872. *Synthetical Experiments in the Chelidonine–Sanguinarine Group of the Alkaloids. Part IV.*[1]

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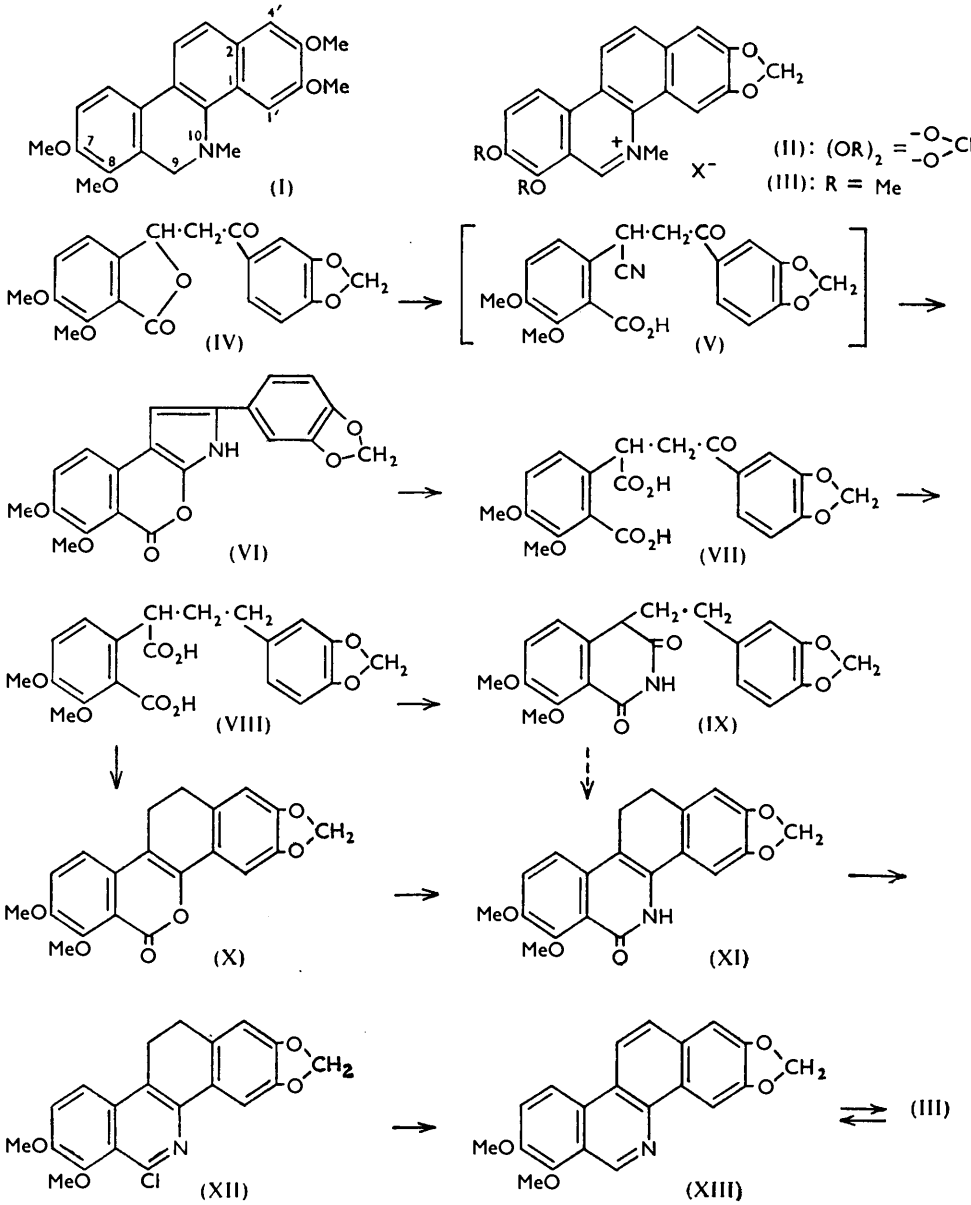
The synthesis of 7 : 8-dimethoxy-10-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridinium chloride (chelerythrine chloride) is described.

In Parts II and III [1] of this series the synthesis of 9 : 10-dihydro-7 : 8 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridine (I) from opianic acid was described. This compound had previously been obtained from sanguinarine (II) and chelerythrine (III),[2] and its synthesis confirmed the structures for the two alkaloids. The method of forming the 1 : 2-benzophenanthridine ring system has now been extended to a synthesis of chelerythrine (III).

