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CONSTITUTION AND SYNTHESIS OF ENDOCROCIN

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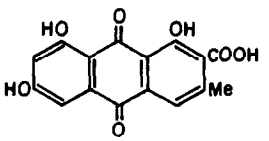
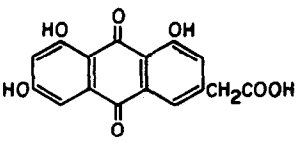
AMONG the naturally occurring pigments derived from anthraquinone endocrocin is of special interest as a likely intermediate in the biogenesis of emodin and other hydroxy-2-methylanthraquinones.[1] The structure (I) proposed for endocrocin by Asahina and Fuzikawa[2] was supported by adequate degradative evidence, which however did not exclude the possibility of the alternative structure, 1,6,8-trihydroxyanthraquinonyl-3-acetic acid (II). The infra-red spectrum of endocrocin shows three bands in the carbonyl region at 1615, 1666 and 1718 cm^{-1}. The 1615 and 1666 cm^{-1} bands can obviously be assigned to a chelated carbonyl and an unchelated carbonyl group in anthraquinone, but the 1718 cm^{-1} band appears to be at too high a frequency for an aromatic carboxylic acid.



I



II

Table 1 records the carbonyl stretching frequencies of a number of anthraquinone carboxylic acids, including 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (III), which has the same orientation of substituents as

[1] R. Robinson, The Structural Relations of Natural Products p. 10. Clarendon Press, Oxford (1955).

[2] Y. Asahina and F. Fuzikawa, Ber. Dtsch. Chem. Ges. 68, 1558 (1935).

TABLE 1

Infra-red Spectra (1600-1750 cm^{-1} region) of
Anthraquinone Carboxylic Acids in Paraffin mull

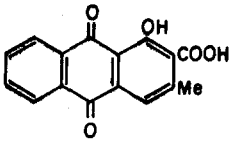
Substitution in anthraquinone	C=O stretching vibrations
1-COOH	1668
2-COOH	1685
1,3-$(OH)_2$-2-COOH (munjistin)	1669; 1620
1,8-$(OH)_2$-3-COOH (rhein)	1692; 1634
1,6-$(OH)_2$-2-COOH	1685; 1650
1,6,8-$(OH)_3$-3-COOH (emodic acid)	1704; 1616
1-OH-3-Me-2-COOH	1670; 1633
2-CH_2COOH	1708; 1680
1-OH-2-CH_2COOH	1729; 1668; 1639
1,6,8-$(OH)_3$-3-CH_2COOH	1721; 1670; 1616
Endocrocin	1718; 1666; 1615

structure (I) for endocrocin in the ring carrying the carboxyl group, and which was synthesized by two methods for examining its infra-red spectrum and for establishing feasible routes for the synthesis of (I). The acid (III) absorbs at 1633 cm^{-1} (chelated carbonyl of the anthraquinone nucleus) and at 1670 cm^{-1} (overlap of the carbonyl of the carboxyl group and the unchelated carbonyl of anthraquinone). 1-Hydroxyanthraquinone-2-acetic acid[3] absorbs at 1639, 1668 and 1729 cm^{-1}, the last band being assignable to the carbonyl of the aliphatic carboxyl group. Structure (II) for endocrocin cannot therefore be ruled out completely, although further support for I was obtained by Shibata[4], while our work was in progress, by

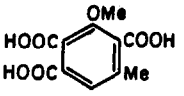
[3] Ch. Marschalk, F. Koenig and N. Ourousoff, Bull. Soc. Chim. Fr. 1545 (1936).

[4] Professor S. Shibata, private communication.

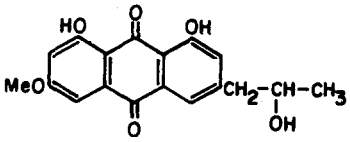
a direct comparison and proof of identity of isocochenillic acid methyl ether, a degradation product of endocrocin trimethyl ether, with the acid (IV) synthesized by Mühlemann[5].



