211. *The Alkaloids of* Artabotrys suaveolens.

By (the late) GEORGE BARGER and LEWIS J. SARGENT.

The three alkaloids obtained from this member of N.O. *Anonaceæ* are found to belong to the aporphine group and are thus similar in structure to those of related botanical orders. Artabotrine, $C_{20}H_{23}O_4N$, is probably 10-hydroxy-4 : 5 : 6-trimethoxyaporphine, and suaveoline 4 : 10-dihydroxy-5 : 6-dimethoxyaporphine. The aliphatic 10-hydroxy-group is a novel feature in this group of alkaloids. It is not contained in artabotrinine, $C_{18}H_{17}O_3N$, a secondary base, probably 2-methoxy-5 : 6-methylenedioxynoraporphine and possibly identical with the methyl ether of anolobine from *Asimina triloba* (N.O. *Anonaceæ*).

THE numerous *iso*quinoline alkaloids are practically confined to four cohorts,* placed together in Eichler's system as nos. 6—9 of *Choripetalæ*. In two of them, represented in alkaloidal chemistry respectively by *Salsola* and *Cactaceæ*, alkaloids are scarce and have a simple constitution, without a benzene nucleus other than that present as *iso*quinoline. The other two cohorts are rich in alkaloids, mainly derived from benzyltetrahydro*iso*quinoline, *i.e.*, from two phenylalanine or tyrosine molecules, instead of from a single molecule of an aromatic amino-acid. In the cohort *Ranales* considerable insight has been obtained into the structure of the alkaloids of *Ranunculaceæ*, *Menispermaceæ*, *Lauraceæ*, *Monimiaceæ*, and *Berberidaceæ*, whereas *Nymphæaceæ*, *Magnoliaceæ* and *Anonaceæ* have been but little investigated in this respect. The present paper is concerned with a member of the last-named order, *Artabotrys suaveolens* Bl., a woody climber occurring in India, the Malayan and Philippine Islands. An alkaloid was detected in it by de Rochebrune ("Toxicologie africaine," 1897, I, 431) and by Greshoff (*Meded. 's Lands Plantent.*, 1898, **25**, 10); the latter reported about 0·1% of an alkaloid in the bark, not present in the leaves, and causing tetanic convulsions in frogs (this is also a property of related alkaloids, *e.g.*, laurotetanine). Artabotrine was named and cursorily examined by Marañon (*Philippine J. Sci.*, 1929, **38**, 259) and further investigated by Santos and Reyes (*Univ. Philippines Nat. Appl. Sci. Bull.*, 1932, **2**, 409), who assigned to it the formula $C_{21}H_{25}O_4N = C_{17}H_{13}O(OMe)_3NMe$. They could not ascertain the nature of the fourth oxygen atom and obtained in the second stage of the Hofmann degradation trimethylamine and a nitrogen-free product, which they did not investigate further on account of its "unpromising appearance."

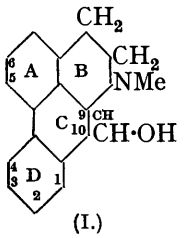
We find that artabotrine is in reality $C_{16}H_{11}O(OMe)_3NMe$, which formula is in agreement with the number of carbon and hydrogen atoms of an aporphine skeleton. The novel feature is the nature of the fourth oxygen atom. Since artabotrine contains one reactive hydrogen atom, as shown by the Zerewitinoff method and by the formation of a basic *monoacetyl* derivative, the fourth oxygen atom must be present as a hydroxyl group; preformed diazomethane does not act on this group, but nascent diazomethane converts it into a (fourth) methoxy-group. Since artabotrine is insoluble in sodium hydroxide solution, the hydroxyl group must be aliphatic, in the middle ring C, either at position 9 or 10; we supply evidence in favour of position 10. Of the three methoxy-groups of the alkaloid, two are almost certainly in positions 5 and 6, the third is probably in position 4; the methoxy-groups are not indicated in the formulæ on page 992.

The nearest analogy to the secondary alcohol group in position 10 is supplied by alkaloids of the hydrastine-narcotine type,† where this group is, however, not free, but present in a lactone ring. It modifies the degradation of the alkaloid by oxidation, and in the second

* Such curare alkaloids as are derived from *iso*quinoline do not occur in the genus *Strychnos* (cf. King, J., 1937, 1476). Emetine and its allies seem to be the only *iso*quinoline alkaloids obtained from a plant not belonging to the four cohorts, and their structure, not thoroughly established, is of a peculiar type. If data concerning alkaloids can be used at all in taxonomy, they would favour placing *Cactifloræ* between *Curvembryæ* and *Polycarpicæ* (= *Ranales*), as Eichler and Warming have done, rather than Engler's system, in which *Opuntiales* (= *Cactifloræ*) are widely separated from the other three cohorts.

