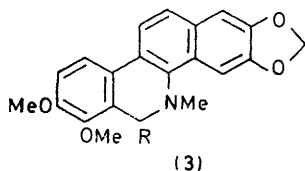
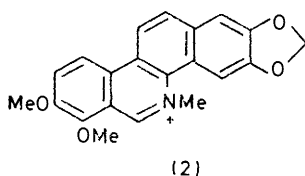
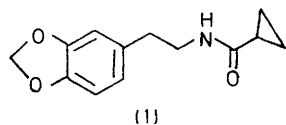


## Isolation, Identification, and Synthesis of Rubesamide, a New Naturally Occurring Cyclopropanecarboxamide from *Fagara rubescens*

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Rubesamide [*N*-(3,4-methylenedioxyphenethyl)cyclopropanecarboxamide] (1) has been isolated, together with chelerythrine and dihydrochelerythrine, from the light petroleum extract of the root bark of *Fagara rubescens* Planch *ex* Hook (f) (Rutaceae). Its identification and synthesis are reported.

TREATMENT of the light petroleum extract of the powdered root bark of *Fagara rubescens*<sup>1</sup> with 2*N*-hydrochloric acid gave a mixture which was separated by the method of Scheur *et al.*<sup>2</sup> to give the free bases dihydrochelerythrine (3; R = H) and 9-ethoxydihydrochelerythrine (3; R = OEt), a known artefact of



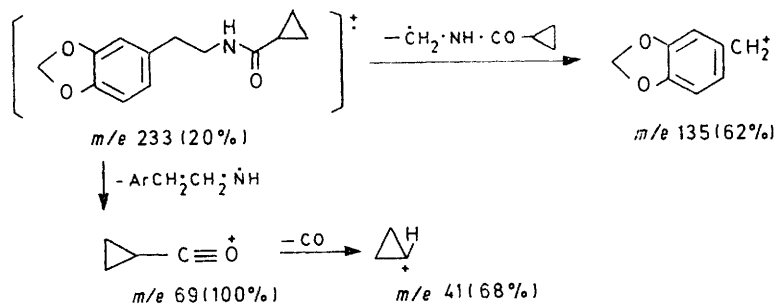
chelerythrine chloride (2) (*cf.* ref. 3). Basification of the acid-soluble fraction with ammonia, followed by extraction with chloroform and work-up, gave a mixture of crude bases. Chromatography of this on alumina afforded the new amide (1).

by the i.r. spectrum, and the n.m.r. spectrum showed aromatic proton signals at  $\tau$  2.45. The presence of a methylenedioxy-group attached to an aromatic ring was shown by i.r. bands at 945 and 1480  $\text{cm}^{-1}$ , and by a two-proton n.m.r. singlet at  $\tau$  4.10. The i.r. spectrum showed a carbonyl stretching band at 1640  $\text{cm}^{-1}$  and this, together with a sharp band at 3310  $\text{cm}^{-1}$ , suggested the presence of a secondary amide group, further supported by a broad one-proton n.m.r. signal at  $\tau$  4.38 which disappeared on shaking with  $\text{D}_2\text{O}$ . In the n.m.r. spectrum, a broad quartet at  $\tau$  6.56 was assigned to a non-benzylic methylene group, and the pattern of the aromatic proton signals was consistent with the presence of an *N*-(3,4-methylenedioxyphenethyl) group. The observation of three adjacent multiplets between  $\tau$  8.75 and 9.35, in the order 1 H, 2 H, and 2 H from low to high field, consistent with the presence of a monosubstituted cyclopropane ring bearing an electron-withdrawing group, suggested the complete structure (1).

The mass spectrum of the natural product showed a molecular ion at  $m/e$  233 and a fragmentation pattern in accord with the assigned structure (see Scheme). The structure (1) was confirmed by unambiguous synthesis from 3,4-methylenedioxyphenethylamine<sup>5</sup> and cyclopropanecarbonyl chloride.<sup>6</sup>

### EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined with a Perkin-Elmer 257G spectrophotometer, n.m.r. spectra for solutions in deuteriochloroform with a Perkin-Elmer R12A or Varian HA 100D



The u.v. spectrum showed  $\lambda_{\text{max}}$  233 ( $\epsilon$  4300) and 287 nm ( $\epsilon$  4660), indicative of a dioxxygenated benzene ring.<sup>4</sup> The aromatic character was further supported

<sup>1</sup> F. R. Irvine, 'Woody Plants of Ghana,' Oxford University Press, 1961, p. 499.

