619. *Triterpenoids. Part XIV.* The Constitution of Quinovic Acid.*

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On the basis of published evidence two formulæ are possible for quinovic acid. By stepwise degradational experiments a distinction between the two possibilities has been made. A new formulation for novic acid is advanced and justified by chemical and physical evidence.

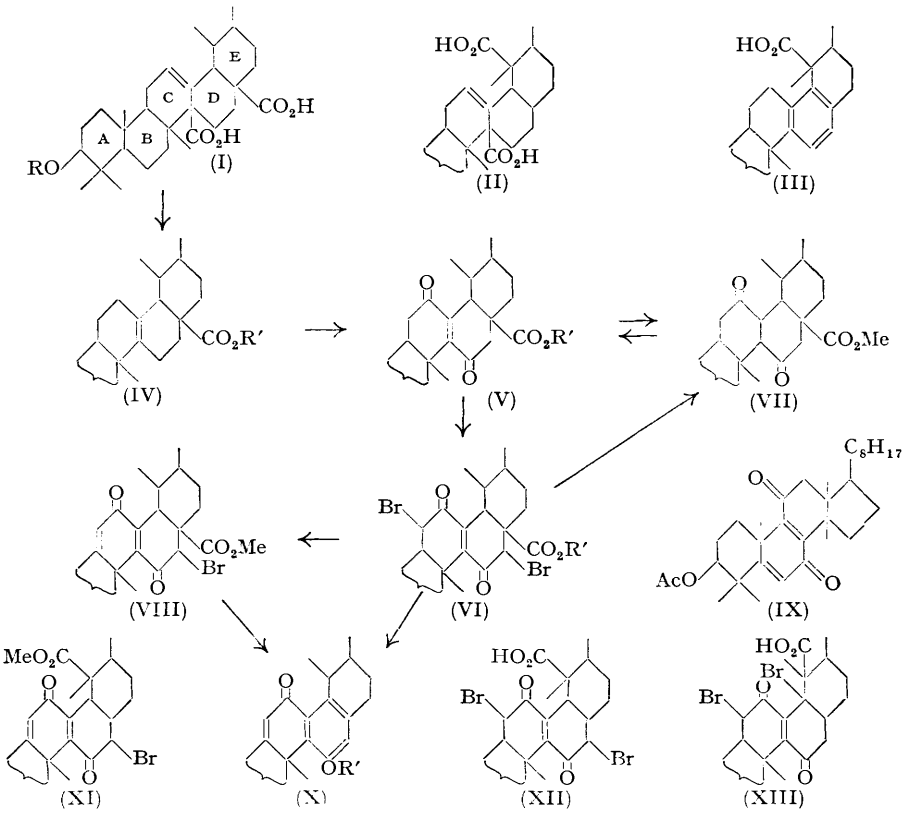
Quinovic acid, a triterpenoid hydroxy-dicarboxylic acid present in cinchona bark and in the leaves and bark of several *Mitragyna* species (Badger, Cook, and Ongley, *J.*, 1950, 867), has been the subject of extensive investigations by the schools of Wieland and of Ruzicka (for summaries see Elsevier's " Encyclopaedia of Organic Chemistry," Vol. XIV, pp. 580, 1102 *et seq.*). The work has been crowned by Jeger's proposal (" Fortschritte der Chemie der organischen Naturstoffe," Springer-Verlag, 1950, Vol. VII, p. 69; Brossi, Bischof, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 244) of formula (I; R = H) for quinovic acid.

Whilst this formula provides in most respects an excellent representation of the chemistry of quinovic acid, it seemed to us that the published literature made (II; R = H), which also obeys the isoprene rule, equally admissible. Thus the evidence of Schmitt and Wieland (*Annalen*, 1945/1947, **557**, 1) proves that the carboxyl group which is *not* eliminated easily is in the γ-position with respect to the more substituted end of the double bond. It does not, however, distinguish between (I; R = H) and (II; R = H) for quinovic acid. Indeed the latter would provide a better explanation for the formation of the aromatic pyroquinovatrienic acid [which would then be represented by (III; R = H)]. It was the main objective of the experiments described in the present paper to secure a distinction between the two formulæ.

