Clausindine, a Novel Cyclopropylcoumarin [1]

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From the roots of *Clausena indica* Oliv., a new coumarin, clausindine, has been isolated and shown to have the structure 6-(2,2-dimethylcyclopropyl)furo[3,2-*g*][1]benzopyran-7-one (I) mainly on spectroscopic evidence. The structure has been confirmed by a synthesis of dihydroclausindine (II). The furanoquinone, furo[3,2-*g*]-[1]benzopyran-4,7,9-trione (XII) has also been isolated from the roots of this plant.

Clausena indica Oliv. (Rutaceae) is a small tree commonly found in the evergreen forests of Western Ghats, India. Previous papers have described the isolation and determination of structure of two new carbazole alkaloids, 6-methoxyheptaphylline [2] and indizoline.[3] The roots of this tree proved to be a rich

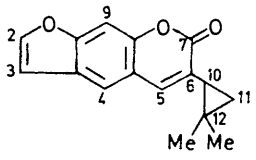
[1] B. S. Joshi, V. N. Kamat, and D. H. Gawad, *Experientia*, 1974, **30**, 223.

[2] B. S. Joshi, D. H. Gawad, and V. N. Kamat, *Indian J. Chem.*, 1972, **10**, 1123.

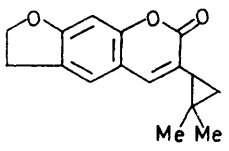
[3] B. S. Joshi and D. H. Gaward, *Indian J. Chem.*, in the press.

source of coumarins, and isolation of the known coumarins, imperatorin, phellopterin, chalepensin, and chalepin has been described earlier.[4] We have now isolated as minor constituents a new coumarin designated clausindine (I)* and the furanoquinone (XII), from the hexane extract of the roots.

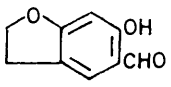
Clausindine, m.p. 128°, has molecular formula $C_{16}H_{14}O_3$ (M^+ at *m/e* 254); $\lambda_{max.}$ 248, 303, and 332 nm (log ε 4·3, 4·1, and 4·0).† The i.r. spectrum showed bands at 1720 and 1630 (conjugated lactone) and 1580 cm^{-1} (aromatic). From the u.v. and i.r. spectra it could be inferred that clausindine is a linear furanocoumarin. The n.m.r. spectrum (Figure) showed the furan protons as an AB quartet at δ 7·6 (2-H) and 6·8 (3-H) (*J* 2 Hz each) and the aromatic protons at δ 7·58 (4-H) and 7·4 (9-H). The 5-proton appeared as a sharp singlet at δ 7·35 indicating that the 6-position of the furanocoumarin nucleus is substituted.[5] Double irradiation experiments showed that the furan protons are mutually *ortho* and the 3-proton exhibits long range coupling with 9-H.[6,7] The attachment of a five



(I)



(II)

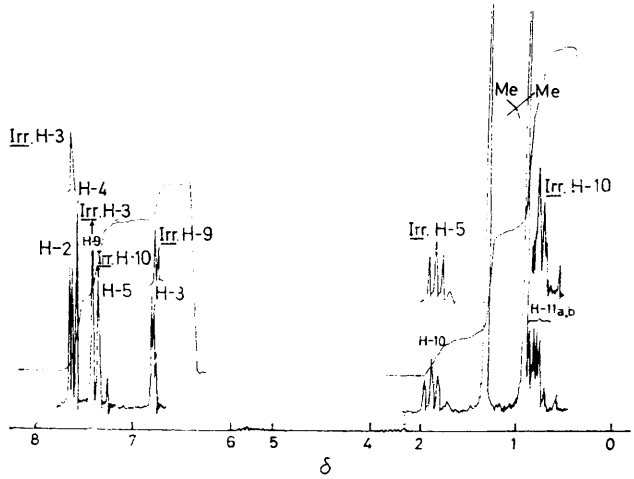


(III)

carbon unit (C_5H_9) in the form of a *gem*-dimethylcyclopropane unit at C-6 of the furanocoumarin could be deduced from the n.m.r. spectrum. The methyls appeared as singlets at δ 0·9 and 1·3. The cyclopropane methylene protons appeared as a two-proton multiplet at δ 0·8 and the methine proton as a slightly split triplet at δ 1·9 (<1 and 7·5 Hz).[8] Irradiation of the proton at δ 1·9 affected the methylenes as well as the 5-proton. The long-range coupling of the methine and 5-protons could be shown by irradiation at δ 7·35 which resulted in a sharp triplet at δ 1·9. Hydrogenation of clausindine gave dihydroclausindine, m.p. 200°, (II). This formulation was in accordance with its u.v. and n.m.r. spectra.