† A probably even closer analogy is to be found in hydroxycodeine (Knorr, *Ber.*, 1906, **39**, 1414, 3130; 1907, **40**, 2042).

stage of the Hofmann method. It seems to have quite feeble acidic properties; for instance, it can be methylated, not only by nascent diazomethane, but also by the action of methyl sulphate on finely divided artabotrine, suspended in sodium hydroxide solution: the resulting *methosulphate* is transformed by potassium iodide into the *methiodide* of *artabotrine methyl ether*. A few drops of ethereal ferric chloride, added to a solution of artabotrine in a non-hydroxylic solvent (chloroform, acetone, benzene), produce a yellow or brownish



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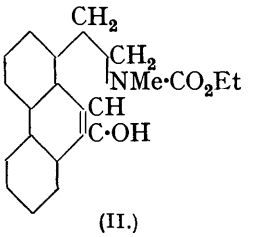

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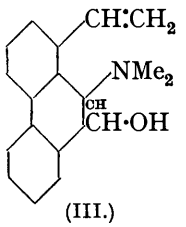

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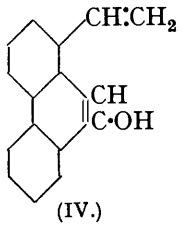


(IV.)

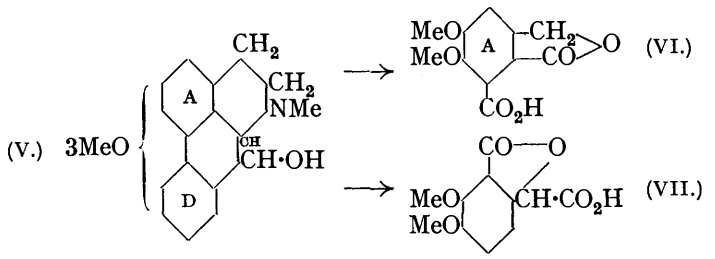
precipitate, reminiscent of a similar reaction for aliphatic hydroxyl adjoining a double bond (H. Meyer, " Analyse und Konstitutionsermittlung," 1931, 324). We are unfortunately unable to remove the hydroxyl at position 10, by first replacing it by chlorine; the action of thionyl chloride led to polyhalogenated substances, which could not be reduced to an aporphine derivative.

That artabotrine is a tetrahydro*iso*quinoline follows from the opening of the heterocyclic ring by ethyl chloroformate, and since the *product* (II) * is optically inactive, artabotrine belongs to the aporphine and not to the benzyltetrahydro*iso*quinoline (laudanosine) type (Gadamer and Knoch, *Arch. Pharm.*, 1921, **259**, 146). Artabotrine cannot be reduced catalytically by ordinary means, so no aliphatic double bond is present, and hence the number of hydrogen atoms in the molecule requires the existence of four rings; additional evidence for the aporphine structure is supplied by *X*-ray analysis (see appendix). The Hofmann degradation proceeded quite satisfactorily when the *methiodide* was boiled with alcoholic, instead of the aqueous potassium hydroxide used by Santos and Reyes. We obtained the optically active, crystalline *methine* (III) in a yield of 80% and showed the presence of a vinyl group by reduction to the *dihydromethine*. The alcoholic hydroxyl group is not affected by the first stage of the Hofmann degradation, and is not attached to either carbon atom of the vinyl group; in position 9 it would be tertiary and would have been eliminated as water by boiling potassium hydroxide; we therefore think it is in position 10. In the second stage of the degradation the *methine methiodide* yields trimethylamine and a crystalline substance (IV) which shows a blue fluorescence in solution and has the composition and properties of a *trimethoxyvinylphenanthrol* (yield, 70%). The Hofmann degradation was also carried out with artabotrine methyl ether; the vinyl derivative rapidly polymerised and yielded on oxidation only a small quantity of a crystalline acid, which could not be fully investigated.