Opianic acid was condensed with 3 : 4-methylenedioxyacetophenone, giving 6 : 7-dimethoxy-3-(3 : 4-methylenedioxyphenacyl)phthalide (IV). Addition of hydrogen cyanide to this gave a crude nitrile (V) which was cyclised to the pyrrolo*iso*coumarin (VI) by hydrochloric acid. This reaction has been shown [3] to be general for nitriles of type (V). Alkaline hydrolysis of the compound (VI) afforded α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-methylenedioxyphenyl)-γ-oxobutyric acid (VII), reduction of which in acetic acid containing perchloric acid with a palladium–charcoal catalyst [4] smoothly yielded α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-methylenedioxyphenyl)butyric acid (VIII). This method of reducing a keto-group was selected to avoid the drastic conditions of the Clemmensen

[1] Part II, Bailey and Robinson, *J.*, 1950, 1375; Part III, Bailey, Robinson, and Staunton, *ibid.*, p. 2277.
[2] Späth and Kuffner, *Ber.*, 1931, **64**, 2034.
[3] Bailey and Staunton, *J.*, 1952, 2153; Bailey and Swallow, *J.*, 1956, 2477.
[4] Rosenmund and Karg, *Ber.*, 1942, **75**, 1850; Kindler, Metzendorf, and Dschi-yin-Kwok, *Ber.*, 1943, **76**, 308; Baker and Jenkins, *J. Amer. Chem. Soc.*, 1946, **68**, 2102; Johnson and Graber, *ibid.*, 1950, **72**, 925.

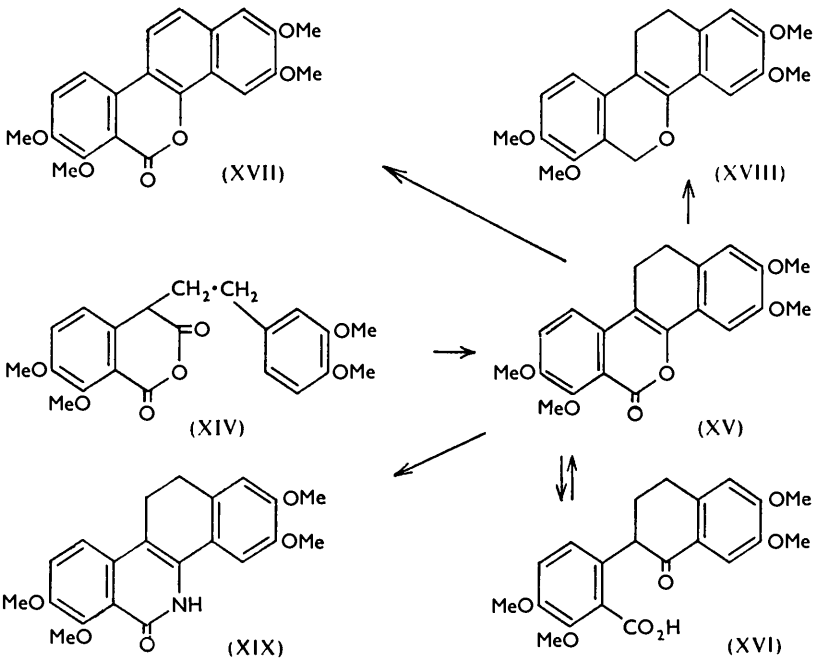
or Wolff–Kishner method. Heating the ammonium salt of the acid (VIII) gave the homophthalimide (IX). Unfortunately, treatment of this with polyphosphoric acid failed to give the desired product (XI): the dark amorphous material obtained gave an intense colour with ferric chloride, indicating loss of the methylenedioxy-group. The cyclisation could also not be accomplished by using boron trifluoride or hydrogen fluoride.



Preliminary experiments were then carried out with α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)butyric acid and its anhydride (XIV) since they were available [1] from previous work. Heating either with polyphosphoric acid afforded the dihydronaphtho*iso*coumarin (XV), a reaction analogous to the formation of 3-phenyl*iso*coumarin from homophthalic anhydride and benzene in the presence of aluminium chloride.[5]

[5] Graebe and Trümpy, *Ber.*, 1898, **31**, 375.

The infrared spectrum of the product (XV) contained a band at 1721 cm.$^{-1}$, expected of an enol ester; and the compound was rapidly hydrolysed to the keto-acid (XVI), which re-formed the *iso*coumarin above its melting point. The structure (XV) was supported by dehydrogenation to the fully aromatic compound (XVII). The latter was also obtained from the keto-acid (XVI) on treatment with thionyl chloride followed by ammonia in an attempt to make its amide; this reaction must involve chlorination followed by removal of hydrogen chloride. Reduction of the *iso*coumarin (XV) with lithium aluminium hydride at room temperature yielded the naphtho*iso*chromen (XVIII) which did not contain a keto- or hydroxy-group (infrared spectrum): reduction of homophthalic anhydride with lithium aluminium hydride [6] gives some *iso*chroman as well as the expected glycol, and Conover and Tarbell [7] have observed that reduction, by lithium aluminium hydride, of aromatic ketones having methoxy- or amino-groups *para* to the carbonyl group reduces the latter to methylene. The formation of the *iso*chromen (XVIII) from the *iso*coumarin (XV) is similar to the formation of a dialkylchromen on reaction of a Grignard reagent with an *iso*coumarin.[8]



Heating the dihydronaphtho*iso*coumarin (XV) at 150° with a solution of ammonia [9] in ethanol gave a satisfactory yield of the dihydro-1 : 2-benzophenanthridone (XIX), identical with the compound obtained in Part II of this series.[1]

Having established this method of obtaining the 1 : 2-benzophenanthridine ring system we applied it to the acid (VIII). Heating the latter with polyphosphoric acid gave amorphous dark material, and so the acid was converted into its chloride, which was then cyclised with stannic chloride at 0°, giving the dihydronaphtho*iso*coumarin (X). The infrared spectrum of this contained a band at 1733 cm.$^{-1}$ (enol lactone), and its ultraviolet spectrum was almost identical (see diagram) with that of the analogue (XV). Alkaline hydrolysis gave the corresponding keto-acid which could not be obtained free from solvent of crystallisation, but when heated above its melting point gave the *iso*coumarin (X). The