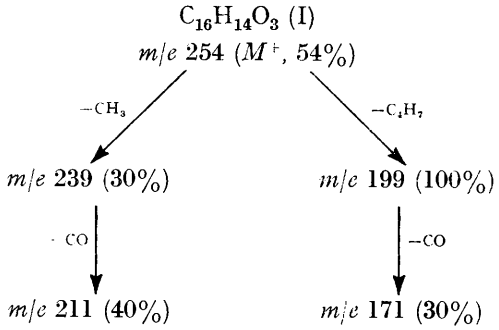
The following mass spectral fragmentations also supported the structure of clausindine, and these fragments showed an increase of two mass units in dihydroclausindine.

The structure of clausindine has been confirmed by an unambiguous synthesis of (II). 5-Formyl-6-hydroxycoumaran (III) was prepared from resorcinol [9] and it was proposed to synthesize the desired coumarin ring by condensation with 2,2-dimethylcyclopropaneacetic acid.



N.m.r. spectrum (100 MHz) of clausindine in $CDCl_3$ and effect of double resonance experiments

However, attempts to prepare the cyclopropaneacetic acid from 2,2-dimethylcyclopropanecarboxylic acid were not successful. The coumarincarboxylic acid (IV)



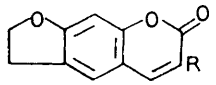
prepared by condensation of (III) with malonic acid was converted into the corresponding acid chloride (V) and then reduced to the aldehyde (VI). Wittig reaction of (VI) with methoxycarbonylmethylenetriphenylphosphorane [10] gave the olefinic ester (VII). Addition of 2-diazopropane [11] to the olefin (VII) gave a pyrazoline formulated as (VIII) [12] on spectral evidence. The ester (VIII) on hydrolysis with alkali gave the carboxylic acid (IX) which on heating with quinoline and copper-bronze formed a mixture of compounds.

* *Note added in proof:* A recent publication (F. Kuffner, A. Nikiforov, and G. Schulz, *Monatsh.*, 1973, **104**, 911) assigns structure (I) to ' rutolid,' isolated from *Ruta montana*. The name rutolid has precedence.

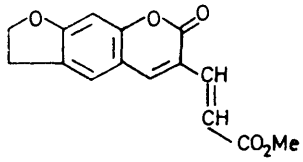
† Clausindine should be racemic since it showed neither optical rotation nor optical rotary dispersion.

[4] B. S. Joshi and D. H. Gawad, *Phytochemistry*, 1971, **10**, 480.
[5] W. Steck and B. K. Bailey, *Canad. J. Chem.*, 1969, **47**, 3578.
[6] E. A. Abu-Mustafa and M. B. E. Fayez, *Canad. J. Chem.*, 1967, **45**, 325.
[7] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 1963, 590; 1964, 981.
[8] D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1963, **85**, 3218.
[9] J. S. H. Davies, P. A. McCrea, W. L. Norris, and G. R. Ramage, *J. Chem. Soc.*, 1950, 3206.
[10] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, 1957, **40**, 1242.
[11] S. D. Andews, A. C. Day, P. Raymond, and M. C. Whiting, *Org. Synth.*, 1970, **50**, 27.
[12] T. L. Jacobs, ' Heterocyclic Compounds,' vol. 5, ed. R. C. Elderfield, Wiley, New York, 1957, p. 45.

