409. *Colombo Root Bitter Principles. Part II.* The Constitution of Columbin.*

By D. H. R. Barton and Dov Elad.

Dehydrogenation of various columbin derivatives has afforded 1 : 2 : 5-trimethylnaphthalene, 1-methyl-2-naphthoic acid, and 1 : 5-dimethyl-2-naphthoic acid. The number of *C*-methyl groups in columbin has been determined. Based on these and other observations as well as on extensive earlier work, complete constitutions have been deduced for columbin (IX) and all of its derivatives.

In Part I of this series * the functional groups of columbin, $C_{20}H_{22}O_6$, the major bitter principle of Colombo root, were characterised as follows: (i) a $\beta\gamma$-unsaturated α-hydroxy-δ-lactone system (A) with the ethylenic linkage present as (–CH=CH–) in a six-membered ring (I), and (ii) a second γ- or δ-lactone system (B) attached to a β-substituted furan ring as in (II). We now discuss the incorporation of these functional groups within the framework of the columbin molecule.

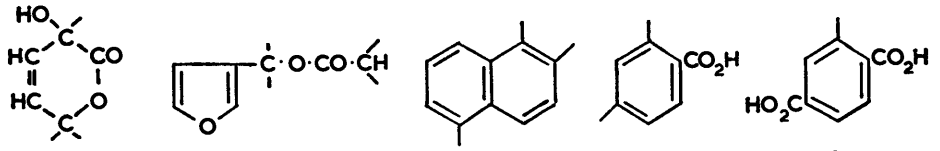
The earlier work by Wessely and by Feist and their respective collaborators has already been cited in full in Part I. The degradation of columbin under vigorous conditions was studied by Feist and his co-workers [1-3] with results which can be summarised as follows. Distillation of columbin or of *iso*columbin with zinc dust gave *o*-cresol and 1 : 2 : 5-trimethylnaphthalene (III). Fusion of columbin with potassium hydroxide afforded 2 : 4-dimethylbenzoic acid (IV) and 2-methylterephthalic acid (V). Oxidation of columbin with manganese dioxide and sulphuric acid furnished benzene-1 : 2 : 3-tri- and -1 : 2 : 3 : 4-tetra-carboxylic acid. Dehydrogenation of decarboxycolumbin with selenium was said [1] to give a lactone, $C_{15}H_{16}O_2$, m. p. 205°. Columbin and decarboxycolumbin furnished one mol. of acetic acid on Kühn–Roth oxidation.

The formation of 1 : 2 : 5-trimethylnaphthalene (III) on zinc dust distillation suggests an appropriately substituted bicyclic nucleus, the degree of substitution of which is further supported by the isolation of the *two* polycarboxylic acids on oxidation. In confirmation reduction of decarboxyoctahydrocolumbinic acid [3-5] with lithium aluminium hydride and dehydrogenation of the product with selenium gave the hydrocarbon (III) in good yield. In order to locate lactone system (A)—the lactone group which is lost as carbon dioxide on going to decarboxycolumbin—it was planned to reduce octahydrocolumbinic acid with lithium aluminium hydride and dehydrogenate the product This it was expected would afford a tetramethylnaphthalene the orientation of which would determine the site of attachment of lactone (A). However the product was again only the trimethylnaphthalene (III). Clearly one of the methyl groups of this hydrocarbon (III), when it is formed from decarboxycolumbin, must result from the migration of a methyl group from a quaternary position. Several experiments confirmed this conclusion. Thus reaction of methyl

* Part I, preceding paper.

[1] Feist, Kuntz, and Brachvogel, *Annalen*, 1935, **519**, 124.
[2] Feist and Brachvogel, *ibid.*, 1936, **522**, 185.
[3] Feist and Völksen, *ibid.*, 1938, **534**, 41.
[4] Feist, Rintelen, and Kuntz, *ibid.*, 1935, **517**, 119.
[5] Wessely, Münster, and Schönol, *Monatsh.*, 1936, **68**, 313.