As a $\beta\gamma$-unsaturated acid quinovic acid readily loses carbon dioxide on melting and affords, with double-bond shift (see Barton and Brooks, *J.*, 1951, 257; Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457), pyroquinovic acid (IV; R = R′ = H). Oxidation of methyl pyroquinovate acetate (IV; R = Ac, R′ = Me) afforded methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me) (Wieland, Hartmann, and Dietrich, *Annalen*, 1936, **522**, 191). On treatment with bromine in acetic acid (V; R = Ac, R′ = Me) furnished a dibromo-derivative (cf. Wieland and Kraus, *Annalen*, 1932, **497**, 140)

* Part XIII, *J.*, 1953, 2178.

which, on the basis of its further reactions, must be formulated as (VI; R = Ac, R′ = Me). That bromination was not attended with rearrangement was shown as follows. Reduction of (V; R = Ac, R′ = Me) with zinc dust in acetic acid gave the saturated 1 : 4-dione (VII; R = Ac). Interestingly, the latter was re-oxidised to (V; R = Ac, R′ = Me) simply by boiling 5% methanolic potassium hydroxide (followed by remethylation and



reacetylation). Similar reduction and reoxidation of (VI; R = Ac, R′ = Me) likewise afforded (V; R = Ac, R′ = Me).

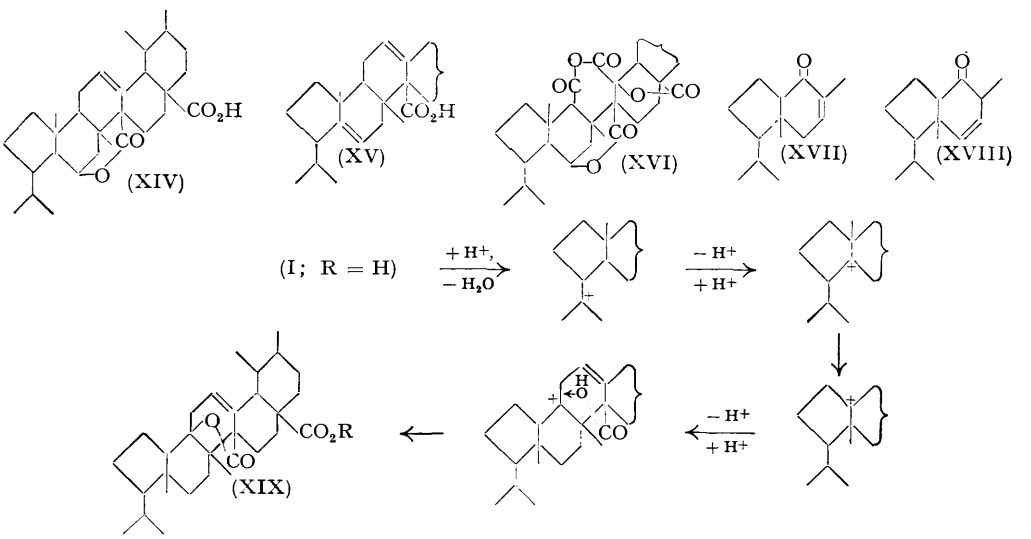
Treatment of the dibromo-ester (VI; R = Ac, R′ = Me) with silver nitrate and pyridine at room temperature (compare Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80; Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334) gave in good yield methyl monobromodiketopyroquinovadienoate acetate (VIII; R = Ac). The constitution assigned to the latter is based on the following considerations. (*a*) The ultra-violet absorption spectrum showed a maximum at 272 mμ corresponding in both position and intensity with that recorded for 7 : 11-diketolanosta-5 : 8-dienyl acetate (IX) (Voser, Montavon, Günthard, Jeger and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893). (*b*) The infra-red spectrum showed bands at 1736, 1277, and 1240 (tertiary CO_2Me and acetate), 1692 (·CHBr·CO·C:C), and 1650 cm.$^{-1}$ (·C:C·CO·C:C·). The appropriate corresponding bands are also shown by (IX) (Voser *et al.*, *loc. cit.*).

The mono-bromo-compound (VIII; R = Ac) was also obtained readily by refluxing (VI; R = Ac, R′ = Me) with collidine or pyridine. On further treatment with these reagents (VIII; R = Ac) was recovered unchanged. However, when heated with collidine at 210° in a sealed tube, both (VI; R = Ac, R′ = Me) and (VIII; R = Ac) were smoothly converted into the phenol (X; R = Ac, R′ = H), further characterised as the diacetate (X; R = R′ = Ac). The constitution assigned to the phenol is supported by the ultra-

violet spectrum taken in both neutral and alkaline solution (see Experimental section) and by the infra-red spectrum which showed bands at 1730 and 1242 (acetate), and 1648 cm.$^{-1}$ (·C:C·CO·C:C·). In comparison the analogous *m*-hydroxyacetophenone showed a carbonyl maximum at 1688 cm.$^{-1}$. The shift to 1648 cm.$^{-1}$ in the phenol (X; R = Ac, R′ = H) demonstrates the conjugating effect of the extra ethylenic double bond.

