329. *The Nonadrides. Part I. Introduction and General Survey*

By D. H. R. BARTON and J. K. SUTHERLAND

Previous work on glauconic, glaucanic, and byssochlamic acids is reviewed in the light of the structures established in later Papers. Reference is made where appropriate to the important contributions of *X*-ray crystallography.[1] Possible biosynthetic routes to the nine-carbon ring of the nonadrides are considered.

THE isolation of glauconic, $C_{18}H_{20}O_7$, and glaucanic, $C_{18}H_{20}O_6$, acids from a mould (at first called *Penicillium glaucum*) was described by Wijkman in 1931.[2] Glauconic acid was later isolated [3] from *Penicillium purpurogenum*, and, more recently, from a similar strain.[4] The earlier work on the chemistry of glauconic and glaucanic acids was carried out by Wijkman, Sutter, Kraft, and their collaborators.[2,5]

Glauconic and glaucanic acids are bisanhydrides, as is a further mould metabolite, byssochlamic acid,[6] an isomer of glaucanic acid. A biogenetic connection between these three C_{18}-bisanhydrides seemed probable, and was found as we shall show.

Our interest in the three compounds was first aroused by Professor H. Raistrick, F.R.S., who supplied us with initial quantities of glauconic and byssochlamic acids and with his unpublished work on the latter. Dr. J. W. Cook, F.R.S., and Dr. J. D. Loudon permitted us to quote from their unpublished work on byssochlamic acid and provided us with reference compounds.

In our earlier Paper [7] we described in detail the earlier work on glauconic and glaucanic acids, and we shall refer to it in detail only where necessary for comprehension of our own contributions.

The earlier workers [2,5] showed that glauconic acid was a bisanhydride with an easily acylable hydroxyl group. Pyrolysis afforded αβ-diethylacraldehyde (I) and a compound, $C_{11}H_8O_6$, glauconin, which was formulated as (II). The earlier workers rejected structure (III) for glauconin, but our reading of the earlier literature led us to favour this structure. The ultraviolet and infrared spectra of gluconin were in accord with (III), whilst the n.m.r.

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[1] Cf. J. M. Robertson, *Proc. Chem. Soc.*, 1963, 229.

[2] N. Wijkman, *Annalen*, 1931, **485**, 61.

[3] J. L. Yuill, *Biochem. J.*, 1934, **28**, 222.

[4] M. Takashima, A. Kitajima, and K. Otauka, *J. Agric. Chem. Soc. Japan*, 1955, **29**, 25 (*Chem. Abs.*, 1958, **52**, 20,379).

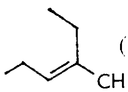
[5] H. Sutter and N. Wijkman, *Annalen*, 1933, **505**, 248; 1935, **519**, 97; H. Sutter, F. Rottmayer, and H. Porsch, *ibid.*, 1936, **521**, 189; K. Kraft and H. Porsch, *ibid.*, 1937, **527**, 168; K. Kraft, *ibid.*, 1937, **530**, 20.

[6] H. Raistrick and G. Smith, *Biochem. J.*, 1933, **27**, 1814.

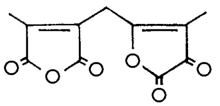
[7] J. E. Baldwin, D. H. R. Barton, J. L. Bloomer, L. M. Jackman, L. Rodriguez-Hahn, and J. K. Sutherland, *Experientia*, 1962, **18**, 345.

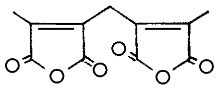
spectrum in trifluoroacetic acid showed eight protons in two sharp singlets. The two vinylic methyl groups (six protons) absorbed at 7·70 τ and the two methylene protons at 6·26 τ. The constitution (III) was confirmed by synthesis. The hydroxyl group of glauconic acid clearly becomes the aldehyde group of diethylacraldehyde, and glauconic acid must have a secondary hydroxyl, as its oxidation to the ketone confirmed.

