Tetrahedron. Vol 29. pp. 3091 to 3094. Pergamon Press 1973. Printed in Great Britain

STRUCTURE OF CRYPTOCARYONE

A CONSTITUENT OF *CRYPTOCARYA BOURDILLONI* GAMB.[a]

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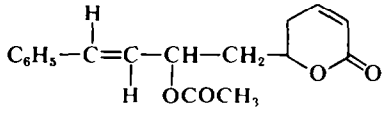
(*Received in the UK 8 May 1973; Accepted for publication 22 May 1973*)

Abstract—From the roots of *Cryptocarya bourdilloni*, a new 5',6'-dihydrochalcone, designated cryptocaryone, has been isolated. Based on spectral and degradative evidence, structure **2** has been proposed for cryptocaryone and confirmed by converting it to the hitherto unknown 5-carboxymethylflavone synthesized by a 6-step procedure from 7-methoxy-indan-1-one (**4**).

The genus *Cryptocarya* belonging to the family Lauraceae is known[1] to contain aporphine alkaloids. From the roots of *Cryptocarya bourdilloni* Gamb., a plant common on the West Coast of India, we had reported[2] the isolation of a new Kawa-type lactone named cryptocaryalactone possessing structure **1**.



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From the same source a new dihydrochalcone designated cryptocaryone was isolated and in a preliminary note[3], we had adduced evidence for its structure as **2**. We wish to record here details of this work and also present additional evidence leading to the structure **2**. Cryptocaryone, $C_{17}H_{14}O_4$, M^+ 282, m.p. 153°, $[\alpha]_D$ +776·6° showed spectral properties (UV, IR and NMR) suggestive of the presence of a 5-membered saturated lactone, an extended cinnamoyl chromophore and an enolized β-diketonic function (Experimental). With ferric chloride, it gave a dark brown colour. The NMR spectrum (Fig 1) of cryptocaryone is in consonance with the structure, supported further by irradiation studies. Thus irradiation of H_b resulted in H_d becoming a doublet of doublets with J = 10 and 2 Hz (J_{dc}10 Hz and J_{da}2 Hz); H_g and H_h each appeared as a doublet with J = 17 Hz. Upon irradiation of H_a, H_b became a broadened doublet of doublets (broadening due to long-range coupling with H_d) with J = 9 and 12 Hz; H_d appeared as a broadened doublet with J = 10 Hz and H_c a doublet with J = 10 Hz. With D_2O, H_e simplified to a doublet with J = 16 Hz.

Conclusive evidence for the structure of cryptocaryone was obtained in the following manner: Conventional methods of dehydrogenation of cryptocaryone failed to yield any characterisable products. However, brief exposure of cryptocaryone to SeO_2 in hot amyl alcohol by the method[4] of Mahal *et al.* gave the corresponding 5,6-dihydroflavone, $C_{17}H_{12}O_4$, M^+ 280, m.p. 181–183°, $[\alpha]_D$ +376·21°. The NMR spectrum of this com-

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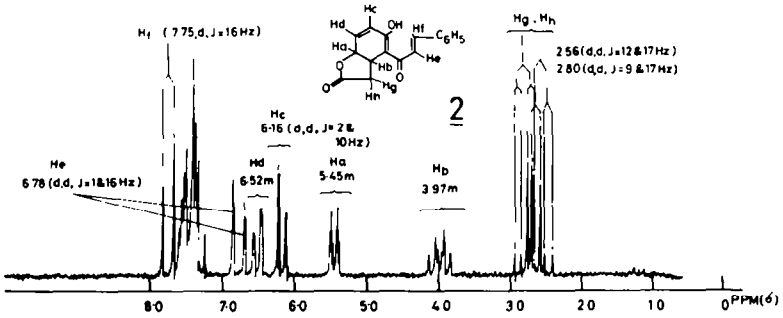


Fig 1. 100 MHz NMR spectrum of cryptocaryone (**2**) in $CDCl_3$.