[6] Anderson and Holliman, *J.*, 1950, 1037.
[7] Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586; cf. "Organic Reactions," Vol. VIII. Wiley, New York, 1953, pp. 269, 283.
[8] Ghosh, Todd, and Wilkinson, *J.*, 1940, 1393.
[9] Gabriel, *Ber.*, 1885, **18**, 2433, 3470; 1886, **19**, 830, 1653.

latter was recovered unchanged after being heated at 150° with ethanolic ammonia, although these conditions sufficed for the transformation of the analogue (XV) into the phenanthridone (XIX); this is probably due to the fact that the *iso*coumarin (X) is much higher-melting and less soluble in organic solvents than its analogue. However, in ethylene glycol containing ammonia the benzophenanthridone (XI) was produced at 210°, and refluxing the phenanthridone with phosphorus oxychloride yielded the 9-chloro-derivative (XII). When hydrogen was bubbled through a boiling *p*-cymene solution of this

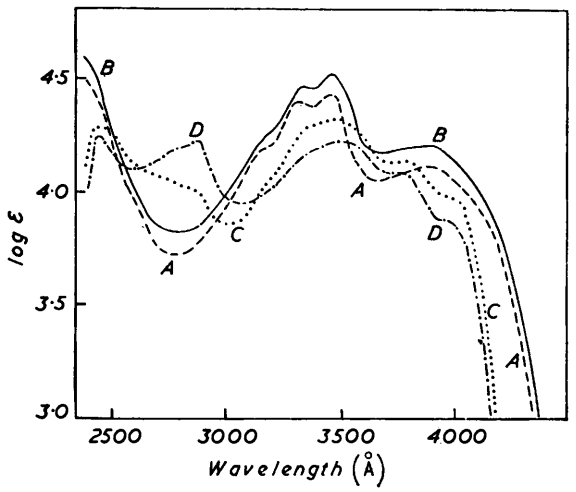


FIG. 1. *Absorption spectra of*: 3′:4′-*dihydro*-7:8:6′:7′-*tetramethoxy*-(— — —)(*A*) *and* 3′:4′-*dihydro*-7:8-*dimethoxy*-6′:7′-*methylenedioxynaphtho*(1′:2′-3:4)iso-*coumarin* (——) (*B*); 3:4-*dihydro*-7:8:2′:3′-*tetramethoxy*- (. . . .) (*C*) *and* 3:4-*dihydro*-7:8-*dimethoxy*-2′:3′-*methylenedioxy*-1:2-*benzophenanthridone* (— . — . —) (*D*) (*all in* $CHCl_3$).

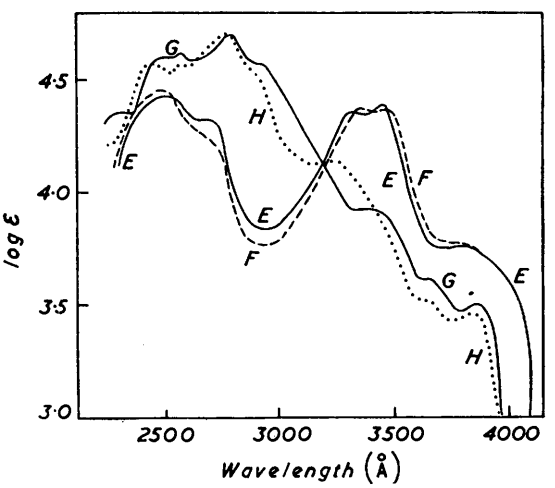


FIG. 2. *Absorption spectra of*: 9-*chloro*-3:4-*dihydro*-7:8:2′:3′-*tetramethoxy* (——) (*E*), 9-*chloro*-3:4-*dihydro*-7:8-*dimethoxy*-2′:3′-*methylenedioxy*- (— — —) (*F*), 7:8:2′:3′-*tetramethoxy*- (——) (*G*), *and* 7:8-*dimethoxy*-2′:3′-*methylenedioxy*-1:2-*benzophenanthridine* (. . . .) (*H*).

containing palladium–charcoal, the chlorine atom was removed and the compound simultaneously dehydrogenated. This method had previously [1] been used on the tetramethoxy-analogue of (XII). The product, 7:8-dimethoxy-2′:3′-methylenedioxy-1:2-benzophenanthridine (XIII), was identical (m. p., mixed m. p., infrared spectrum, R_F value) with the material obtained by sublimation of chelerythrine chloride at 200°/0·05 mm.; the decomposition of a quaternary ammonium chloride to give an alkyl chloride is a well-known reaction.[10] Sarkar [11] has observed that sanguinarine chloride loses methyl chloride

[10] "Sidgwick's Organic Chemistry of Nitrogen," Taylor and Baker, Oxford Univ. Press, 1937, pp. 28, 553; for recent examples in alkaloid chemistry see: Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853; Gellért, Raymond-Hamet, and Schlittler, *ibid.*, 1951, **34**, 642; Schlittler and Hohl, *ibid.*, 1952, **35**, 29; Ewing, Hughes, Ritchie, and Taylor, *Nature*, 1952, **169**, 618.