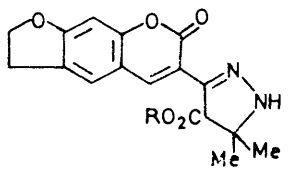
This on separation by preparative t.l.c. on silica gel yielded the desired compound (II), m.p. 200°. It was



(IV) R = CO_2H
(V) R = COCl
(VI) R = CHO

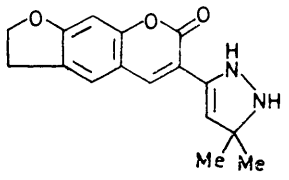


(VII)

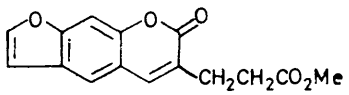


(VIII) R = Me
(IX) R = H

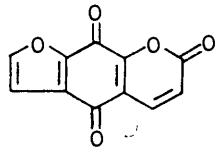
identical with dihydroclausindine on the basis of mixed m.p., t.l.c., i.r., and mass spectral data. Attempts to dehydrogenate (II) to (I) were not successful. The



(X)



(XI)



(XII)

decarboxylated pyrazoline (X) was also isolated from the reaction mixture. In an attempt to dehydrogenate the dihydrofuran ring, the olefinic ester (VII) was heated with palladium–charcoal in diphenyl ether. This gave compound (XI), which was probably formed by catalytic disproportionation.[13]

During the chromatographic separation of clausindine, a red crystalline compound, $C_{11}H_4O_5$, m.p. 255°, was isolated. On the basis of spectral data this was identified as the furanoquinone (XII). This quinone was synthesized earlier by the nitration of bergapten and oxidation of the derived amine [14] or by the oxidation of byak-angelicol.[15] This is the first instance when the quinone (XII) has been isolated from a natural source.

Clausindine appears to be of some biogenetic interest.[16] Obviously, the C_5H_9 unit containing the cyclopropane is derived from an isopentenyl group. Cyclopropane-containing mono-, sesqui-, di-, and tri-terpenes are known. Although the attachment of an isoprenoid unit to natural oxygen heterocycles and phenolic compounds such as coumarins, flavonoids, xanthones, and many alkaloids is common, this is probably the first example where it is attached to the coumarin nucleus as a dimethylcyclopropane.

[13] R. P. Linstead, K. O. A. Michaelis, and S. L. S. Thomas, *J. Chem. Soc.*, 1940, 1139.
[14] H. Thoms and E. Baetcke, *Ber.*, 1912, **45**, 3705.

EXPERIMENTAL

U.v. spectra were measured with a Beckman DK-2A spectrophotometer and i.r. spectra were taken on a Perkin-Elmer Infracord spectrophotometer. N.m.r. spectra were run on a Varian A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard.

Isolation of Clausindine (I) *and the Furanquinone* (XII).—Powdered roots of *Clausena indica* (20 kg) were extracted with hexane (3 × 40 l) and the extract was evaporated *in vacuo* to give a viscous oil (180 g). The oil (100 g) was dissolved in hexane (100 ml) and chromatographed on a column of 15% silver nitrate-impregnated silica gel (1·2 kg). The column was packed in hexane, and gradient eluted with hexane, hexane–benzene, and benzene–chloroform. Fractions (250 ml) were collected and the chromatographic separation was monitored by t.l.c. Fractions 40—50 (eluant, hexane–benzene, 1 : 1) yielded *clausindine* [6-(2,2-dimethylcyclopropyl)furo[3,2-*g*][1]benzopyran-7-one] (I) which on crystallization from ether–hexane gave plates (50 mg), m.p. 128° (t.l.c., silica gel, R_F 0·6, benzene–chloroform, 1 : 1), $[\alpha]_D^{25}$ 0·0° (dioxan), $\lambda_{max.}$ (EtOH) 248, 303, and 332 nm (log ε 4·3, 4·1, and 4·0), $\nu_{max.}$ (KBr) 1720, 1630, 1580, 1540, 1460, 1400, 1380, 1360, 1320, 1285, 1250, 1200, 1170, 1140, 1110, 1090, 1050, 1035, 1015, 965, 955, 935, 905, 880, 870, 830, 810, 790, 770, 755, 745, 725, 705, and 680 cm^{-1}, *m/e* 254 (M^+, 54%), 239 (30), 211 (40), 199 (100), 171 (30), and 155 (27) (Found: C, 75·6; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