<sup>2</sup> P. J. Scheur, M. Chang, and C. Swanholm, *J. Org. Chem.*, 1962, **27**, 1472.

<sup>3</sup> F. Fish and P. G. Waterman, *Phytochemistry*, 1972, **11**, 3007.

spectrometer (tetramethylsilane as internal standard), and mass spectra with an A.E.I. MS 902 instrument.

*Isolation.*—The powdered root bark (3.17 kg) was

<sup>4</sup> A. I. Scott, 'Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964, p. 94.

<sup>5</sup> Y. Tanaka and T. Midzuno, *J. Pharm. Soc. Japan*, 1929, **49**, 255.

<sup>6</sup> C. M. McCloskey and G. H. Coleman, *Org. Synth.*, Coll. Vol. III, 1964, p. 221.

extracted (Soxhlet) with light petroleum (b.p. 60–80°) (22 l) for 4 days. The extract was evaporated under reduced pressure and the dried residue (227 g) was shaken with 2*N*-hydrochloric acid. A reddish-yellow precipitate, contaminated with some resinous material, was filtered off, washed with acetone, and extracted with warm water. This extract gave 9-ethoxychelerythrine on basification followed by extraction with ether and work-up. The water-insoluble fraction similarly gave dihydrochelerythrine. These two compounds were recrystallised from ethanol to afford white needles with m.p.s and spectral properties identical with those reported.<sup>7</sup> The mother liquor from the reddish-yellow precipitate was basified with ammonia. The basic solution (1.5 l) was decanted, leaving a creamy precipitate in 500 ml of solution. Extraction with chloroform (4 × 250 ml) followed by drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation gave a mixture of crude bases (50 g). T.l.c. on silica [benzene–ethyl acetate (7:2)] showed the presence of at least six compounds. The mixture (3 g) was dissolved in chloroform–cyclohexane (7:3) and chromatographed over neutral alumina in the same solvent; three major bands were observed. Slow evaporation of the colourless fraction obtained after elution of the first band gave the amide (1). Recrystallisation from benzene–light petroleum (b.p. 60–80°) (1:9) gave white *needles* (40 mg), m.p. 131.5–132.5° (Found: C, 67.25; H, 6.7; N, 5.8. C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 66.9; H, 6.5; N, 6.0%), λ<sub>max</sub> 233 (ε 4 300) and 287 nm (4 660), ν<sub>max</sub> (Nujol) 3 310, 1 640, 1 550, 1 500, 1 480, and 945 cm<sup>-1</sup>, τ 2.33 (3 H, complex), 4.10 (2 H, s), 4.38br (1 H), 6.56br (2 H, q), 7.28 (2 H, t), 8.78 (1 H, complex), 9.1 (2 H, complex), and 9.33 (2 H, complex), *m/e* 233 (*M*<sup>+</sup>), 149, 135, 69, and 41.

*Rubesamide* [N-(3,4-Methylenedioxyphenethyl)cyclopropanecarboxamide] (1).—Cyclopropanecarboxylic acid (2 g, 23 mmol) and thionyl chloride (3.7 g, 31 mmol) were heated on a steam-bath for 0.5 h. Distillation gave the acid chloride as a liquid (2.3 g, 94%), b.p. 120–123° (lit.,<sup>6</sup> 120–122°). The acid chloride (1 g, 9.5 mmol) in dichloromethane (20 ml) was added over 5 min to a rapidly stirred mixture of 3,4-methylenedioxyphenethylamine oxalate (1.0 g, 3.9 mmol), saturated aqueous sodium hydrogen carbonate (50 ml), and dichloromethane (30 ml) at 0 °C. Stirring was continued for 2 h, the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined extract was washed with saturated brine then dried and evaporated to give the *amide* (542 mg), which crystallised from benzene–light petroleum (1:9) as white needles (300 mg), m.p. 131.5–132.5°, identical (mixed m.p. and spectra) with the natural material (Found: C, 66.8; H, 6.5; N, 6.0. C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 66.9; H, 6.5; N, 6.0%).

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<sup>7</sup> F. G. Torto, P. Sefcovic, B. A. Dadson, and I. A. Mensah, *Ghana J. Sci.*, 1969, **9**, 3.