[11] S. N. Sarkar, D.Phil. Thesis, Oxford, 1948, p. 61.

at 240°, giving the corresponding tertiary base. The base (XIII) with dimethyl sulphate in xylene gave the methosulphate which was not purified but was dissolved in water and on addition of hydrochloric acid then yielded chelerythrine chloride (III; X = Cl), identical (mixed m. p. and R_F value) with the natural product. The compound gave analyses as for the trihydrate, but after drying for 2 hr. at 100° for the monohydrate. Analyses have been reported for the anhydrous salt,[12, 13] the monohydrate,[12, 14] trihydrate,[15] tetrahydrate,[16] and pentahydrate.[16, 17] The ψ-cyanide was also prepared, identical (mixed m. p. and infrared spectrum) with a specimen obtained from the natural product. The infrared spectra of chelerythrine ψ-cyanide and sanguinarine ψ-cyanide do not contain a band at 2400—2100 cm.$^{-1}$. An example of the compound which contains a ·CN group and does not show any absorption in this region has been reported.[18]

It is interesting that the melting points of the compounds (X), (XI), and (XII) are higher than those of their tetramethoxy-analogues; but (XIII) is lower-melting than its tetramethoxy-analogue. The spectra of (X), (XI), (XII), and (XIII) are shown in the Figures, along with those of the corresponding tetramethoxy-compounds.

The separation of chelerythrine and sanguinarine, and the chemical detection of small quantities of one compound as a contaminant of the other, are difficult. We have found that the two alkaloids can easily be separated by paper chromatography using butanol–acetic acid–water, sanguinarine having R_F 0·64 (orange spot) and chelerythrine R_F 0·72 (yellow spot). The two substances could not be separated when phenol–water was used since both substances moved with the solvent front. It was found that a specimen of chelerythrine chloride supplied by Dr. Manske contained a trace of sanguinarine, easily detected by this method.

The colour of chelerythrine salts has been variously described as lemon-yellow, golden-yellow, orange-yellow, and orange. This may be due to contamination with sanguinarine or to the different hydrates formed. The synthetic compound sometimes appeared lemon-yellow, at other times orange-yellow. A drop of an aqueous solution of chelerythrine chloride placed on a filter paper gave a clear yellow spot with no trace of orange in the colour.

Added, September 27th, 1956.—Slavík and Slavíková (*Coll. Czech. Chem. Comm.*, 1954, **20**, 21) separated chelerythrine from sanguinarine by paper chromatography with butanol–acetic acid–water.

Experimental

Ultraviolet absorption spectra were determined in chloroform unless otherwise stated, and infrared spectra were measured on Nujol mulls. Paper chromatograms were run on Whatman No. 1 paper with butan-1-ol–acetic acid–water (4 : 1 : 5), and examined in visible and ultraviolet light.

1-(3 : 4-Methylenedioxyphenyl)ethanol[19] was oxidised with finely powdered potassium permanganate[20] in acetone solution to 3 : 4-methylenedioxyacetophenone, b. p. 170—190°/18 mm., m. p. 86—87° (from methanol).

6 : 7-*Dimethoxy*-3-(3 : 4-*methylenedioxyphenacyl*)*phthalide* (IV).—3 : 4-Methylenedioxyacetophenone (35 g.) was dissolved in warm ethanol (250 c.c.) containing opianic acid (42 g.), and potassium hydroxide (21 g.) in water (35 c.c.) was added dropwise. The orange-coloured solution was kept at room temperature for 36 hr., then acidified with dilute hydrochloric acid. The oil which separated rapidly solidified; it was collected, washed with water, and crystallised

[12] Karrer, *Ber.*, 1917, **50**, 212.
[13] Govindachari and Thyagarajan, *J.*, 1956, 769.
[14] Bauer and Hedinger, *Arch. Pharm.*, 1920, **258**, 167.
[15] Gadamer and Stichel, *ibid.*, 1924, **262**, 494.
[16] König and Tietz, *ibid.*, 1893, **231**, 145, 161.
[17] Cannon, Hughes, Ritchie, and Taylor, *Austral. J. Chem.*, 1953, **6**, 86.
[18] Potts and Robinson, *J.*, 1955, 2466.
[19] Böttcher, *Ber.*, 1909, **42**, 253; Balfe, Downer, Evans, Kenyon, Poplett, Searle, and Tárnoky, *J.*, 1946, 801.
[20] Richardson, Robinson, and Seijo, *J.*, 1937, 835.

from acetic acid–methanol, forming white felted needles (59 g.), m. p. 152—153° (Found: C, 64·0; H, 4·5. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%).

During one preparation the material separated as a yellow solid, obviously the αβ-unsaturated ketone; attempted crystallisation from ethanol gave the colourless cyclisation product (IV).