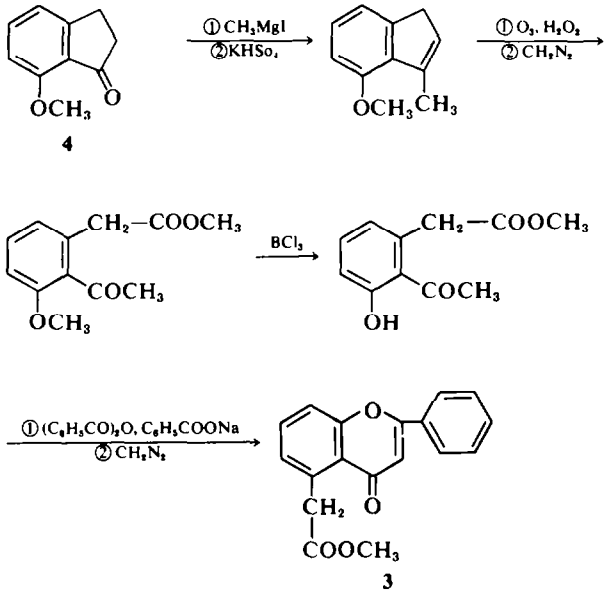
pound showed a sharp one-proton singlet at 6·73 reminiscent of a γ-pyrone H of a flavone. On isomerisation the dihydroflavone gave a flavone carboxylic acid, $C_{17}H_{12}O_4$, m.p. 260–262° (d), the methyl ester, $C_{18}H_{14}O_4$, M^+ 294, m.p. 167–169°, of which was found to be identical in all respects (m.p., mixed m.p., TLC, IR and NMR) with an authentic specimen of the methyl ester of 5-carboxymethyl flavone (3), synthesized by the scheme depicted below from 7-methoxyindan-1-one[5] (4).

Hence the dihydroflavone described above should be formulated as 5 and therefore cryptocaryone must be represented by the structure 2.

316, m.p. 150–151°, $[\alpha]_D$ −48·97°. On the basis of the spectral data outlined above, the acid has been tentatively assigned the structure 6, *presumably* formed from cryptocaryone by the mechanism depicted in the next page.

In the NMR spectra of cryptocaryone 2 (Fig 1) and the dihydroflavone 5, the proton H_b appears at a lower field (3·97 and 4·02 respectively) than one would expect and this may be due to this proton lying nearly in the plane of the CO group which is the region of negative shielding of the anisotropic CO group.[6] This situation would arise only when the lactone ring is *cis*-fused.

Cryptocaryone represents the first example of



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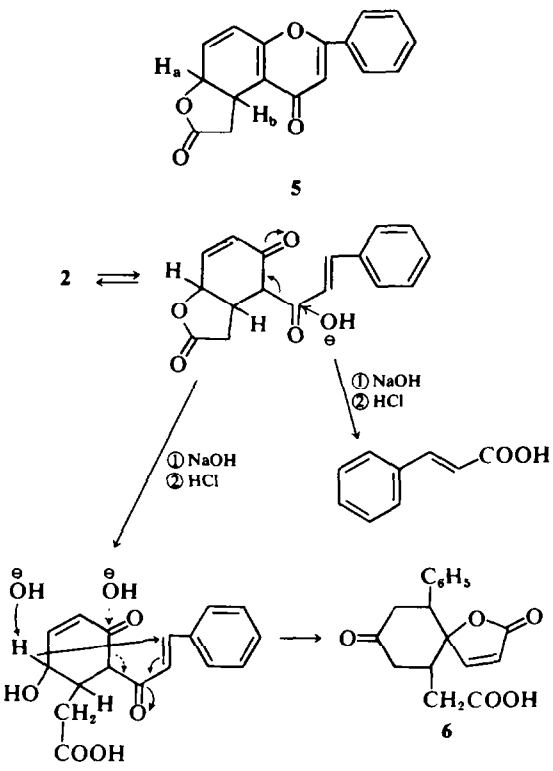
It is of interest to note that cryptocaryone is extremely labile to alkali. On warming with 1 N NaOH besides cinnamic acid, it gave a new optically active acid, $C_{17}H_{16}O_5$, M^+ 300, m.p. 182–184° (d), $[\alpha]_D$ −54·02°, whose UV spectrum showed only a benzenoid absorption. The IR spectrum displayed bands at 1760 (α,β-unsat. 5-memb lactone), 1728 (sat. 6-memb carbonyl) and 1700 cm^{-1} (carboxylic acid). On methylation with CH_2N_2, the acid formed a methyl ester, $C_{18}H_{18}O_5$, M^+ 314, m.p. 166–167°, $[\alpha]_D$ −23·35° and its IR spectrum still showed the presence of an α,β-unsat 5-memb lactone (1758 cm^{-1}) besides the CO (1720 cm^{-1}) and ester (1730 cm^{-1}) bands. The NMR spectrum of the methyl ester was particularly informative since it showed that the double bond, conjugated with the lactone CO, was unsubstituted (6·13, d, J = 6 Hz, α-proton; 7·22, d, J = 6 Hz, β-proton and the magnitude of coupling (J = 6 Hz) showed that the lactone must be 5-membered). On hydrogenation the methyl ester formed a dihydro derivative, $C_{18}H_{20}O_5$, M^+ a 5′,6′-dihydrochalcone to be encountered in Nature.