Fractions 104—110 (eluant, benzene) gave a reddish oil from which brown crystals deposited on addition of ether. These were collected (150 mg) and recrystallized from methanol, m.p. 255°, $\lambda_{max.}$ (EtOH) 275 and 312 nm (log ε 4·04 and 3·92), $\nu_{max.}$ (KBr) 1740, 1710, 1680, 1615, and 1580 cm^{-1}, δ [$(CD_3)_2SO$] 8·3 (1H, d, *J* 2·3 Hz, H-2), 8·0 (1H, d, *J* 10 Hz, H-5), 7·15 (1H, d, *J* 2·3 Hz, H-3), and 6·75 (1H, d, *J* 10 Hz, H-6), *m/e* 216 (M^+, 42%), 188 (65), 160 (100), 130 (38), and 104 (70) (Found: C, 61·0; H, 1·9. Calc. for $C_{11}H_4O_5$: C, 61·1; H, 1·9%). This material was identical with furo[3,2-*g*][1]benzopyran-4,7,9-trione (XII) obtained by oxidation of byak-angelicol.[15]

Dihydroclausindine (II).—Clausindine (10 mg) dissolved in ethanol (20 ml) was hydrogenated for 10 min over 5% palladium–charcoal (5 mg) catalyst. The mixture was filtered, the solvent removed and 2,3-*dihydro*-6-(2,2-*dimethylcyclopropyl*)*furo*[3,2-g][1]*benzopyran*-7-*one* (II) crystallized from methanol to give needles (7 mg), m.p. 200°, $\lambda_{max.}$ (EtOH) 260infl, 303infl, and 337 nm (log ε 3·8, 3·9, and 4·25), $\nu_{max.}$ (KBr) 1710, 1630, 1580, 1480, 1440, 1400, 1380, 1272, 1231, 1158, 1130, 1010, 990, 970, 950, 890, 880, 820, and 790 cm^{-1}, δ ($CDCl_3$) 7·2br (2H, s, H-4, H-5), 6·7 (1H, s, H-9), 4·65 (2H, t, *J* 8 Hz, $-OCH_2-$), 3·25 (2H, t, *J* 8 Hz,

[15] T. Noguchi and M. Kawanami, *Ber.*, 1938, **71**, 344.
[16] H. G. Floss, 'Recent Advances in Phytochemistry,' vol. 4, ed. V. C. Runeckles, Appleton-Century-Crofts, New York, 1972, p. 143.

$-ArCH_2-$), 1·8 (1H, t, *J* 7·5 Hz, H-10), and 0·8 (2H, m, H-11), *m/e* 256 (M^+, 85%), 241 (65), 239 (40), 227 (18), 213 (85), 201 (100), 187 (22), 185 (15), 173 (30), 128 (35), and 115 (40).

2,3-*Dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*carboxylic Acid* (IV).—To a solution of malonic acid (2·08 g) in pyridine (8 ml) was added 5-formyl-6-hydroxycoumaran (III) (1·64 g) and aniline (3 drops). The mixture was left at 45° for 24 h. The crystalline mass which had separated was triturated with methanol and filtered. The residue on crystallization from methylene chloride–methanol gave the *acid* (IV) (1·2 g), m.p. 246°, δ [$(CD_3)_2SO$] 8·6 (1H, s, H-5), 7·62 (1H, s, H-4), 6·75 (1H, s, H-9), 4·75 (2H, t, *J* 8 Hz, $-OCH_2-$), and 3·3 (2H, t, *J* 8 Hz, $-ArCH_2-$) (Found: C, 62·1; H, 3·8%; *m/e*, 232. $C_{12}H_8O_5$ requires C, 62·1; H, 3·5%; *M*, 232).