7 : 8-*Dimethoxy*-5′-(3 : 4-*methylenedioxyphenyl*)*pyrrolo*(2′ : 3′-3 : 4)iso*coumarin* (VI).—**6** : 7-Dimethoxy-3-(3 : 4-methylenedioxyphenacyl)phthalide (20 g.) was dissolved in boiling 2-methoxyethanol (70 c.c.) containing crystalline sodium acetate (8 g.). To the mixture, at 100°, potassium cyanide (10 g.) in water (20 c.c.) was added during 2 min. through a funnel reaching to the bottom of the flask. After 10 minutes' heating with occasional stirring, the mixture was cooled and dilute hydrochloric acid (200 c.c.) added. Thirty minutes later the aqueous liquor was decanted from the gum which had separated; the gum was then washed with distilled water by decantation and dissolved in boiling acetic acid (70 c.c.), and 17% hydrochloric acid (20 c.c.) added. A yellow precipitate immediately separated. The mixture was then heated on a water-bath for 5 min. and, after cooling, the solid *product* was collected, washed with dilute acetic acid, then with methanol, and dried (9—13 g.; m. p. 280—286°). Two crystallisations from pyridine gave yellow needles, m. p. 287—289° (decomp.) (Found: C, 65·7; H, 3·9; N, 3·9. $C_{20}H_{15}O_6N$ requires C, 65·8; H, 4·1; N, 3·8%), $\lambda_{max.}$ 2370 (ε 24,800), 3240 (ε 20,500), and 4100 Å (ε 8080).

α-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyric Acid* (VII).—7 : 8-Dimethoxy-5′-(3 : 4-methylenedioxyphenyl)pyrrolo(2′ : 3′-3 : 4)*iso*coumarin (20 g.) was refluxed with 10% sodium hydroxide solution (200 c.c.). An orange-red solution was formed as the lactone dissolved, ammonia was evolved, and the solution became pale yellow. When the evolution of ammonia ceased (2—3 hr.), the solution was filtered and acidified with dilute hydrochloric acid. The gum which separated slowly solidified. Crystallisation from 50% acetic acid gave the *acid* as colourless rods (15·2 g.), m. p. 181—183° (decomp.) (Found: C, 59·9; H, 4·6. $C_{20}H_{18}O_9$ requires C, 59·7; H, 4·5%). The *anhydride* formed clusters of rods (from acetic acid), m. p. 194—195° (Found: C, 62·8; H, 4·0. $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%).

α-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-γ-(3 : 4-*methylenedioxyphenyl*)*butyric Acid* (VIII).—A solution of the foregoing acid (5 g.) in acetic acid (40 c.c.) containing 60% perchloric acid (0·5 c.c.) was hydrogenated at 60°/1 atm. in the presence of 5% palladium–charcoal (1 g.); two mols. of hydrogen were absorbed during 1·5 hr. The catalyst was filtered off, water (20 c.c.) added, the solution evaporated *in vacuo* to *ca.* 10 c.c., and then more water (10 c.c.) added. An oil separated which slowly solidified (3·4 g.; m. p. 148—150°). Crystallisation from toluene or 50% ethanol gave the *acid* as colourless rhombs, m. p. 150—152° (decomp.) (Found: C, 61·8; H, 5·1%; equiv., 194. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·2%; equiv., 194).

Reduction of α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)-γ-oxobutyric acid by the same method gave α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-dimethoxyphenyl)-butyric acid, m. p. 169—171°, not depressed by a specimen obtained [1] by Clemmensen reduction.

7 : 8-*Dimethoxy*-4-(3 : 4-*methylenedioxyphenylethyl*)*homophthalimide* (IX).—The acid (VIII) (2 g.) was dissolved in ammonia (3 c.c.; *d* 0·88), and the solution evaporated to dryness *in vacuo*. Ammonium carbonate (0·5 g.) was added and the mixture heated for 30 min. *in vacuo* at 160° (oil-bath). The temperature of the bath was then raised to 190° for 15 min. and the resulting glass crystallised from benzene. The *imide* formed rods, m. p. 131—132° (Found: C, 65·1; H, 5·2; N, 3·8. $C_{20}H_{19}O_6N$ requires C, 65·1; H, 5·2; N, 3·8%), and gave a yellow colour with sodium hydroxide solution.

3′ : 4′-*Dihydro*-7 : 8-*dimethoxy*-6′ : 7′-*methylenedioxynaphtho*(1′ : 2′-3 : 4)iso*coumarin* (X).—A mixture of α-(2-carboxy-3 : 4-dimethoxyphenyl)-γ-(3 : 4-methylenedioxyphenyl)butyric acid (6 g.) and chloroform (75 c.c.) was heated under reflux and thionyl chloride (40 c.c.) slowly added. After 10 min. the yellow solution was evaporated on a water-bath *in vacuo*, the residual gum dissolved in hot chloroform (30 c.c.), and stannic chloride (7 c.c.) added to the ice-cold solution. A dark gum immediately separated which crystallised at 0°. After 4 hr. the supernatant liquid was decanted and the solid triturated with 17% hydrochloric acid and chloroform. The organic layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were washed with dilute hydrochloric acid, dilute sodium hydroxide solution (which removed some dark-coloured impurity), and water. Removal of the solvent gave a pale brown solid (3·9 g.). 3′ : 4′-*Dihydro*-7 : 8-*dimethoxy*-6′ : 7′-*methylenedioxynaphtho*-(1′ : 2′-3 : 4)iso*coumarin* separated from acetic acid as yellow needles which softened at 230—233°, m. p. 240—243°. This behaviour on heating still occurred after the compound had been crystallised from anisole, 2-methoxyethanol, or pyridine, and after chromatography on alumina

(Found: C, 68·5; H, 4·6. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%), $\lambda_{max.}$ 3340 (ε 27,950), 3475 (ε 32,000), and 3850 Å (ε 15,700). The infrared spectrum had bands at 1733, 1645, and 1605 cm.$^{-1}$.