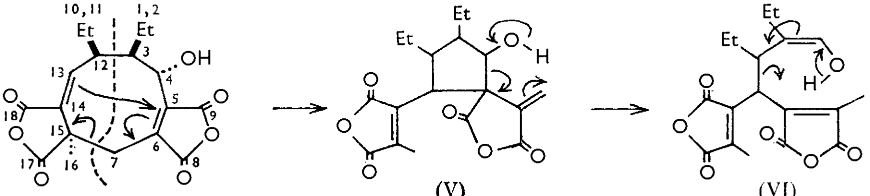
Although the pyrolysis products are formed under mild conditions, *e.g.*, refluxing in mesitylene, the carbon skeleton of glauconin does not appear in glauconic acid. From the extensive chemical work,[7] confirmed by *X*-ray crystallography,[8] glauconic acid has the constitution (IV). To account for the formation of the two pyrolysis products one must first postulate a Cope rearrangement [9] to the intermediate (V) which is further pyrolysed [10] to the aldehyde form of (VI). The enolic form of (VI) (as written) must then split into αβ-diethylacraldehyde (I) and glauconin (III). The final step is the equivalent of a reversed Michael reaction.



(I)


(II)


(III)



(IV) (V) (VI)

Another important degradation product isolated by the earlier workers was the so-called dihydroglauconic acid, formed by reduction of glauconic acid with zinc dust and acetic acid. This is a monocarboxylic acid anhydride containing a γ-lactone ring. With dimethyl sulphate and alkali the anhydride ring is opened, giving a trimethyl ester which still contains the γ-lactone group (band at 1775 cm.$^{-1}$). The reduction can be represented as in (VII), proceeding through intermediate (VIII), to give dihydroglauconic acid (IX).

Glaucanic acid has been simply related [7] to glauconic acid in that reduction of glauconic acid acetate with zinc dust and acetic acid affords glaucanic acid. Glauconic and glaucanic acids show very similar ultraviolet, infrared, and n.m.r. spectra. Glaucanic acid must be (XI), being formed from the acetate (X) as indicated. Glaucanic acid, itself, should also be reducible [(XI); see arrows] by zinc and acetic acid. The reduction is not so facile as with glauconic acid or its acetate, but it had been effected,[2,5] and amongst the products were dihydroglaucanic acid, now to be formulated as (XII), and, apparently, the corresponding dicarboxylic acid from hydration of the saturated anhydride ring. The reduction of glauconic acid itself is no doubt assisted by intramolecular solvation of anhydride carboxyl by the secondary hydroxyl group.[11] In the acetate this internal solvation cannot occur, and, therefore, the expulsion of acetate anion takes preference over reduction as an ene-1,4-dione system.

Glauconic (IV) and glaucanic (XI) acids are obviously constructed from two identical C_9-fragments, and the numbering system [7] takes cognisance of this. The oxidation level of glaucanic acid is such that the two C_9-fragments could, at least formally, be represented

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[8] G. Ferguson, G. A. Sim, and J. M. Robertson, *Proc. Chem. Soc.*, 1962, 385.

[9] A. C. Cope and E. M. Hardy, *J. Amer. Chem. Soc.*, 1940, **62**, 441; A. C. Cope, K. E. Hoyle, and E. M. Hardy, *ibid.*, 1941, **63**, 1843; A. C. Cope, C. F. Hofmann, and E. M. Hardy, *ibid.*, 1941, **63**, 1852.

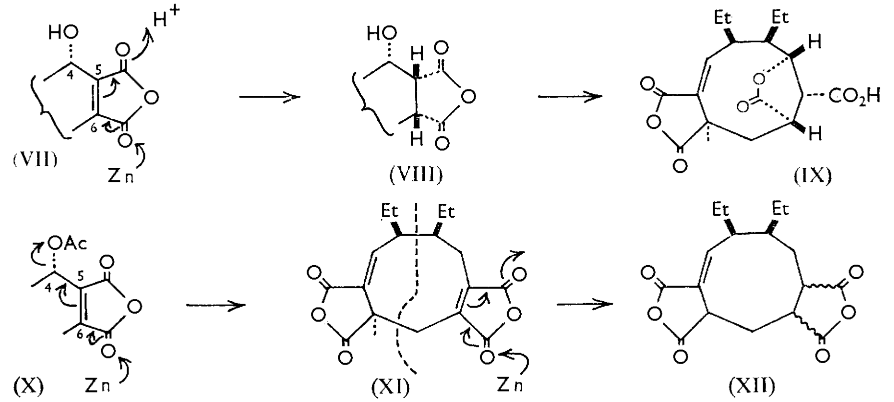
[10] Cf. R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, 1959, **81**, 6443; 1960, **82**, 4918; *J. Org. Chem.*, 1960, **25**, 129.