decarboxyoctahydrocolumbinate with methylmagnesium iodide gave, after alkaline hydrolysis, an acidic product in which >CO had been converted into >CMe·OH. Since decarboxycolumbin and decarboxyoctahydrocolumbinic acid give a very strong Zimmermann test,[6] it was easy to check that the ketone group had reacted completely. Reduction of the alcohol with lithium aluminium hydride and dehydrogenation with selenium again afforded the trimethylnaphthalene (III) and not a tetramethylnaphthalene. When decarboxyoctahydrocolumbinic acid was reduced by the Wolff–Kishner method and the product dehydrogenated with selenium at 310°, 1-methyl-2-naphthoic acid [7] (VI) resulted. Since rearrangements in selenium dehydrogenations are minimised if carbonyl or hydroxyl



(I) (II) (III) (IV) (V)

groups are removed,[8] the formation of a monomethyl, not a dimethyl, compound is in agreement with views outlined above. Finally perchloric acid-catalysed hydrogenation of decarboxy-octahydro- to -decahydro-columbinic acid (>CO ⟶ >CH·OH) and dehydrogenation with selenium at 310° gave a fair yield of 1 : 5-dimethyl-2-naphthoic acid (VII), the synthesis of which was effected along standard lines.[7] This compound is also produced, although in inferior yield, by dehydrogenation of decarboxyoctahydrocolumbinic acid itself and is the so-called " lactone, $C_{15}H_{16}O_2$ " referred to above. It is fully confirmed, therefore, that the 5-methyl group in the hydrocarbon (III) and the acid (VII) must result from rearrangement during dehydrogenation. This 5-methyl group must also mark the position of attachment of the lactone (A) carbonyl group. It is implied, therefore, that there must be a methyl group at the adjacent quaternary centre. This is in agreement with the isolation of *o*-cresol in earlier degradations, because the hydroxyl group of this must surely represent the ketone group of decarboxycolumbin. The formation of the acids (VI) and (VII) is also important in that it proves the position of lactone (B) relative to the bicyclic nucleus.

We now consider evidence as to the number of *C*-methyl groups in columbin. Kühn–Roth oxidation of columbin gave 5·0% of *C*-Me, of *iso*columbin 4·0 and 4·3% of *C*-Me, and of dihydrocolumbin 4·65 and 5·0% of *C*-Me. These figures are in agreement with earlier work referred to above, since the calculated figure for one *C*-Me group is 4·1%. They show clearly that at least two *C*-Me groups must be present. The number of *C*-Me groups was also determined by quantitative infrared measurements in carbon tetrachloride solution on the 1380-cm.$^{-1}$ *C*-Me band of decarboxyoctahydrocolumbinic acid, with stearic acid as reference compound. The results showed that two *C*-Me groups were present.

With these and earlier facts (see Part I) in mind, two possible consitutions (VIII) and (IX) can be considered for columbin. In our opinion constitution (IX) is the correct one for several reasons. First, it explains the formation of *o*-cresol on degradation, whereas the alternative (VIII) should afford 2 : 3-dimethylphenol. Secondly, it accounts for the formation of 2 : 4-dimethylbenzoic and 2-methylterephthalic acid better than does the alternative (VIII), which should afford either 2 : 3 : 4-trimethyl- or 3 : 4-dimethyl-benzoic acid.

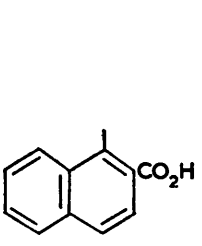
Based on constitution (IX), all other derivatives can be logically formulated as follows : decarboxycolumbin (X), decarboxycolumbin acetate (XI; R = Ac), decarboxymethyl*iso*columbin (XI; R = Me), decarboxyoctahydrocolumbinic acid (XII), octahydrocolumbinic

[6] W. Zimmermann, *Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47; Barton and de Mayo, *J.*, 1954, 887; Broadbent and Klyne, *Biochem. J.*, 1954, **56**, xxx.

[7] Von Auwers and Moeller, *J. prakt. Chem.*, 1925, **109**, 146; see also Mayer and Schnecko, *Ber.*, 1923, **56**, 1410; Mousseron and Nguyen-Phuoc-Du, *Compt. rend.*, 1944, **218**, 281.