2-(2-*Carboxy*-3 : 4-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*-1-*oxonaphthalene*.—3′ : 4′-Dihydro-7 : 8-dimethoxy-6′ : 7′-methylenedioxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (X) (0·5 g.) was refluxed with 2N-sodium hydroxide solution (25 c.c.) and ethanol (10 c.c.). The material slowly dissolved, and after 1 hr. the clear solution was diluted with water (75 c.c.), filtered, and acidified with dilute hydrochloric acid. The solid tetralone which separated was crystallised twice from ethyl acetate, forming colourless plates of *solvate* which, dried at 100°/0·05 mm., had m. p. 154—155° (decomp.) [Found: C, 63·8, 64·1; H, 5·4, 5·6. $(C_{20}H_{18}O_7)_2,C_4H_8O_2$ requires C, 63·8; H, 5·4%]. Crystallisation of the acid from toluene gave another *solvate*, as colourless prisms, m. p. 175—178° (decomp.) [Found: C, 68·2; H, 5·3. $(C_{20}H_{18}O_7)_2,C_7H_8$ requires C, 67·8; H, 5·3%]. The acid rapidly formed the *iso*coumarin (X) at its m. p.

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridone* (XI).—3′ : 4′-Dihydro-7 : 8-dimethoxy-6′ : 7′-methylenedioxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (0·5 g.) and ethylene glycol (15 c.c.) containing anhydrous ammonia (3 g.) were heated together for 17 hr. at 210° (sealed tube). The mixture was diluted with ethanol, and the solid collected, washed with ethanol, and crystallised from pyridine (0·38 g.; m. p. 290—292°). Crystallisation from anisole gave 3 : 4-*dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridone* in the form of pale yellow plates, m. p. 292—295° (decomp.) (Found: C, 68·7; H, 5·1; N, 3·6. $C_{20}H_{17}O_5N$ requires C, 68·4; H, 4·9; N, 4·0%), $\lambda_{max.}$ 2450 (ε 17,600), 2880 (ε 16,760), 3520 (ε 16,200), 3790 (ε 11,900), and 3990 Å (ε 7260); infrared bands were at 3077 (broad band), 1639, and 1625 cm.$^{-1}$.

9-*Chloro*-3 : 4-*dihydro*-7 : 8-*dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridine* (XII).—The preceding phenanthridone (1 g.) and phosphorus oxychloride (25 c.c.) were refluxed (oil-bath) together for 1 hr., the orange solution cooled and poured on ice, and excess of dilute ammonia solution added. The resulting solid was collected, washed with water, and dried. The material was extracted with boiling toluene, the extracts were evaporated, and the residue was crystallised from ethyl acetate, giving the *chloro-compound* (0·62 g.), pale yellow needles, m. p. 226—228° (Found: C, 65·3; H, 4·5; N, 3·8; Cl, 9·3. $C_{20}H_{16}O_4NCl$ requires C, 65·0; H, 4·4; N, 3·8; Cl, 9·6%), $\lambda_{max.}$ 2475 (ε 28,450), 3340 (ε 22,850), 3450 (ε 24,480), and 3760 Å (ε 5980).

7 : 8-*Dimethoxy*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridine* (XIII).—(*a*) Chelerythrine chloride was sublimed at 200°/0·05 mm. The pale yellow sublimate was crystallised from toluene and then from 1 : 1 butan-1-ol–2-methoxyethanol, forming colourless plates, m. p. 212—214° (slight decomp.) (Found: C, 72·2; H, 4·4; N, 4·0. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%), $\lambda_{max.}$ 2150 (ε 17,600), 2430 (ε 38,150), 2560 (ε 37,350), 2770 (ε 51,000), 3240 (ε 14,000), and 3840 Å (ε 3010) in ethanol.

(*b*) A solution of 9-chloro-3 : 4-dihydro-7 : 8-dimethoxy-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine (0·3 g.) in *p*-cymene (4 c.c.) was refluxed for 7 hr. (oil-bath at 200—210°) with 30% palladium–charcoal (0·15 g.) and a slow stream of hydrogen bubbled through the liquid; hydrogen chloride was steadily evolved. The solution was filtered and the catalyst extracted with *p*-cymene (2 c.c.). On cooling, a colourless solid (m. p. 195—205°) separated. Crystallisation from toluene gave fine needles (100 mg.; m. p. 203—208°), and crystallisation from butanol–2-methoxyethanol yielded colourless plates, m. p. 211—213°, mixed m. p. with the specimen obtained from chelerythrine chloride as under (*a*) 212—214° (Found: C, 71·8; H, 4·6; N, 4·3%). The infrared spectra of the two specimens were identical, and they had the same R_F value (0·87). The compound showed a faint blue fluorescence in dilute alcoholic solution.