[11] Cf. H. B. Henbest and B. J. Lovell, *J.*, 1957, 1965; S. M. Kupchan and W. S. Johnson, *J. Amer. Chem. Soc.*, 1956, **78**, 3864.

as in (XIII). An anionic-type coupling mechanism as thus written (see arrows) would furnish glaucanic acid with the two ethylenic linkages in the correct positions. The hydroxyl group of glauconic acid might then be inserted into glaucanic acid as the final step of biogenesis. Of course, alternative ways for the introduction of hydroxyl at a much earlier stage in the biogenesis can easily be devised.

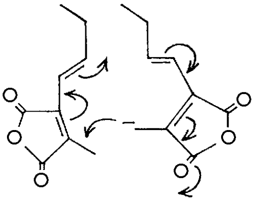
Byssochlamic acid, the isomer of glaucanic acid, is unreactive towards electrophilic reagents, and the chemical determination of its constitution was difficult. Accordingly, we submitted a suitable heavy-atom derivative for *X*-ray crystallography. One of us (J. K. S.) pointed out that, if the combination of the two C_9-units in glaucanic acid be regarded as head-to-head coupling, then head-to-tail coupling would also be conceivable. One possibility, summarised in (XIV), leads to the formula (XV) for byssochlamic acid; the *X*-ray results[12] established this and it was confirmed chemically.[13]

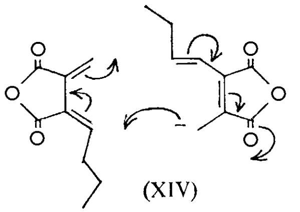
The absolute configurations of glauconic, glaucanic, and byssochlamic acids have been determined by chemical methods,[13,14] and it is of interest that the absolute configuration of the " right hand " C_9-unit is different in glaucanic (XII) and byssochlamic (XV) acids.

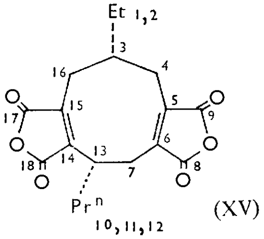


(VII) (VIII) (IX)

(X) (XI) (XII)


(XIII)


(XIV)



(XV)

At present we are working[15] on the hypothesis that the C_9 unit is derived from a modified citric acid cycle. The constitutions of *inter alia* the microbial products lichesterenic acid[16] and mineoluteic acid[17] provide analogy for the carbon skeleton of our C_9-unit.

Since glauconic, glaucanic, and byssochlamic acids are all bisanhydrides, and apparently derived from two C_9-units, we suggested[7] the name " nonadrides " which appears to have been generally accepted.[18]

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[12] T. A. Hamor, I. C. Paul, J. M. Robertson, and G. A. Sim, *Experientia*, 1962, **18**, 352; *J.*, 1963, 5502.

[13] J. E. Baldwin, D. H. R. Barton, and J. K. Sutherland, *J.*, 1965, 1787.

[14] D. H. R. Barton, L. D. S. Godinho, and J. K. Sutherland, *J.*, 1965, 1779.

[15] J. L. Bloomer, C. E. Moppett, and J. K. Sutherland, in preparation.

[16] M. Asano and T. Kanematsu, *Ber.*, 1932, **65**, 1175.

[17] J. H. Birkinshaw and H. Raistrick, *Biochem. J.*, 1934, **28**, 828.

[18] See *Ann. Rep.*, 1962, **59**, 286.

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