 1969, **269** *C*, 335.
[2] J. A. D. Jeffreys and G. Ferguson, *J. Chem. Soc.* (*B*), 1970, 826; C. Tamura and G. A. Sim, *ibid.*, 1970, 991.
[3] N. A. Pilewski, Ph.D. Dissertation, Ohio State University, Columbus, Ohio, 1967.
[4] F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75**, 2705; H. Ziegler and M. Carr, *J. Org. Chem.*, 1962, **27**, 3335.
[5] F. E. King, T. J. King, and L. C. Manning, *J. Chem. Soc.*, 1957, 563.
[6] W. I. Taylor and A. R. Battersby, "Oxidative Coupling of Phenols," Marcel Dekker, Inc., New York, 1967; A. I. Scott, *Quart. Rev.*, (London) 1965, **19**, 1.