EXPERIMENTAL

General experimental procedure. M.ps and b.ps are uncorrected. UV spectra were measured for 95% EtOH solns on a Beckman DK 2A spectrophotometer, IR spectra on a Perkin-Elmer model 421 spectrophotometer and optical rotations were taken in $CHCl_3$. NMR measurements were run in $CDCl_3$ solns on a Varian A-60 or HA-100-D spectrometer with TMS as an internal standard and the chemical shifts are expressed in ppm as δ-values. The following abbreviations are used to express the multiplicity of the signals: s = singlet, d = doublet, d,d, = doublet of doublets and m = multiplet. The coupling constants (J) are given in Hertz (Hz).

Isolation of cryptocaryone (2) *from Cryptocarya bourdilloni.* 10 kg of the dry powdered roots were extracted exhaustively in the cold with hexane. The combined extract coloured yellow was concentrated *in vacuo* to 100 ml and set aside at room temp for 2 days. The yellow crystalline material that separated was filtered off and recrystallized from ether to give pure cryptocaryone



(1·1 g), $C_{17}H_{14}O_4$, m.p. 153°, M^+ 282, $[\alpha]_D^{25}$ +776·6° (*c* = 2); UV: λ_{max} 237, 243, 287, 385 and 396 nm (log ε 4·00, 3·96, 4·00, 4·36 and 4·36); IR (CH_2Cl_2): 1788 (5-memb lactone) and 1643 cm^{-1} (unsat CO). (Found: C, 71·95, 71·87; H, 5·08, 5·14. $C_{17}H_{14}O_4$ requires: C, 72·33; H, 5·00%).

Action of alkaline H_2O_2 on cryptocaryone

The title compd (0·3 g) suspended in 1N NaOH (5 ml) was diluted with water (10 ml) and treated in the cold with H_2O_2 (7 ml, 10%). The mixture was gently warmed on the water-bath and left at room temp for 2 hr. Acidification with 2N HCl and extraction with $CHCl_3$ gave a semi-solid which was crystallised from C_6H_6-hexane to yield cinnamic acid (60 mg), m.p. 133–134°, identical in all respects with an authentic specimen. (Found: C, 72·85; H, 5·46. $C_9H_8O_2$ requires: C, 72·96; H, 5·44%).