2,3-*Dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*carbonyl Chloride* (V).—The acid (IV) (5·1 g) was refluxed with thionyl chloride (30 ml) for 4 h. On cooling, the crystalline product which separated was collected and recrystallized from benzene–hexane to give the *acid chloride* (V) (5·5 g), m.p. 188° (Found: C, 57·8; H, 3·1%; *m/e* 252/250. $C_{12}H_7ClO_4$ requires C, 57·5; H, 2·8%; *M*, 250·6).

2,3-*Dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*carbaldehyde* (VI).—A stream of hydrogen was passed into a refluxing solution of the acid chloride (V) (1·5 g) in dry xylene (40 ml) in the presence of 5% palladium–barium sulphate (500 mg) poisoned with quinoline–sulphur (0·08 ml), till the evolution of hydrogen chloride gas ceased. The mixture was cooled, filtered, and diluted with hexane. The precipitate was collected and chromatographed over alumina and the *aldehyde* (VI) (400 mg) crystallized from methylene chloride–methanol, m.p. 230°, $\lambda_{max.}$ (EtOH) 257, 266infl, and 380 nm (log ε 3·83, 3·77, and 4·16), δ [$(CD_3)_2SO$] 9·9 (1H, s, CHO), 8·4 (1H, s, H-5), 7·6 (1H, s, H-4), 6·66 (1H, s, H-9), 4·7 (2H, t, *J* 8 Hz, $-OCH_2-$), and 3·25 (2H, t, *J* 8 Hz, $-ArCH_2-$), *m/e* 216 (M^+, 32%), 188 (95), 160 (100), 131 (55), and 103 (17) (Found: C, 66·6; H, 4·0. $C_{12}H_8O_4$ requires C, 66·6; H, 3·7%).

Methyl β-(2,3-*Dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*yl*)*acrylate* (VII).—A solution of the aldehyde (III) (9·5 g) and methoxycarbonylmethylenetriphenylphosphorane [10] (15·9 g) in benzene (1·6 l) was left at 25° for 24 h and the crystalline product which had separated was filtered off. Crystallization from methylene chloride–benzene gave yellow needles of the *ester*, m.p. 262° (4·5 g), $\lambda_{max.}$ (EtOH) 264, 317infl, and 373 nm (log ε 4·02, 3·8, and 4·41), *m/e* 272 (M^+, 90%), 241 (40), 213 (100), 185 (20), 173 (4), 157 (10), 128 (30), and 115 (14) (Found: C, 65·9; H, 4·4. $C_{15}H_{12}O_5$ requires C, 66·1; H, 4·4%).

Methyl β-(7-*Oxofuro*[3,2-g][1]*benzopyran*-6-*yl*)*propionate* (XI).—A mixture of (VII) (100 mg), 10% palladium–charcoal (200 mg), and diphenyl ether (10 ml) was heated at 200° in a current of nitrogen for 10 h. The mixture was filtered and chromatographed on silica gel. The column was eluted with hexane, methylene chloride, and methylene chloride containing 2% methanol. The last fraction gave a residue which on crystallization from chloroform–methanol gave *needles* of (XI) (25 mg), m.p. 165°, $\lambda_{max.}$ (EtOH) 246, 295, and 325 nm (log ε 4·3, 4·1, and 3·95), δ ($CDCl_3$) 7·75 (3H, m, H-2′, H-4′, H-5′), 7·45 (1H, s, H-9′), 6·8 (1H, d, *J* 2 Hz, H-3′), 3·65 (3H, s, CO_2Me), and 2·85 (4H, q, $-CH_2CH_2-$), *m/e* 272 (M^+, 60%), 241 (35), 213 (100), 212 (100), 199 (90), 184 (90), and 171 (85).