The difficulties of synthesising trimethoxyphenanthrols made us attempt to determine the position of the methoxy-groups by oxidation, and here again the free hydroxy-group had considerable influence. The production by nitric acid of benzene-1 : 2 : 3 : 4-tetracarboxylic acid, of great evidential value for the aporphine structure, failed in the present case owing to the instability of the central ring. With sulphuric acid and potassium dichromate a deep red basic *o*-quinone-like compound was produced, giving the Laubenheimer reaction and decolorised by sulphurous acid. It was only obtained in small quantity, but is not produced at all from related alkaloids devoid of the aliphatic hydroxyl. With potassium permanganate a small quantity of a novel oxidation product was obtained, a *monocarboxylic lactone acid*, $C_{11}H_{10}O_6$, containing two methoxy-groups. This must therefore be a phthalidecarboxylic acid, with the free carboxyl attached either to the benzene ring, as in (VI), or to the phthalide group, as in (VII) [in (VI) and (VII) the positions of the methoxy-groups are illustrative and arbitrary]. The oxidation product could be

* This formula is supported by the facts that the product is soluble in alkali solution and couples readily with diazotised aniline.

sublimed unchanged in a vacuum and melted without evolution of a gas; it gave the fluorescein reaction. Hence the free carboxyl group must be attached to the benzene ring, as in (VI). Various α-phthalidecarboxylic acids of type (VII) melted with effervescence and none gave the fluorescein reaction. Now an acid of type (VI) is only obtainable from ring A, so this ring contains two methoxy-groups; whether these are in artabotrine in positions 5 and 6 [as implied by (VI)] or in 5 and 7, or in 6 and 7, can only be determined



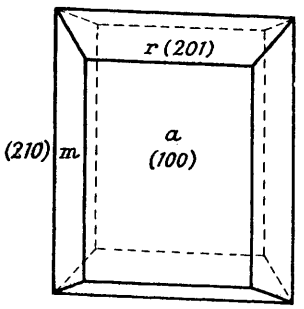
by a synthesis of the oxidation product; the 5 : 6 arrangement is, however, very probable, and the others would be without analogy. Although the type (VII) seems to be excluded for the reasons given, we nevertheless attempted a comparison of the oxidation product with the six possible isomerides of type (VII). Three were already known and could be eliminated by their recorded m. p.'s, or by their m. p. when mixed with the oxidation product. We synthesised 2 : 4- and 2 : 5-dimethoxyphthalide-α-carboxylic acids with the same result, but could not prepare the sixth isomeride (4 : 5), so this particular process of elimination remains incomplete. The sixth isomeride would imply methoxy-groups in artabotrine in positions 1 and 2, unknown in this numerous group of alkaloids. Our repeated attempts to obtain an oxidation product with a single methoxy-group were unsuccessful, and hence we are unable to assign its position in ring D with certainty. It seems, however, to be in position 4, since artabotrine is the methyl ether of suaveoline, in which a hydroxy-group appears to be in that unusual position (see below). A direct spectrographic comparison showed a close similarity between artabotrine and pukateine (OH in position 4; the aliphatic hydroxyl in the former has little affect on the spectrum); there is, however, also a close agreement with data for laureline (OMe in position 3), as recorded by Girardet (J., 1931, 2630).

	Frequencies.					Frequencies.			
	Maxima.		Minima.			Maxima.		Minima.	
Artabotrine	3210	3490	3745	3990	Laureline	3220	3500	3710	3940
Pukateine	3240	3520	3745	3970	Dicentrine	3200	3380	3540	3900

The absorption spectra of dicentrine and laurotetanine, with substituents in positions 2 and 3, were obviously quite different, but the spectrographic evidence does not appear to exclude the possibility of two substituents in positions 3 and 4, or to differentiate between a single substituent in these two positions (pukateine and laureline). The evidence from *X*-ray analysis makes the presence of a substituent in position 2 unlikely (see appendix).

Suaveoline is the name given by Santos and Reyes to a base, $C_{20}H_{23}O_4N$, m. p. 182°, $[\alpha]_D^{30°}$ +202 — 206°, obtained from the " phenolic " fraction of the alkaloids of *Artabotrys suaveolens*. Following their procedure and shaking the ethereal solution of the total alkaloids with N-sodium hydroxide, we obtained about 4 g. of an alkaloidal mixture which consisted almost entirely of artabotrine, for which Santos and Reyes had given the formula $C_{21}H_{25}O_4N$, m. p. 186°, and $[\alpha]_D^{30°}$ +198·7°. This illustrates the acidic properties of artabotrine, referred to above, but they are very feeble; the solid so extracted from ethereal solution did not dissolve appreciably in sodium hydroxide solution. From the mother-liquors of the crude artabotrine, however, there separated, on concentration and keeping, 320 mg. (0·0013% of the bark) of a truly phenolic alkaloid, $C_{19}H_{21}O_4N$, m. p. 232°, $[\alpha]_D^{15°}$ +164°, for which we retain the name suaveoline. It has two active hydrogen atoms (one in the alcoholic, one in the phenolic hydroxyl) and two methoxy-groups: it gives a