Action of alkali on cryptocaryone

The title compd (0·3 g), which went into soln slowly with 1N NaOH (5 ml), was gently warmed on the water-bath in an atmosphere of N_2 for 1 hr. The mixture was then acidified with 2N HCl and extracted repeatedly with $CHCl_3$. The residue from the chloroform extract was chromatographed over a column of silica and eluted with $CHCl_3$ and then with $CHCl_3$, MeOH (1%). Initial fractions gave cinnamic acid identical with an authentic sample and the latter fractions on crystallisation from ether gave the acid **6** as fluffy white needles (35 mg), m.p. 182–184° (d), M^+ 300, $[\alpha]_D^{25}$ −54·02° (*c* = 1·16 in pyridine); UV: λ 210 and 225 nm (log ε 3·85 and 3·38), λ_{max} 259, 264 and 270 nm (log ε 2·72, 2·64 and 2·51); IR (Nujol): 1760 (unsat 5-memb lactone), 1728 (sat 6-memb ketone) and 1700 cm^{-1} (carboxylic acid). (Found: C, 67·98, 67·66; H, 5·92, 5·61. $C_{17}H_{16}O_5$ requires: C, 67·99; H, 5·37%).

The methyl ester of the foregoing acid, prepared by the action of ethereal CH_2N_2, melted at 166–167°, M^+ 314, $[\alpha]_D^{24}$ −23·35° (*c* = 0·75 in $CHCl_3$); UV: λ_{max} 258, 264 and 270 nm (log ε 2·65, 2·54 and 2·30), λ 210 and 225 nm (log ε 4·30 and 3·81); IR (Nujol): 1758, (unsat 5-memb lactone), 1730 (—COOMe) and 1720 cm^{-1} (sat 6-memb CO); NMR: 3·60 (s,—COOC$\underline{H}_3$), 6·13 (d, J = 6 Hz, α-proton of the lactone) and 7·22 (d, J = 6 Hz, β-proton of the lactone). (Found: C, 68·44; H, 6·23. $C_{18}H_{18}O_5$ requires: C, 68·78; H, 5·77%).

The dihydro derivative of the above ester was made by shaking an alcoholic soln of the compd with H_2 at atm press using 10% Pd/C as the catalyst. The product crystallised from ether as white needles, m.p. 150–151°, M^+ 316, $[\alpha]_D^{25}$ −48·97° (*c* = 1·45 in $CHCl_3$); UV: λ 220 and 225 nm (log ε 3·60 and 2·89), λ_{max} 252, 258 and 264 nm (log ε 2·51, 2·41 and 2·48); IR (Nujol): 1770 (sat 5-memb lactone), 1735 (—COOMe), 1720 (sat 6-memb CO) and 1410 cm^{-1} (—CO—CH_2). (Found: C, 68·48; H, 6·58. $C_{18}H_{20}O_5$ requires: C, 68·34; H, 6·37%).

Action of SeO_2 on cryptocaryone

A mixture of the title compd (189 mg), freshly sublimed SeO_2 (360 mg) and amyl alcohol (7 ml) was refluxed gently in an oil-bath for 3 hr. The crude product was taken up in benzene, filtered from selenium and the solvents were removed completely *in vacuo*. The dark residue was then chromatographed over silica packed with a layer of dry Ag_2O and the column was eluted first with C_6H_6, then with C_6H_6:$CHCl_3$ (1:1), $CHCl_3$ and finally with $CHCl_3$, MeOH (1%). The fractions eluted with $CHCl_3$, 1% MeOH were homogeneous on TLC; evaporation of the solvent from the combined fractions *in vacuo* gave a gum which solidified readily on trituration with acetone. Recrystallisation from acetone gave white cubes (65 mg), m.p. 181–183°, M^+ 280, $[\alpha]_D^{22}$ +376·21° (*c* = 1·83 in $CHCl_3$); UV: λ_{max} 312 nm (log ε 3·81); IR (KBr): 1650 (pyrone CO) and 1770 cm^{-1} (sat 5-memb lactone); NMR ($CDCl_3$): 100 MHz, 2·65, 3·15 (d,d, J = 9 and 18 Hz, H_f and H_g), 4·02 (m, H_b), 5·50 (d,d, J = 3 and 10 Hz, H_a), 6·30 (d,d, J = 3 and 10 Hz, H_d), 6·45 (d, J = 10 Hz, H_c), 6·73 (s, H_e) and 7·80 (m, C_6H_5). (Found: C, 72·82; H, 4·41. $C_{17}H_{12}O_4$ requires: C, 72·85; H, 4·32%).