[8] See, for example Barton, Fawcett, and Thomas, *J.*, 1951, 3147; Voser, Mijovic, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1585; Barton and Overton, *J.*, 1955, 2639.

acid (XIII), dihydrocolumbin (XIV), the derived trisnor-acid (XV; R = CO_2H), the derived keto-acid (XV; R = $CO{\cdot}CO_2H$), and columbindiol and its diacetate (XVI; R = H or Ac respectively).



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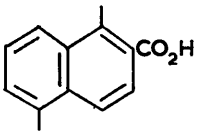

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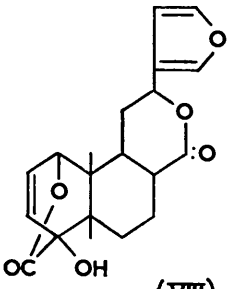

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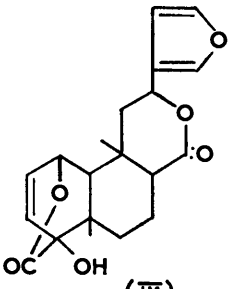
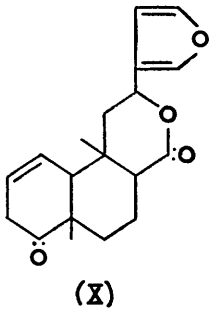


(IX)

We conclude with a description of several transformations which support the proposed constitution (IX). Quantitative bromination of the acid (XII) led to an uptake of 1·64 mols. of bromine in agreement with only two replaceable α-hydrogen atoms. The bromination product was not crystalline, but on brief treatment with collidine it afforded an



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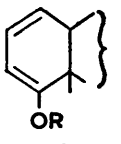

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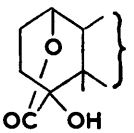

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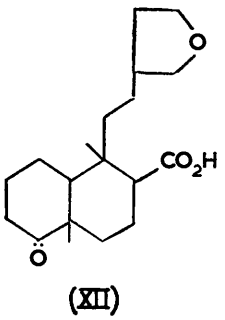

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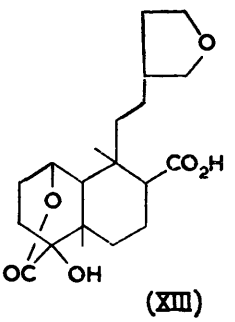

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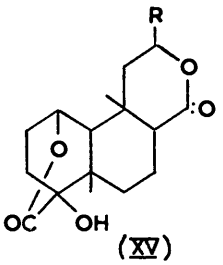

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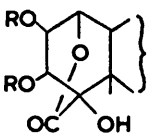

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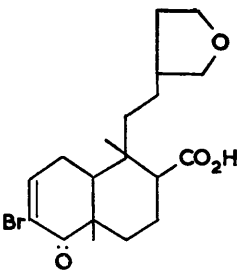

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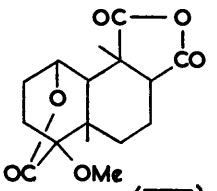


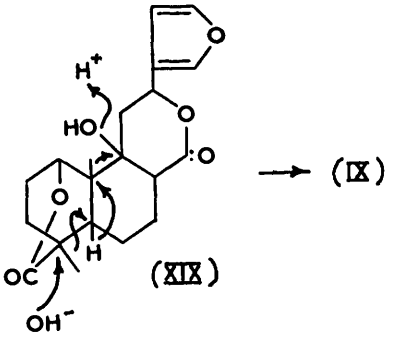
(XVIII)

αβ-unsaturated α-bromo-ketone (XVII), whose ultraviolet absorption spectrum was in agreement with the chromophore postulated.[9] Conversion of dihydrocolumbin into dihydromethyl*iso*columbin and oxidation with potassium permanganate gave an oily dicarboxylic acid which on sublimation furnished a crystalline anhydride (XVIII), whose infrared spectrum showed bands (in $CHCl_3$) at 1850 and 1777 cm.$^{-1}$ indicative [10] of a substituted succinic anhydride. In agreement, succinic anhydride itself showed bands (in $CHCl_3$) at 1860 and 1780 cm.$^{-1}$.