7 : 8-*Dimethoxy*-10-*methyl*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridinium Chloride* (III; X = Cl).—A mixture of xylene (10 c.c.) and the tertiary base (XIII) (0·3 g.) was heated to boiling (oil-bath), a few drops of xylene were distilled out to remove traces of water, then dimethyl sulphate (1 c.c.) was added and the mixture refluxed for 40 min., a further 0·3 c.c. of dimethyl sulphate being added after 15 min. An orange-coloured solid rapidly separated from the solution. The mixture was cooled, and the methosulphate collected, washed with benzene and light petroleum (b. p. 40—60°), and dried (300 mg.). The methosulphate was warmed with water, most of the product dissolving, the solution was filtered from a small quantity of insoluble material, left to cool, and again filtered, and a few drops of concentrated hydrochloric acid were added to the filtrate. Fine orange-yellow needles separated. The *chloride*, crystallised from water containing a small quantity of hydrochloric acid, had m. p. and mixed m. p. with chelerythrine chloride 203—205° (decomp.). This m. p. is very sensitive to the rate of heating

from a bath at 185° chelerythrine chloride has m. p. 207—209° (Found: C, 57·1; H, 5·3. $C_{21}H_{18}O_4NCl,3H_2O$ requires C, 57·5; H, 5·5. Found, after drying at 100° for 2 hr.: C, 62·1; H, 4·9; N, 3·2. $C_{21}H_{18}O_4NCl,H_2O$ requires C, 62·7; H, 5·0; N, 3·5%) (lit.: [13,17] m. p. 210°; 202—203°).

The *ψ*-cyanide formed colourless prisms (from 2-methoxyethanol), m. p. 258—260° (decomp.), mixed m. p. 258—260°: recorded values [13,17,21,22] range from 256° to 263°.

3′:4′-*Dihydro*-7:8:6′:7′-*tetramethoxynaphtho*(1′:2′-3:4)iso*coumarin* (XV).—Phosphoric oxide (2 g.) was dissolved in syrupy phosphoric acid (6 c.c.), and the finely powdered anhydride of α-(2-carboxy-3:4-dimethoxyphenyl)-γ-(3:4-dimethoxyphenyl)butyric acid (0·4 g.) was added to the warm solution. The resulting pale yellow solution was heated on a water-bath for 20 min. After 5 minutes' heating a yellow solid started to separate and then the whole solidified. Ice-water was added and the residual gum slowly hardened. The solid was collected, washed with water, ground with sodium carbonate solution, collected, again washed with water, and crystallised from methanol (m. p. 168—169°; 0·36 g.). Two crystallisations from methanol gave the iso*coumarin* as pale, lemon-yellow needles, m. p. 171—172° [Found: C, 68·6; H, 5·6%; *M* (cryoscopic in camphor), 393. $C_{21}H_{20}O_6$ requires C, 68·5; H, 5·4%; *M*, 368], $\lambda_{max.}$ 3340 (ε 24,400), 3470 (ε 26,600), and 3880 Å (ε 12,900). The infrared spectrum contained bands at 1721, 1634, 1605, and 1580 cm.$^{-1}$. The compound was soluble in benzene and acetic acid, insoluble in cold sodium carbonate and sodium hydroxide solutions; it did not give a colour with ferric chloride or 2:4-dinitrophenylhydrazine.

The *iso*coumarin may be obtained by heating the free acid with polyphosphoric acid. The product is best isolated by chloroform extraction, the extract being washed with sodium carbonate solution.

2-(2-*Carboxy*-3:4-*dimethoxyphenyl*)-1:2:3:4-*tetrahydro*-6:7-*dimethoxy*-1-*oxonaphthalene* (XVI).—The *iso*coumarin (2 g.) was refluxed with a mixture of 2N-aqueous sodium hydroxide (25 c.c.) and ethanol (6 c.c.). After 5 min. all the solid had dissolved; the colourless solution was cooled, diluted with water (20 c.c.), filtered from a trace of insoluble material, and acidified with dilute hydrochloric acid. The resulting *acid* was collected, washed with water, and crystallised from ethanol (1·9 g.). Crystallisation from methanol and then from ethyl acetate gave colourless plates which lost solvent at 135—140°, and had m. p. 176—178° (decomp. to a clear, yellow melt) (Found: C, 65·3; H, 5·8%; equiv., 394. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%; equiv., 386). The 2:4-*dinitrophenylhydrazone* formed orange prisms (from 2-ethoxyethanol), m. p. 250—252° (decomp.) (Found: C, 57·2; H, 4·7; N, 9·7. $C_{27}H_{26}O_{10}N_4$ requires C, 57·3; H, 4·6; N, 9·9%).

The keto-acid was heated in an oil-bath at 180° for 5 min.; the resulting yellow glass crystallised when warmed with ethanol, then having m. p. and mixed m. p. with the *iso*coumarin (XV) 170—171°.