The resistance of (VIII; R = Ac) to dehydrobromination, except under forcing conditions which involve concomitant decarbomethoxylation, is explained much better by that formula [based on (I; R = Ac)] than by the alternative (XI; R = Ac) [based on (II; R = Ac)]. Even more decisive evidence was obtained in the following way. Alkaline hydrolysis of methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me), followed by reacetylation, afforded the known acetate acid (V; R = Ac, R′ = H) (Wieland and Hoshino, *Annalen*, 1930, **479**, 179). That stereoisomerisation was not induced by the alkaline conditions was confirmed by remethylation to the parent ester (V; R = Ac, R′ = Me). Bromination of the acetate acid (V; R = Ac, R′ = H) under the conditions used for the methyl ester gave a dibromo-acid (VI; R = Ac, R′ = H), the constitution of which was proved by remethylation to the above-mentioned dibromo-ester (VI; R = Ac, R′ = Me). Treatment of the dibromo-acid with silver nitrate in pyridine solution at room temperature furnished the phenol (X; R = Ac, R′ = H). The smooth elimination of carbon dioxide in this reaction is explained by the β-bromo-acid formulation of (VI; R = Ac, R′ = H). It would find no explanation on the basis of formula (XII; R = Ac), itself derived from (II; R = Ac). A variant formula (XIII; R = Ac) for the dibromo-acid, based on (II; R = Ac), would explain the ease of decarboxylation, but the product of reaction would not be a phenol. On the basis of all this evidence we regard formula (I; R = H) for quinovic acid as substantiated.

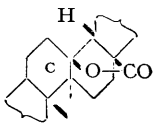
On treatment with strongly acidic reagents, quinovic acid affords, with loss of water, novic acid. Jeger (*loc. cit.*) has formulated the latter as (XIV). It seemed to us that this formula was somewhat improbable for the following reasons. (*a*) It involves a very stable δ-lactone ring. (*b*) The latter is postulated as being formed by non-Markownikoff addition to (XV). (*c*) The formula does not explain why the acid anhydride, which would be (XVI) on the



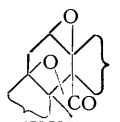
basis of (XIV), of the dicarboxylic acid derived from novaquinone gives two *ketones* [now formulated as (XVII) and (XVIII)] on pyrolysis. We took the view that, granted the accuracy of the expression (I; R = H) for quinovic acid, novic acid would be better regarded as the γ-lactone (XIX), formed from (I; R = H) by the mechanism indicated.

The accuracy of the expression (XIX; R = H) for novic acid has been justified in the following way. In the infra-red novic acid shows a somewhat displaced γ-lactone band at

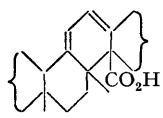
1766 cm.$^{-1}$ as well as the unconjugated carboxylic acid band at 1694 cm.$^{-1}$. In comparison oleanolic acid lactone (XX; R = H) (Barton and Holness, *J.*, 1952, 78) showed a γ-lactone band at 1774 cm.$^{-1}$, and 18-*iso*oleanolic lactone acetate bands at 1732 and 1240 (acetate) and 1770 cm.$^{-1}$ (γ-lactone). The displacement of the γ-lactone band of novic acid from its usual position is to be attributed to the double bond, for when the latter was saturated by conversion of methyl novate (XIX; R = Me) into methyl novate oxide (XXI; R = Me) the latter showed bands at 1732 and 1236 (acetate) and 1772 cm.$^{-1}$, the last being a clear indication of a γ-lactone grouping. Wieland and Erlenbach (*loc. cit.*) observed that when novic acid was heated with methanolic potassium hydroxide it was isomerised to a dicarboxylic acid designated " anhydroquinovic acid," from which it was regenerated by treatment with zinc chloride in acetic acid (Wieland and Utzino, *Annalen*, 1931, **488**, 242). On the basis of Jeger's novic acid formula, " anhydroquinovic acid " must be (XV); on the basis of (XIX; R = H) it must be the conjugated homoannular diene (XXII). We have found that, in agreement with (XXII), " anhydroquinovic acid " has $\lambda_{max.}$ 294 mμ (ε = 6000). Its strongly positive rotation ($[\alpha]_D$ +310°) is also in agreement with its formulation as a pentacyclic triterpenoid in which ring C is diunsaturated. On pyrolysis Wieland and Erlenbach (*loc. cit.*) showed that, like other $\beta\gamma$-unsaturated acids, " anhydroquinovic acid " was readily decarboxylated to " pyroanhydroquinovic acid." Following the discussion by Barton and Brooks (*J.*, 1951, 278) of pyrolysis of



(XX)



(XXI)



(XXII)

similar dienic acids we would predict that the latter acid should not be a conjugated diene. This has been confirmed. Other aspects of novic acid chemistry are readily explained by (XIX; R = H) and do not call for further comment here.