5-Carboxymethylflavone

The foregoing compd (351 mg), freshly distilled diphenyl ether (15 ml) and Pd/C (10%, 100 mg) were heated at 210° in a gentle current of CO_2 bubbled through the soln for 2 hr. At the end of this period, the mixture was cooled and the catalyst was filtered off and washed repeatedly with C_6H_6. The combined filtrate was concentrated *in vacuo* and the residue was chromatographed over a column of silica gel. The column was first eluted with hexane to remove the diphenyl ether, then with C_6H_6, C_6H_6:$CHCl_3$ (1:1) and $CHCl_3$, 1% MeOH. The last eluted a crystalline compd, recrystallised from MeOH to yield the title compd as fluffy needles (141 mg), m.p. 260–262° (d), UV: λ_{max} 255–258, 294 nm (log ε 4·34 and 4·34), λ_{shl} 312 nm (log ε 4·21); IR (Nujol); 1738 (—COOH) and 1630 cm^{-1} (flavone CO); NMR (DMSO-d_6): 4·17 (s, —$C\underline{H}_2$—COOH) and 6·78 (s, pyrone $\underline{H}$). (Found: C, 73·16; H, 4·58. $C_{17}H_{12}O_4$ requires: C, 72·85; H, 4·32%).

Methyl ester of 5-carboxymethylflavone (3)

The above acid suspended in MeOH was esterified with ethereal CH_2N_2 to afford the methyl ester as white

needles, m.p. 167–169°, M^+ 294, UV: λ_{max} 255–260 and 294 nm (log ε 4·30 and 4·31), λ_{sh} 311 nm (log ε 4·21); IR (KBr): 1725 (—COOMe) and 1638 cm^{-1} (flavone CO); NMR ($CDCl_3$): 3·73 (s, —COOC$\underline{H}_3$), 4·28 (s, —C$\underline{H}_2$—COOCH_3) and 6·70 (s, pyrone $\underline{H}$). (Found: C, 73·67; H, 5·04. $C_{18}H_{14}O_4$ requires: C, 73·46; H, 4·80%).

4-Methoxy-3-methylindene

7-Methoxyindan-1-one (5 g) dissolved in dry ether (80 ml) was added dropwise with stirring to a Grignard reagent prepared from Mg (2·5 g) and MeI (10 ml) in dry ether (40 ml). The mixture was stirred overnight at room temp. Work-up as usual gave a dark brown gum which was distilled in C_6H_6 (50 ml) and heated under reflux with $KHSO_4$ (5 g) for 12 hr. Removal of the solvent *in vacuo* and distillation of the residue *in vacuo* gave the indene as a colourless liquid (3·2 g), b.p. 100°/0·2 mm, η_D^{27} 1·565, NMR (CCl_4): 2·30 (m, —C$\underline{H}_3$), 3·13 (m, —C$\underline{H}_2$—), 3·67 (s, OC$\underline{H}_3$) and 5·87 (m, vinyl $\underline{H}$). (Found: C, 82·39; H, 7·81. $C_{11}H_{12}O$ requires: C, 82·46; H, 7·55%).

Methyl 2-acetyl-3-hydroxyphenylacetate

The above indene (1·75 g) dissolved in $CHCl_3$ (50 ml) was treated with ozonised O_2 at 0° for 6 hr. After removal of the solvent *in vacuo*, the residue was warmed gently on the water-bath with H_2O_2 (10%, 20 ml), H_2O (20 ml) and $NaHCO_3$ (5 g). The mixture was then left overnight at room temp. Acidification of the aqueous layer gave an acid which was dissolved in ether and methylated with ethereal CH_2N_2 to give the methy ester as a colourless liquid (350 mg), b.p. 135°/0·2 mm; NMR (CCl_4): 2·42 (s, —COC$\underline{H}_3$), 3·58 (s, —COOC$\underline{H}_3$), 3·78 (s, —C$\underline{H}_2$—COOMe) and 3·80 (s, —OC$\underline{H}_3$). (Found: C, 64·87; H, 6·39. $C_{12}H_{14}O_4$ requires: C, 64·85; H, 6·35%).