[9] Nussbaum, Mancera, Daniels, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3263.
[10] Stork and Breslow, *ibid.*, 1953, **75**, 3291; Elming, Vogel, Jeger, and Prelog, *Helv. Chim. Acta*, 1952, **35**, 2541.

It is our intention to report in due course on the constitutions of chasmanthin and palmarin, and the stereochemistry of the Colombo root bitter principles.

From the biogenetic point of view, constitution (IX) can be regarded as derived from a normal diterpenoid structure such as (XIX), by the appropriate methyl migrations. Such a scheme might have stereochemical implications upon which we also hope to report in due course.



Experimental

For general experimental directions see ref. 11. Infrared spectra were kindly determined by Dr. G. Eglinton and his associates. Ultraviolet absorption spectra were taken in ethanol with the Unicam S.P. 500 Spectrophotometer. $[\alpha]_D$ are recorded for pyridine solutions unless stated otherwise. Microanalyses were carried out by Mr. J. M. L. Cameron and his colleagues.

The following general procedure for dehydrogenations was adopted. The compound, mixed with twice its weight of selenium, was heated under nitrogen at the temperature specified overnight. The containing flask and its contents were ground in a mortar and thoroughly extracted with ether (Soxhlet; 3 hr.). The ethereal solution was washed with aqueous potassium hydroxide (5%), and the aqueous layer separated. Acidification and re-extraction into ether gave the acid product (if any). The neutral fraction, after removal of the ether *in vacuo*, was chromatographed over alumina in light petroleum (b. p. 60—80°), elution being with the same solvent. The fractions were converted into picrates in the usual way.

Synthesis of 1 : 5-*Dimethyl-2-naphthoic Acid.*—Ethyl acetoacetate (22·5 g.) was added to a stirred solution of sodium ethoxide [prepared by dissolving sodium (3·9 g.) in absolute ethanol (60 ml.)] on a steam-bath. After 5 min. 2-*o*-tolylethyl bromide [12] (26·5 g.) was added dropwise during 15 min. and the solution heated under reflux with stirring for 7 hr. (precipitation of sodium bromide). The mixture was diluted with 2N-hydrochloric acid and extracted with ether. The ethereal layer was shaken vigorously with potassium hydroxide (50 g.) in water (50 ml.).[13] The resulting precipitate was filtered off and washed with ether. The ethereal filtrate was re-extracted in the same way. The precipitate and combined alkaline solutions were acidified with cold dilute hydrochloric acid and at once extracted into ether. The dried (Na_2SO_4) ethereal layer gave an oil (12 g.), b. p. 135—137°/0·5 mm., on distillation. This oil (7·0 g.) in concentrated sulphuric acid (50 ml.) at 0° was left for 1 hr., then poured on ice, and the precipitate was filtered off (5·3 g.; crude). Crystallisation from hexane gave 3 : 4-*dihydro*-1 : 5-*dimethyl-2-naphthoic acid*, m. p. 160—162° (Found : C, 77·25; H, 6·7. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%). This acid (1·6 g.), palladised charcoal (30%; 2·0 g.), and *p*-cymene (40 ml.) were heated under reflux for 3 hr. Removal of the catalyst and extraction into aqueous sodium hydroxide (5%) gave, on acidification, 1 : 5-*dimethyl-2-naphthoic acid* (1·0 g.). Crystallised from *n*-hexane containing a little benzene and sublimed at 130—140°/0·1 mm., this melted at 205—207° (Found : C, 78·25; H, 6·3. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·05%). The acid was converted into the *methyl ester* by ethereal diazomethane. Recrystallised from aqueous methanol this had m. p. 77—78°, $\lambda_{max.}$ 240, 288, and 334 mμ (ε 55,300, 7600, and 1400 respectively), $\lambda_{min.}$ 260 and 315 mμ (ε 3400 and 1200 respectively) (Found : C, 78·45; H, 6·15. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

In an alternative dehydrogenation procedure 3 : 4-dihydro-1 : 5-dimethyl-2-naphthoic acid (500 mg.), *N*-bromosuccinimide (500 mg.), and carbon tetrachloride (20 ml.) were heated under reflux for 30 min. Chloroform was added and the succinimide removed by filtration. The solvents were removed under reduced pressure and the residue treated with ethanolic potassium hydroxide (10%; 30 ml.) on the steam-bath for 1 hr. The acidic product gave, after crystallisation from *n*-hexane, 1 : 5-dimethyl-2-naphthoic acid (200 mg.) (m. p. and mixed m. p.).