Addition of 2-Diazopropane to the Ester (VII).—To a solution of the ester (VII) (500 mg) in bis-(2-methoxyethyl) ether (500 ml) cooled in ice, an excess of 2-diazopropane [11] in ether was added and the mixture stirred at 0 for 2 h. It was left at room temperature for 16 h, the solvent removed under vacuum, and the oily residue diluted with ice to give a precipitate of the crude pyrazoline. Crystallization from methanol gave *methyl* 3-(2,3-*dihydro*-7-*oxofuro*-[3,2-g][1]*benzopyran*-6-*yl*)-5,5-*dimethyl*-2-*pyrazoline*-4-*carboxylate* (VIII), m.p. 242° (240 mg), $\lambda_{max.}$ (EtOH) 225infl, 250, 262, 299, and 338 nm (log ε 4·05, 3·82, 3·86, 4·19, and 4·29), δ [$CDCl_3$ + $(CD_3)_2SO$] 7·2, 7·1 (each 1H, s, H-5′, H-4′), 6·75 (1H, s, H-9′), 4·7 (2H, t, *J* 8 Hz, $-OCH_2-$), 4·25 (1H, s, $CH{\cdot}CO_2Me$), 3·75 (3H, s, CO_2Me), 3·2 (2H, t, *J* 8 Hz, $-ArCH_2-$), and 1·42 and 1·15 (each 3H, s, Me), *m/e* 342 (M^+, 12%), 327 (17), 314 (22), 295 (100), 254 (20), 242 (15), 227 (50), 226 (100), and 198 (17) (Found: C, 63·4; H, 5·6; N, 8·3. $C_{18}H_{18}N_2O_5$ requires C, 63·1; H, 5·3; N, 8·2%).

Hydrolysis of the Ester (VIII).—The ester (VIII) (100 mg) in ethanol (14 ml) was refluxed for 2 h with 1% ethanolic sodium hydroxide (6 ml). The clear solution was cooled, acidified with dilute hydrochloric acid, and extracted with methylene chloride. The organic layer was washed with water, dried (Na_2SO_4), and the solvent removed to give a residue which on crystallization from methanol gave 3-(2,3-*dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*yl*)-5,5-*dimethyl*-2-*pyrazoline*-4-*carboxylic acid* (IX) (50 mg), m.p. 185°, $\lambda_{max.}$ (EtOH) 225infl, 252, 262, 295, and 339 nm (log ε 4·01, 3·82, 3·86, 4·11, and 4·24) (Found: C, 62·1; H, 5·3; N, 8·6. $C_{17}H_{16}N_2O_5$ requires C, 62·2; H, 4·9; N, 8·5%).

Pyrolysis of the Acid (IX).—A solution of the acid (IX) (300 mg) in freshly distilled quinoline (12 ml) was heated with copper-bronze (20 mg) at 230° for 1 h in a current of nitrogen. The mixture was cooled, diluted with excess of hexane, and filtered. The insoluble residue (400 mg) was collected and the filtrate was evaporated to dryness. The residue was taken up in chloroform and washed with dilute HCl and water. The chloroform layer was evaporated and the residue chromatographed on a thick layer plate of silica gel, using chloroform as solvent. The fastest moving band (R_F 0·4) was collected and extracted with methylene chloride. The residue on crystallization from methanol gave needles of (II) (25 mg), m.p. 200°. This was identical with dihydroclausindine (mixed m.p., t.l.c., i.r., and mass spectral comparison).

The residue insoluble in hexane obtained above (400 mg) was crystallized from aqueous methanol to give needles of 3-(2,3-*dihydro*-7-*oxofuro*[3,2-g][1]*benzopyran*-6-*yl*)-5,5-*dimethyl*-3-*pyrazoline* (X), m.p. 210°, $\lambda_{max.}$ (EtOH) 225infl and 339 nm (log ε 4·07 and 4·76), δ [$(CD_3)_2SO$] 7·55 (2H, s, H-4′, H-5′), 6·75 (1H, s, H-9′), 6·7br (1H, s, pyrazoline-H), 4·7 (2H, t, *J* 8 Hz, $-OCH_2-$), 3·85br (s, NH, exchanged with D_2O), 3·25 (2H, t, *J* 8 Hz, $-ArCH_2-$), 1·32 (3H, s, Me), and 0·9 (3H, s, Me), *m/e* 284 (M^+, 100%), 269 (60), 256 (5), 241 (8), 228 (60), 227 (60), 213 (15), 201 (25), 199 (25), 184 (32), 172 (25), and 128 (20) (Found: C, 67·3; H, 5·9; N, 9·4. $C_{16}H_{16}N_2O_3$ requires C, 67·6; H, 5·7; N, 9·8%).

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