deep purple colour with alcoholic ferric chloride (in contradistinction to artabotrine) and is readily soluble in sodium hydroxide solution. It gives the Pellagri reaction, indicating that the *p*-position of a phenolic hydroxyl is unsubstituted (Gadamer, *Arch. Pharm.*, 1911, **249**, 509). Pukateine also gives this reaction and has been synthesised (Barger and Girardet, *Helv. Chim. Acta*, 1931, **14**, 481; Barger and Schlittler, *ibid.*, 1932, **15**, 381). It is 4-hydroxy-5 : 6-methylenedioxyaporphine and was at that time the only alkaloid with a lone substituent in position 4. Substitution in position 3, corresponding to the phenolic group of a tyrosine residue, is biochemically more intelligible, and occurs in laureline among aporphine alkaloids, also in coclaurine and in the bisbenzyltetrahydro*iso*quinolines of the oxyacanthine group. When position 3 is already substituted, the entry of a second hydroxyl in position 4 or 2 creates no surprise, and is indeed very common. Suaveoline seems, however, to be the second example, after pukateine, of an alkaloid containing a lone phenolic hydroxyl in position 4 (or in the less likely position 1, which would also make the Pellagri reaction positive). Since we were able to convert suaveoline into artabotrine, it follows that the latter alkaloid must have a methoxy-group in position 4.



Artabotrinine. After the extraction of the crude ethereal solution of total alkaloids with hydrochloric acid, a small quantity of crystals separated from the acid solution on keeping. They proved to be the very sparingly soluble hydrochloride of a third alkaloid, for which the name artabotrinine is suggested. The free base could not be crystallised, but readily yielded crystalline salts and a *nitroso*-derivative. It is $C_{16}H_{11}(OMe)(O_2CH_2)NH$ and lacks the alcoholic hydroxyl of the other two alkaloids. If, as seems likely, the methylenedioxy-group is in positions 5 : 6, the methoxy-group must be in position 2, for *N*-methylartabotrinine is not identical with either pukateine methyl ether or with laureline (although isomeric with these alkaloids). The small amount available did not permit of further investigation; probably artabotrinine is the methyl ether of anolobine (2-hydroxy-5 : 6-methylenedioxynoraporphine), recently isolated from the bark of *Asimina triloba* (another member of N.O. *Anonaceæ*) by Manske (*Canadian J. Res.*, 1938, **16**, *B*, 76).

Appendix. Crystallography of Artabotrine. By C. J. Brown and E. G. Cox.—We are greatly indebted to these gentlemen for the following account:

Artabotrine crystallises in large tabular orthorhombic crystals (see figure) exhibiting the forms *a*[100], *m*[210] and *r*[201]. ($m : a = 49°\ 46'$, $r : a = 56°\ 27'$). Measurements of *X*-ray rotation photographs gave for the cell dimensions [a] = 23·13, [b] = 9·89 and [c] = 7·51 A. and the density was found by flotation to be 1·29 g./c.c., so there are four molecules of $C_{20}H_{23}O_4N$ in the unit cell (*M*, by *X*-rays, 332. Calc., 341). From the analysis of a series of *X*-ray oscillation photographs the space-group was found to be $P2_12_12_1$, so the possibility of the cell containing two molecules of $C_{40}H_{48}O_8N_2$ is excluded.

The refractive indices (for sodium light) are $\alpha = 1{\cdot}50$ (approx.), $\beta = 1{\cdot}67$ and $\gamma = 1{\cdot}75$. [a] is the acute bisectrix, and *c* (001) the plane of the optic axes. The optic axial angle $2V$ is 70° approx.

From the above results it appears probable that the longest direction of the molecules is approximately parallel to [b] and that the planes of the molecules are more nearly parallel to *a* (100) than to *c* (001). On account of the relatively short length of the [b] axis it seems unlikely that the third methoxy-group is in position 2.

Experimental.