III



IV



V

It was therefore considered desirable to synthesize both the acids (I) and (II). Emodic acid trimethyl ether was converted to the trimethyl ether methyl ester of (II) through the acid chloride and diazoketone; it melted at 228-230°, but it depressed considerably the m.p. (225-226°) of the ether-ester of natural endocrocin. Incidentally, the acid (II) may be a precursor of nalgiovensin (V), the synthesis of which is in progress.[6]

One of us has discussed elsewhere[7] some of the difficulties encountered in the synthesis of I. Structure (I) for endocrocin has now been confirmed by the synthesis of its tetramethyl ether-ester following two routes. Both involved as the first three steps the dinitration of 2,3-dimethylanthraquinone, separation of the 1,5-dinitro derivative, and its reduction by boiling dimethylaniline to 1-nitro-2,3-dimethyl-5-aminoanthraquinone (VI), m.p. 360°. Dibromination of VI and deamination yielded 6,8-dibromo-2,3-dimethyl-1-nitroanthraquinone, m.p. 278°, which was converted to the isoxazole (VII) by treatment with 20 per cent oleum at 28-30° or aluminium chloride at 150-160°. Hydrolysis of VII with boiling methanolic barium hydroxide gave 1-amino-6,8-dibromo-3-methylanthraquinone-2-carboxylic acid.

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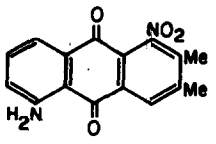
5 H. Mühlemann, Pharm. Acta Helv. 24, 351 (1949).

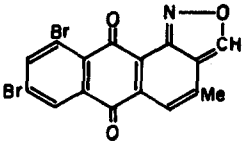
6 H. Raistrick and J. Ziffer, Biochem. J. 49, 563 (1951); A.J. Birch and R.A. Massy-Westropp, J. Chem. Soc. 2215 (1957); A.J. Birch and C.J. Moye, Ibid. 4691 (1961).

7 K. Venkataraman, J. Ind. Chem. Soc. 37, 247 (1960).

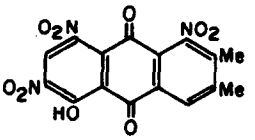
The amino group was replaced by hydroxyl through the diazonium salt, and the bromine atoms by hydroxyl by heating with lime under pressure at 220° in presence of copper oxide. The product was methylated by the acetone-potassium carbonate method, and chromatography of a benzene solution on alumina finally yielded a compound, m.p. 225-226°, which gave correct elementary analysis and which did not depress the m.p. of natural endocrocin ether-ester. The infra-red spectra were superposable.



VI



VII



VIII

In the alternative route the amine (VI) was converted to 5-hydroxy-2,3-dimethyl-1,6,8-trinitroanthraquinone (VIII), m.p. 268°, by treatment with conc nitric acid on a steambath, following an observation[8] that α-aminoanthraquinone is converted to 1-hydroxy-2,4-dinitroanthraquinone in 55 per cent yield under these conditions. Reduction, diazotization and hydrolysis yielded 1,5,6,8-tetrahydroxy-2,3-dimethylanthraquinone, m.p. 310-325° (decomp). When this compound was submitted to the well-known purpurin → xanthopurpurin reduction by treatment with aqueous sodium dithionite and sodium hydroxide, atmospheric oxidation of the leuco compound gave 1,6,8-trihydroxy-2,3-dimethylanthraquinone (2-methyl emodin), m.p. 269-270°. The action of N-bromosuccinimide and benzoyl peroxide on the triacetate[9] gave the 2-bromomethyl derivative accompanied by a minor amount of the 3-bromomethyl isomer. The preferential bromination of the 2-methyl group was demonstrated in the first instance by the action of NBS on

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[8] P. Jayaraman, Ph.D. Thesis, University of Bombay (1957).

[9] B.S. Joshi, N. Parkash and K. Venkataraman, Curr. Sci. 23, 330 (1954).

1-acetoxy-2,3-dimethylanthraquinone, m.p. 191°, the product being converted through the acetoxymethyl derivative to 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (III), m.p. 276°, identical with the acid of authentic structure obtained from 1-nitro-2,3-dimethylanthraquinone through the isoxazole route. The reason for the preferential attack of the sandwiched methyl group is not clear, and we are examining the action of NBS on 3-acetoxy-o-xylene. Treatment of the bromination product of 1,6,8-triacetoxy-2,3-dimethylanthraquinone with sodium acetate and acetic anhydride yielded 1,6,8-triacetoxy-2-acetoxymethyl-3-methylanthraquinone, m.p. 162-165°. Oxidation of the tetraacetate with silver oxide and aqueous sodium hydroxide[10] gave endocrocin (I), identical in all its properties with the natural pigment. The tetramethyl ether-ester, m.p. 225-226°, was identical with the ether-ester obtained by the first method and with natural endocrocin ether-ester.

We are greatly indebted to Professor S. Shibata and Dr. B. Franck for samples of endocrocin and its trimethyl ether methyl ester and for informing us of their work in this field in advance of publication.

[10] Cf. Oxidation of lucidin to munjistin: N.R. Ayyangar and K. Venkataraman, J. Sci. Ind. Res. 15B, 359 (1956).