The above ester (720 mg) dissolved in dry CH_2Cl_2 (10 ml) was cooled to −70°. To this was added dropwise during ½ hr a cooled soln of BCl_3 (3 ml) in dry CH_2Cl_2 (15 ml). The mixture was stirred for 2½ hr and then treated cautiously with water. The crude product was chromatographed over silica and the column was eluted with C_6H_6 and the fractions were monitored on TLC. Fractions eluted with C_6H_6, which were homogeneous on TLC, were combined and the residue was crystallised from light petroleum (40–60°) to yield the phenol (320 mg) as white needles, m.p. 70–72°; NMR ($CDCl_3$): 2·62 (s, —COC$\underline{H}_3$), 3·72 (s, —COOC$\underline{H}_3$), 3·87 (s, —OC$\underline{H}_3$), 10·13 (s, —O$\underline{H}$, disappears on addn of D_2O). (Found: C, 64·33; H, 6·10. $C_{11}H_{12}O_4$ requires: C, 63·45; H, 5·81%).

Methyl ester of 5-carboxymethylflavone (3)

(a) *Allan-Robinson method.* The above phenolic ketone (150 mg), C_6H_5COONa (150 mg) and $(C_6H_5CO)_2O$ (300 mg) were intimately mixed and heated at 180° for 6 hr in a gentle stream of N_2. At the end of this period, 1N NaOH (5 ml) and MeOH (20 ml) were added and the product warmed on the water-bath for ½ hr. The solvent was then removed *in vacuo* and the residue was extracted with $CHCl_3$, washed with $NaHCO_3$ aq. The latter on acidification gave an acid which was methylated with ethereal CH_2N_2 and the gummy product was chromatographed over silica using C_6H_6 as the eluent. C_6H_6: $CHCl_3$ (1:1) eluted from the column a white crystalline compd (35 mg), m.p. 168–169°, identical in all respects (mixed m.p., TLC and IR) with the flavone derived from cryptocaryone.

(b) *Baker-Venkataraman transformation.* The foregoing ketone (42 mg), dry pyridine (0·5 ml) and freshly distilled C_6H_5COCl (0·5 ml) were warmed on the water-bath for 1 hr and then left at room temp overnight. Work-up by the usual procedure gave a crude benzoyl ester, which was dried, dissolved in pyridine (1·5 ml) and treated with stirring with powdered KOH (80 mg). After stirring for 3 hr, aqueous AcOH (1:1) was added and the separated yellow gum was extracted repeatedly with $CHCl_3$. The residue from the combined $CHCl_3$ extract was dissolved in gla AcOH (1 ml) and freshly fused AcONa (40 mg) was added, refluxed gently for 2 hr and the product worked up as usual. The flavone crystallised from ether as white fluffy needles (18 mg), m.p. 166–168°, identical (mixed m.p., TLC and IR) in all respects with the flavone derived from cryptocaryone. (Found: C, 73·63; H, 4·90. $C_{18}H_{14}O_4$ requires: C, 73·46; H, 4·80%).

Acknowledgements—We wish to thank Dr. H. Fuhrer, CIBA-GEIGY Ltd., Basle, for the 100 MHz NMR spectra and decoupling experiments, Dr. K. Nagarajan for valuable discussions and Dr. S. Selvavinayakam and his associates for the analytical and spectral data.

REFERENCES

[1]H. G. Boit, *Ergebnisse der Alkaloid-Chemie bis 1960* Akademic-Verlag, Berlin (1961)
[2]T. R. Govindachari and P. C. Parthasarathy, *Tetrahedron Letters* 3401 (1971)
[3]T. R. Govindachari and P. C. Parthasarathy, *Ibid.* 3419 (1972)
[4]H. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.* 866 (1935)
[5]J. D. Loudon and R. K. Razdan, *Ibid.* 4299 (1954)
[6]L. M. Jackman, *Applications of NMR spectroscopy in organic chemistry* Chap. 7. Pergamon Press, New York (1959); N. Bhacca, M. E. Wolff and R. Kwok, *J. Am. Chem. Soc.* **84**, 4978 (1962)