Separation of the Alkaloids.—The ground bark (25 kg.) was percolated with cold 95% alcohol, and the extract evaporated under reduced pressure. We are indebted to the Forestry Service of the Philippine Islands for the collection, and to Dr. J. J. Blackie, of Messrs. Duncan, Flockhart & Co., for the extraction of the bark. The thick tarry extract (4·25 kg.) was ground with sand and saturated aqueous sodium carbonate, and the fine suspension so obtained was extracted with ether. The latter was shaken with N-hydrochloric acid, which overnight deposited 3 g.

(0·012% of the bark) of artabotrinine hydrochloride. The filtrate from this was basified with ammonia and extracted with ether. After another passage through acid, the second ethereal solution was shaken with N-sodium hydroxide and then with N-hydrochloric acid. The latter, on addition of ammonia, yielded 44 g. of crude crystalline artabotrine. From the former solution the supposed phenolic alkaloid was precipitated by carbon dioxide. After filtration and solution in hydrochloric acid, ether removed some colouring matter. After a second passage through acid the ethereal extract was dried and greatly concentrated; 3—4 g. of crystalline artabotrine then separated, making with the main quantity a total of 0·19%. The green ethereal mother-liquor on further concentration deposited after a week 320 mg. (0·0013%) of crystalline suaveoline. Artabotrine forms flat rhombs with bevelled edges from acetone (see appendix above); also stout prisms. After three crystallisations they had m. p. 185—186°. The base is readily soluble in methanol, ethyl alcohol, acetone and benzene, sparingly in ether and ethyl acetate, and very sparingly in ligroin. The reaction with ethereal ferric chloride is mentioned on p. 992; there was no coloration with an alcoholic solution [Found: C, 70·6, 70·8; H, 7·0, 7·0; N, 4·1; OMe, 26·9; NMe, 3·6; active H, 0·308, 0·284; equiv. with hydrochloric acid and methyl-red, 331. Calc. for $C_{16}H_{10}(OH)(OMe)_3NMe$: C, 70·4; H, 6·8; N, 4·1; OMe, 27·3; NMe, 4·4; active H, 0·293%; equiv., 341]. $[\alpha]_D^{15°}$ +194·8° (*c* 1·86, chloroform). The hydrochloride obtained in the determination of the equivalent, after two crystallisations from methanol, formed colourless needles, m. p. 226—227°. Gaebel's test for methylenedioxy-groups was negative; after treatment with hydroxylamine the alkaloid was recovered unchanged; bromine in chloroform, and permanganate in pure acetone, were not decolorised, and no hydrogen was absorbed on shaking with platinum oxide for 6 hours. Artabotrine yielded with an equal weight of phenyl-*iso*cyanate in chloroform a colourless, neutral, viscous oil; 45% of the alkaloid was recovered unchanged.

Acetylartabotrine. After heating with acetic anhydride and sodium acetate, and addition of water, an oil separated which in a few hours crystallised to a mass of fine needles. After recrystallisation from 90% alcohol the hydrated substance melted at 97—99° [Found: C, 63·0; H, 6·7; N, 3·0; $CH_3{\cdot}CO$, 12·1; H_2O, 7·5. $C_{20}H_{22}O_4N(CH_3{\cdot}CO),2H_2O$ requires C, 63·0; H, 6·9; N, 3·3; $CH_3{\cdot}CO$, 10·3; H_2O, 8·6%]; the anhydrous substance had m. p. 118—119°. The *acetyl* compound was soluble in warm dilute hydrochloric acid, but did not readily form a methiodide.