Reduction and Dehydrogenation of Decarboxyoctahydrocolumbinic Acid (XII).—The acid (1·0 g.) in dry ether (20 ml.) was reduced with lithium aluminium hydride (1·0 g.) in the same solvent (50 ml.) under reflux. The oily neutral product (850 mg.) was dehydrogenated at

[11] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.

[12] Shoesmith and Connor, *J.*, 1927, 1768, and references there cited. Ethylene oxide was used instead of ethylene chlorohydrin : see Huston *et al.*, *J. Org. Chem.*, 1941, **6**, 123; 1947, **12**, 90.

[13] Cf. Michael, *Ber.*, 1905, **38**, 2093.

350—360°. Chromatography over alumina gave 1 : 2 : 5-trimethylnaphthalene, isolated as the picrate (35%) and identified by m. p. and mixed m. p. with an authentic specimen and by conversion into the styphnate (m. p. and mixed m. p.) and 1 : 3 : 5-trinitrobenzene adduct (m. p. and mixed m. p.).

Reduction and Dehydrogenation of Octahydrocolumbinic Acid (XIII).—Octahydrocolumbinic acid was reduced with its own weight of lithium aluminium hydride in dry ether in the usual way. The neutral product (1·2 g.) was dehydrogenated at 350°. Chromatography over alumina gave 1 : 2 : 5-trimethylnaphthalene, isolated as the picrate (m. p. and mixed m. p.).

Dehydrogenation of the Wolff–Kishner Reduction Product of Decarboxyoctahydrocolumbinic Acid (XII).—The acid (1·6 g.) was reduced by the modified Huang-Minlon procedure of Barton, Ives, and Thomas.[14] The oily acidic product (1·3 g.) was dehydrogenated at 310° and the material produced was separated into neutral and acidic fractions. Chromatography of the latter in benzene solution over silica gel (30 g.) and elution with 1 : 4 ether–benzene gave 1-methyl-2-naphthoic acid (60 mg.), m. p. [from light petroleum (b. p. 60—80°)] 175—177°, undepressed in m. p. on admixture with an authentic specimen, $\lambda_{max.}$ 231, 283, and 328 mμ (ε 49,200, 6000, and 980 respectively), $\lambda_{min.}$ 260 and 310 (ε 3500 and 850 respectively). The authentic specimen [7] had m. p. 177—178°, $\lambda_{max.}$ 231, 283, and 328 mμ (ε 49,800, 6400, and 990 respectively), $\lambda_{min.}$ 260 and 310 mμ (ε 3500 and 750 respectively).

Reduction and Dehydrogenation of the Product from Methyl Decarboxyoctahydrocolumbate and Methylmagnesium Iodide.—Decarboxyoctahydrocolumbinic acid (XII) (2·0 g.) was esterified with diazomethane, then treated with methylmagnesium iodide [from magnesium (250 mg.) and methyl iodide (1·0 g.) in dry ether (100 ml.)] at room temperature with stirring. The mixture was decomposed with a cold concentrated solution of ammonium chloride, and the organic product (ether-extracted) hydrolysed with potassium hydroxide (5 g.; in 50 ml. of 1 : 4 water–ethanol). Most of the alcohol was removed *in vacuo* and neutral material extracted with ether. Acidification gave the acid fraction which showed *no* colour in the Zimmermann test. This was dissolved in dry ether (50 ml.) and reduced with lithium aluminium hydride (2·0 g.) in the same solvent (150 ml.) under reflux for 1 hr. The neutral product (1·2 g.) was dehydrogenated at 350—360°. It gave 1 : 2 : 5-trimethylnaphthalene, characterised as the picrate (370 mg.) (m. p. and mixed m. p.).