7:8:6′:7′-*Tetramethoxynaphtho*(1′:2′-3:4)iso*coumarin* (XVII).—(*a*) 3′:4′-Dihydro-7:8:6′:7′-tetramethoxynaphtho(1′:2′-3:4)*iso*coumarin (0·3 g.) and 30% palladium–charcoal (70 mg.) were heated together in an atmosphere of hydrogen at 210—220° (metal-bath) for 30 min. Hydrogen was rapidly evolved at 200°. The cold residue was thoroughly extracted with boiling chloroform, the catalyst removed, and the solvent evaporated. The *product* (0·17 g.) formed cream-coloured needles (from dioxan), m. p. 230—231° (Found: C, 68·6; H, 5·1. $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%), $\lambda_{max.}$ 2380 (ε 33,700), 2790 (ε 42,400), 3030 (ε 18,600), 3155 (ε 21,200), and 3640 Å (ε 91,400): the infrared spectrum contained bands at 1742, 1629, and 1590 cm.$^{-1}$.

(*b*) A mixture of the acid (XVI) (0·5 g.), chloroform (20 c.c.), and thionyl chloride (5 c.c.) was refluxed for 10 min., and then evaporated *in vacuo* on a water-bath. The resulting yellow solid was heated with ammonia (20 c.c.; *d* 0·88) for 30 min. at 100°, but no change was apparent. The product (0·3 g.) separated from anisole in pale yellow prisms, m. p. 210—230°. A solution of the solid in ether–chloroform (1:1) was chromatographed on alumina (acid-washed); elution with ether–chloroform (2:1) gave a pale yellow solid, which separated from acetic acid in almost colourless prisms, m. p. 230—231° (softening from 220°) (Found: C, 68·4; H, 4·9%). After crystallisation from dioxan, the material was identical (mixed m. p. and infrared spectrum) with a freshly crystallised specimen of material prepared as under (*a*). The m. p.s of both samples slowly deteriorated.

3′:4′-*Dihydro*-7:8:6′:7′-*tetramethoxynaphtho*(1′:2′-3:4)iso*chromen* (XVIII).—A solution of the *iso*coumarin (XV) (1·0 g.) in warm tetrahydrofuran (30 c.c.) was added to a solution of

[21] Späth and Kuffner, *Ber.*, 1931, **64**, 1123.
[22] Manske, *Canad. J. Res.*, 1943, **21**, 140.

lithium aluminium hydride (0·25 g.) in tetrahydrofuran (12 c.c.). The yellow colour of the *iso*coumarin solution was immediately discharged, and the resulting clear solution was left at room temperature for 2 hr. Excess of hydride was decomposed by a few drops of ethyl acetate, followed by water, and then 2N-sulphuric acid was added. The mixture was extracted with chloroform (3 × 30 c.c.), the extracts were washed with dilute sulphuric acid, water, and dried ($MgSO_4$) and the solvent was removed. Crystallisation of the residue (m. p. 171—174°) from dioxan containing a little ethanol gave colourless, hexagonal plates of the iso*chromen*, m. p. 175—176° (0·73 g.), m. p. unchanged by crystallisation from acetic acid [Found: C, 71·0, 71·4; H, 6·0, 6·4%; *M* (cryoscopic in camphor), 333. $C_{21}H_{22}O_5$ requires C, 71·3; H, 6·2%; *M*, 354], $\lambda_{max.}$ 2480 (ε 11,300) and 3560 Å (ε 19,400); infrared bands were at 1623 and 1603 cm.$^{-1}$. The compound was readily soluble in hot benzene and acetic acid. It contained no active hydrogen and gave negative ferric chloride and 2 : 4-dinitrophenylhydrazine tests. The substance (0·3 g.) was heated with 30% palladium–charcoal (50 mg.) at 200°. Hydrogen was rapidly evolved and the melt solidified; after 20 min. the temperature of the bath was raised to 230° and kept at that temperature for 5 min. The cold melt was extracted with chloroform, the filtered extracts were evaporated, and the residue was digested with methanol (yield, 0·25 g.; m. p. 220—225°). Crystallisation from 2-methoxyethanol gave 7 : 8 : 6′ : 7′-*tetramethoxynaphtho*(1′ : 2′-3 : 4)iso*chromen* as irregular plates, m. p. 225—227° (slight decomp.) (Found: C, 71·5; H, 5·9. $C_{21}H_{20}O_5$ requires C, 71·7; H, 5·7%), $\lambda_{max.}$ 2440 (ε 16,900), 2850 (ε 45,700), 3070 (ε 15,600), and 3240 Å (ε 16,750).

3 : 4-*Dihydro*-7 : 8 : 2′ : 3′-*tetramethoxy*-1 : 2-*benzophenanthridone* (XIX).—3′ : 4′-Dihydro-7 : 8 : 6′ : 7′-tetramethoxynaphtho(1′ : 2′-3 : 4)*iso*coumarin (0·5 g.) was heated for 10 hr. at 150° with ethanol (20 c.c.) which had been saturated with ammonia at −5°. The resulting solid (0·29 g.) was collected and crystallised from butan-1-ol. It formed pale yellow needles, m. p. 259—262°, identical (mixed m. p. and infrared spectrum) with the compound prepared [1] in Part II of this series.

The authors thank Sir Robert Robinson, O.M., F.R.S., for his interest and encouragement, Dr. R. F. H. Manske for a generous gift of chelerythrine chloride, and Dr. S. N. Sarkar for permission to quote from his thesis. One of them (C. R. W.) thanks the Department of Scientific and Industrial Research for financial assistance.

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