O-*Methylartabotrine.* (a) *By nascent diazomethane.* Artabotrine (0·1 g.) in methyl alcohol (20 c.c.) was mixed at 0° with nitroso-*N*-methylurethane (3 c.c.), 10 drops of 25% methyl-alcoholic potassium hydroxide added, and the solution left overnight in a refrigerator. After a further addition of the reagents and again keeping overnight, the solution was diluted with 20 c.c. of acidified water, and the alcohol removed under reduced pressure. On basification and extraction with ether, a colourless syrup (90 mg.) was obtained, which, unlike artabotrine, was readily soluble in ether. *O*-Methylartabotrine had $[\alpha]_D^{16°}$ +182·2° in chloroform (*c*, 2·9). Since the syrup could not be crystallised, it was refluxed in methanol with methyl iodide. O-*Methylartabotrine methiodide* formed fine needles from methanol, m. p. 254—255° [Found: OMe, 26·1. $C_{18}H_{16}N(OMe)_4I$ requires OMe, 25·0%]. (b) *By methyl sulphate.* Finely powdered artabotrine (0·6 g.), suspended in 2N-sodium hydroxide (15 c.c.), was shaken with methyl sulphate (1 c.c.) for 30 minutes, and again after addition of another c.c. After being heated with 4N-sodium hydroxide on the water-bath, the solution was extracted with chloroform. The extract was dried with sodium sulphate and concentrated; 0·6 g. of a crystalline powder separated, which, recrystallised from methyl alcohol–ether, formed minute needles, m. p. 255—256°, soluble in water [Found: C, 57·4; H, 6·2; N, 2·9; S, 6·8; OMe, 32·2. $C_{18}H_{16}O_3NS(OMe)_5$ requires C, 57·4; H, 6·4; N, 2·9; S, 6·6; OMe, 32·2%]. On addition of potassium iodide to an aqueous solution of the above O-*methylartabotrine methosulphate*, the methiodide crystallised, identical with that prepared by means of diazomethane (Found: I, 24·0. Calc. for $C_{22}H_{28}O_4NI$: I, 25·5%).

Action of ethyl chloroformate. Artabotrine (0·5 g.) in chloroform (15 c.c.), to which a little ice had been added, was shaken with ethyl chloroformate (0·32 g.) and solid potassium hydroxide (0·28 g.) for 1 hour. After addition of more ice and the same amounts of the last two reagents and further shaking, the chloroform layer was separated, washed with acid and dried; the acid washings gave no Mayer reaction. The chloroform yielded a syrup, which became solid on rubbing with ether and crystallised from this solvent in faintly orange, rhomb-shaped plates, m. p. 109—110° [Found: C, 66·9; H, 6·6. $C_{20}H_{22}O_4N(CO_2Et)$ requires C, 66·8; H, 6·5%]. The *substance* was optically inactive (in chloroform, *c* 2·9).

Hofmann degradation. Artabotrine methiodide, prepared in quantitative yield by refluxing the alkaloid in methanol with methyl iodide, crystallised from methanol in needles, m. p. 224—

225° (Found: C, 52·2; H, 5·5; N, 2·7; I, 27·6. $C_{20}H_{23}O_4N,CH_3I$ requires C, 52·2; H, 5·4; N, 2·9; I, 26·3%). The methiodide (2·4 g.) was refluxed for 6 hours with 20% alcoholic potassium hydroxide (120 c.c.). After extraction with ether, the dried solution, which had a bluish-violet fluorescence, left 1·45 g. (80%) of crystalline *artabotrine methine*; this formed lustrous rhomb-shaped plates, m. p. 122—123°, from 90% alcohol (Found: C, 70·7; H, 6·9; N, 4·1. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0; N, 4·0%). $[\alpha]_D^{18°}$ −183° in absolute alcohol (*c*, 1·65). The methine decolorised bromine in chloroform and permanganate in acetone; it was completely destroyed when ozonised according to Bruchhausen and Gericke (*Arch. Pharm.*, 1931, **269**, 115) and when oxidised with nitric acid according to Warnat (*Ber.*, 1925, **58**, 2768). *Dihydroartabotrine methine* was obtained by catalytic reduction in absolute alcohol with platinum oxide; 1 mol. of hydrogen was absorbed in 5 minutes; 140 mg. of the methine yielded 107 mg. of a syrup, which crystallised, on addition of water to its solution in 2·5 c.c. of methanol and keeping overnight, in minute truncated prisms, m. p. 80—81° (Found: C, 70·5; H, 7·5. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6%). It was stable to bromine in chloroform.