Dehydrogenation of Decarboxydecahydrocolumbinic Acid.—Decarboxyoctahydrocolumbin (1·0 g.) was hydrogenated over platinum (200 mg.) in ethyl acetate (100 ml.) containing 80% perchloric acid (0·5 ml.). One mol. of hydrogen was rapidly absorbed and the product, decarboxydecahydrocolumbinic acid, showed no Zimmermann colour. This acid (4·0 g.) was dehydrogenated at 310°. The resulting acid fraction (1·2 g.) was chromatographed in benzene over silica gel (40 g.). Elution with 1 : 4 ether–benzene gave 1 : 5-dimethyl-2-naphthoic acid, identified by m. p. and mixed m. p. (Found : C, 78·2, 78·4; H, 6·3, 6·2. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·05%). The identity was confirmed by preparation of the methyl ester (m. p. and mixed m. p.) (Found : C, 78·3; H, 6·45. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·6%), $\lambda_{max.}$ 240, 288, and 334 mμ (ε 51,100, 6800, and 1400 respectively), $\lambda_{min.}$ 260 and 315 mμ (ε 3200 and 1200 respectively).

Bromination of Decarboxyoctahydrocolumbinic Acid (XII).—The acid (69·5 mg.), bromine (1 ml. of a solution containing 19·3 g. of bromine in 100 ml. of " AnalaR " acetic acid), and hydrobromic–acetic acid mixture (0·1 ml.) were made up to 10 ml. with " AnalaR " acetic acid and left at 20°. Titration of aliquot parts showed an uptake of 1·64 mols. of bromine after 14 hr., unchanged after times up to 48 hr.

Decarboxyoctahydrocolumbinic acid (1·0 g.), bromine (20 ml. of a solution as above), and hydrobromic–acetic acid mixture (1·0 ml.) were made up to 100 ml. with " AnalaR " acetic acid and left at room temperature overnight. The non-crystalline product was refluxed with collidine (25 ml.) for 30 min. Chromatography in benzene over silica gel (30 g.) gave, on elution with 2 : 3 ether–benzene, *monobromo-decarboxy-dehydro-octahydrocolumbinic acid* (XVII), m. p. (from benzene) 234—235°, $[\alpha]_D$ −20° (*c* 0·35) $\lambda_{max.}$ 257 mμ (ε 7250) (Found : C, 57·6; H, 6·5. $C_{19}H_{27}O_4Br$ requires C, 57·15; H, 6·8%).

Dihydromethylisocolumbin (with Dr. K. H. Overton and Mr. A. Wylie).—(*a*) Dihydrocolumbin (XIV) (8·5 g.), ethanol (85 ml.), and aqueous sodium hydroxide (12% w/v; 40 ml.) were heated on a steam-bath until all was dissolved. Dimethyl sulphate (6 × 22 ml.) and aqueous sodium hydroxide (12% w/v; 6 × 85 ml.) were added alternately, the temperature being kept at 60—70°. Crystallisation of the product from ethanol gave *dihydromethylisocolumbin*, m. p. 236—238°, $[\alpha]_D$ +63° (*c* 1·36 in $CHCl_3$), +65° (*c* 1·14) (Found : C, 67·2; H, 6·85; OMe, 8·3. $C_{21}H_{26}O_6$ requires C, 67·35; H, 7·0; 1 OMe, 8·2%).

[14] Barton, Ives, and Thomas, *J.*, 1955, 2056.

(*b*) Methyl*iso*columbin was hydrogenated in the usual way over palladised calcium carbonate in 19 : 1 ethyl acetate–acetone. The product was identical (m. p. and mixed m. p.) with that described above.

*Oxidation of Dihydromethyl*iso*columbin with Potassium Permanganate.*—Dihydromethyl*iso*columbin (500 mg.) was oxidised with potassium permanganate according to Feist and Brachvogel's [2] procedure for methylchasmanthin. The oily acidic product was sublimed at 250—260°/0·2 mm., to furnish an oil which solidified when rubbed with *n*-hexane–acetone. The solid (90 mg.) was resublimed at 200°/0·2 mm., to give, on crystallisation from *n*-hexane containing a little acetone, the *anhydride* (XVIII), m. p. 212—214°, $[\alpha]_D$ +64° (*c*, 0·53) (Found : C, 62·15; H, 6·15; OMe, 9·85. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·55; OMe, 10·05%).

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