The methine methochloride (from the methine methiodide and silver chloride) gave no definite product other than trimethylamine when it was treated in aqueous solution according to Hofmann or Emde. Better results were obtained as follows: The methine (1·45 g.) in methanol (20 c.c.) was refluxed with methyl iodide (2·5 c.c.) for 1½ hours and left overnight. The excess of methyl iodide was then boiled off, methyl alcohol (90 c.c.) and solid potassium hydroxide (15 g.) added, and the solution refluxed for 6 hours. Trimethylamine was identified as the picrate. Water (350 c.c.) containing a slight excess of sulphuric acid was added, and the suspension of precipitated potassium sulphate and the *vinyl* compound extracted with ether; the extract had a deep orange colour and a strong blue-violet fluorescence and after washing and drying left 0·85 g. (75%) of the brick-red vinyl compound, m. p. 108—109°. Recrystallised from ligroin (b. p. 100—120°), this formed clusters of stout, yellow-orange prisms, m. p. 115—116° [Found: C, 72·9; H, 6·0; OMe, 29·7. $C_{16}H_9O(OMe)_3$ requires C, 73·5; H, 5·8; OMe, 30·0%], very soluble in chloroform, moderately in acetone and ether, slightly in ethyl alcohol and ligroin. It dissolved very slowly in 25% aqueous potassium hydroxide to a yellow-green solution, from which it was reprecipitated by acid. Its solution in concentrated sulphuric acid was blue-green, changing to deep blue on warming; in cold concentrated nitric acid it dissolved with a deep orange-red colour. The deep red solution in glacial acetic acid rapidly absorbed 1 mol. of hydrogen when shaken with platinum oxide in hydrogen and became practically colourless, but at once turned deep red in contact with air. After this treatment the product could no longer be crystallised. The oxidation of the vinyl compound by permanganate in acetone also failed to yield a crystalline product.

Oxidation with Beckmann's mixture. To artabotrine (1 g.) in 25% sulphuric acid (4 c.c.) at 30—35°, a solution of potassium dichromate (0·32 g.; 1·1 atoms of O) in 25% sulphuric acid (2·5 c.c.) was added during 1 hour. After basification, ether extracted a deep orange-red substance, the colour of which was rapidly discharged by sulphur dioxide. The dried ethereal solution yielded a small quantity of ruby-red prisms, m. p. 172—174°; a mixture with an equal quantity of artabotrine (m. p. 185—186°) had m. p. 176—177°. In a high vacuum, colourless crystals of artabotrine sublimed and the red mixture decomposed. The original red crystals gave the Laubenheimer reaction for phenanthraquinone, but the dye was basic and had to be liberated with sodium hydroxide before extraction with ether or chloroform. Control experiments with pukateine and laurotetanine gave no trace of a coloured oxidation product.

Oxidation with potassium permanganate. Artabotrine (2 g.) was dissolved in very dilute hydrochloric acid, and sodium carbonate added until a slight turbidity occurred. A 3% aqueous permanganate solution was added, 10 c.c. (0·55 O) at a time. After 14 atoms of oxygen had been taken up at room temperature, the oxidation was completed on the water-bath; 23 atoms were taken up in all. The filtered and concentrated solution was acidified and extracted with ether in a continuous apparatus for 48 hours. The residue from the ether was dissolved in 100 c.c. of boiling water, freed from oxalic acid by calcium acetate, and again acidified and continuously extracted. The ether left 43 mg. of a crystalline residue, which formed slightly pink, blade-like needles from absolute alcohol, m. p. 203—204°. The colour could not be completely removed by recrystallisation, but the *acid* sublimed without decomposition at 200—225°/15 mm. in pale yellow needles [Found: C, 55·1; H, 3·6; OMe, 24·3; equiv., 239; equiv. after boiling for 10 minutes with excess of alkali and back-titration, 119·5. $C_8H_3O_2(OMe)_2{\cdot}CO_2H$ requires C, 55·4; H, 4·2; OMe, 25·2%; equiv., 238 and 119]. The substance gave a strong yellow-green fluorescence when heated with resorcinol and sulphuric acid.

2 : 4- *and* 2 : 5-*Dimethoxyphthalide-α-carboxylic Acids.*—2 : 4- and 2 : 5-Dimethoxybenzoic

acids were condensed with chloral and concentrated sulphuric acid in the manner described for the 3 : 4-dimethoxy-acid by Meldrum and Parikh (*Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 437; compare Fritsche, *Annalen*, 1897, **296**, 344; 1898, **301**, 352) and the products were hydrolysed. Both acids were obtained in poor yield. The 2 : 4-acid melted at 149—150°, the 2 : 5-acid at 186—187°, both with decomposition. The m. p.'s of both acids and of 3 : 4-dimethoxyphthalide-α-carboxylic acid (m. p. 206—207°) were all greatly depressed by the oxidation product from artabotrine; none of the three synthetic acids gave the fluorescein reaction.

Suaveoline.—This, after two recrystallisations from methanol, formed bundles of needles and prisms, m. p. 232° [Found : C, 69·8, 69·8; H, 6·5, 6·5; N, 4·3, 4·3; OMe, 17·3; NMe, 3·9; active H, 0·59. Calc. for $C_{16}H_{10}(OH)_2(OMe)_2NMe$: C, 69·7; H, 6·4; N, 4·3; OMe, 18·9; NMe, 4·6; active H, 0·61%]. $[\alpha]_D^{15°}$ +164° in chloroform (*c*, 1·22). Suaveoline is very soluble in chloroform, moderately in methanol, and sparingly in acetone, ether and benzene; it dissolves readily in 2N-sodium hydroxide and gives in alcoholic solution a purple coloration with ferric chloride; it gives the Pellagri test.

Suaveoline (30 mg.), dissolved in methanol (25 c.c.), was methylated with nascent diazomethane, as described for artabotrine, and yielded a syrup (27 mg.), which was converted into a methiodide, m. p. 245—246° [Found : OMe, 25·7. Calc. for $C_{18}H_{16}N(OMe)_4I$: OMe, 25·0%]. A mixture in equal proportions with *O*-methylartabotrine methiodide (m. p. 253°) melted at 248—249°.

Artabotrinine.—The free base liberated from the hydrochloride (see p. 994, separation of alkaloids) could not be crystallised. Its hydrochloride dissolved in 200 parts of water at 50—60°, from which it crystallised on addition of a soluble chloride; *artabotrinine hydrochloride* formed slender needles, m. p. 273—274° [Found : C, 65·2, 65·1; H, 5·4, 5·5; N, 4·3; Cl, 10·7; OMe, 9·6; active H, 0·597. $C_{16}H_{11}(OMe)(CH_2O_2)NH,HCl$ requires C, 65·2; H, 5·4; N, 4·2; Cl, 10·7; OMe, 9·4; active H, 0·603%]. The free base had $[\alpha]_D^{18°}$ −18·9° in chloroform (*c*, 2·69), the hydrochloride $[\alpha]_D^{18°}$ −41·8° ± 4·2° in alcohol (*c*, 0·24). The method of Herzig and Meyer revealed no *N*-methyl group, but the Gaebel test for a methylenedioxy-group was positive. *Nitrosoartabotrinine* formed tan-coloured, hexagonal plates, m. p. 203—204°, from alcohol (Found : N, 8·2. $C_{18}H_{16}O_4N_2$ requires N, 8·6%). N-*Methylartabotrinine* was formed by refluxing the free base (0·6 g.; 1·0 mol.) for 2 hours with formic acid (0·48 g. of a 25% solution; 1·2 mols.) and formaldehyde (0·38 g. of a 40% solution; 2·4 mols.) in 10 c.c. of water. An ethereal extract of the product left, on evaporation, a semicrystalline mixture of the secondary and the tertiary base, which was dissolved in acetic anhydride; next day, when the excess of acetic anhydride was decomposed with N-hydrochloric acid, 30 mg. of an oily *N*-acetyl derivative and 0·28 g. of a base were obtained; the latter formed needles, m. p. 132—133°, from alcohol (Found : C, 74·1; H, 6·0; N, 4·7. $C_{19}H_{19}O_3N$ requires C, 73·8; H, 6·2; N, 4·5%). $[\alpha]_D^{16°}$ −53·8° in absolute alcohol (*c*, 0·424).

A mixture of *N*-methylartabotrinine and the isomeride *O*-methylpukateine (m. p. 137°) melted at 98—99°. *N*-Methylartabotrinine yielded a methiodide, m. p. 223—224°.

Replacement of the methylenedioxy-group by two methoxy-groups. A solution of artabotrinine hydrochloride (0·5 g.) and phloroglucinol (0·7 g.) in 40% sulphuric acid (11 c.c.) was boiled for 5 minutes and then kept at 100° for 16 hours. After dilution with boiling water (2 vols.) the bulky phloroglucinol condensation product was filtered off and washed with hot water. The orange-coloured filtrate was extracted with ether continuously for 16 hours, basified with concentrated aqueous ammonia, and rapidly extracted with ether. The dried ethereal solution was evaporated over paraffin wax in an atmosphere of carbon dioxide. The pale tan-coloured dihydroxy-compound (50 mg.) was amorphous; it gave a deep blue-green coloration with ferric chloride, and only a slight precipitate with Mayer's reagent; it readily reduced Fehling's solution. It reacted violently with nascent diazomethane at 0°; half the material was lost when the mixture exploded. The methylated base gave a heavy precipitate with Mayer's reagent, but the small amount could not be purified [Found : OMe, 22·5. $C_{16}H_{18}N(OMe)_3$ requires OMe, 29·9%].

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