Experimental

For general experimental details see Part VII (*J.*, 1952, 2339). The infra-red spectra were kindly determined in carbon disulphide solution by Dr. J. E. Page and his staff (Messrs. Glaxo Laboratories Ltd.). $[\alpha]_D$ are in chloroform; ultra-violet absorption spectra are in ethanol.

Methyl Dibromodiketopyroquinovate Acetate (VI; R = Ac, R′ = Me).—Methyl diketopyroquinovate acetate (V; R = Ac, R′ = Me), m. p. 219—221°, $[\alpha]_D$ +30° (*c*, 1·96), $\lambda_{max.}$ 270 mμ (ε 7900) (Wieland, Hartmann, and Dietrich, *Annalen*, 1936, **522**, 191) (144 mg.) in acetic acid (9 ml.) containing hydrogen bromide (3 drops of 50% hydrogen bromide in acetic acid) was treated with bromine in acetic acid (10 ml., containing 18 mg. of bromine per ml.) and the solution left at room temperature in the dark for 4 days. The product was crystallised from methanol, to give *methyl dibromodiketopyroquinovate acetate*, m. p. 212—213° (decomp.), $[\alpha]_D$ +51° (*c*, 1·83), +52° (*c*, 1·84), $\lambda_{max.}$ 273 mμ (ε 8600) (Found : C, 55·9; H, 6·4; Br 23·3. $C_{32}H_{44}O_6Br_2$ requires C, 56·1; H, 6·45; Br, 23·4%).

Methyl Bromodiketopyroquinovadienoate Acetate (VIII; R = Ac).—Methyl dibromodiketopyroquinovate acetate (50 mg.) in pyridine–silver nitrate (5 ml.; 20%) was left overnight at room temperature. The product, recrystallised from methanol, gave *methyl bromodiketopyroquinovadienoate acetate*, m. p. 226—228°, $[\alpha]_D$ −62° (*c*, 1·28), $\lambda_{max.}$ 272 mμ (ε 12,800) (Found : C, 63·65; H, 7·1; Br 13·25. $C_{32}H_{43}O_6Br$ requires C, 63·7; H, 7·2; Br, 13·25%). This substance was also obtained by refluxing the parent dibromo-compound (100 mg.) with dry pyridine (13 ml.) or collidine (10 ml.) for 16 hr. and identified by m. p., mixed m. p., and absorption spectrum.

Treatment of Methyl Dibromodiketopyroquinovate Acetate with Collidine.—The dibromo-ester (70 mg.) in collidine (2 ml.) was heated in nitrogen in a sealed tube at 210° for 12 hr. The product, crystallised from methanol, gave the *phenol* (X; R = Ac, R′ = H) (40 mg.), m. p. 330—335° (decomp.), $[\alpha]_D$ +31° (*c*, 1·23), $\lambda_{max.}$ 344, 283, 253 mμ (ε 4300, 8200, and 18,800, respectively), $\lambda_{inflex.}$ 227 (ε 17,100), in 0·2N-ethanolic potassium hydride : $\lambda_{max.}$ 280, 247 mμ (ε 9800 and 21,600 respectively) (Found : C, 77·7; H, 8·8. $C_{30}H_{40}O_4$ requires C, 77·55; H, 8·7%). The same compound, identified by m. p., mixed m. p. and absorption spectrum, was also

obtained smoothly by heating methyl monobromodiketopyroquinovadienoate acetate in collidine in the same way. It was also prepared, although in poor yield, by heating the dibromo-ester with pyridine in a sealed tube for 6 hr. at 150°. The phenol (X; R = Ac, R′ = H), was further characterised by heating it on the steam-bath with acetic anhydride and pyridine for 0·5 hr. This furnished the *acetate* (X; R = R′ = Ac), m. p. (from methanol) 190—191·5°, $[\alpha]_D$ +27° (*c*, 1·42), $\lambda_{max.}$ 257, 275, and 312 mμ (ε 12,600, 11,700, and 4500 respectively) (Found: C, 75·3; H, 8·1. $C_{32}H_{42}O_5$ requires C, 75·85; H, 8·35%).

Bromination of Diketopyroquinovic Acid Acetate (V; R = Ac, R′ = H).—Diketopyroquinovic acid acetate, m. p. 286—288° (Wieland and Hoshino, *Annalen*, 1930, **479**, 179) was prepared by alkaline hydrolysis (refluxing 10% ethanolic potassium hydroxide for 1 hr.) of the methyl ester acetate followed by re-acetylation. On treatment with diazomethane it refurnished the parent methyl diketopyroquinovate acetate, m. p. and mixed m. p. 218—220°, $[\alpha]_D$ +30° (*c*, 2·57).

Diketopyroquinovic acid acetate (100 mg.) in acetic acid (7 ml.) containing bromine (120 mg.) and hydrogen bromide (3 drops of 50% hydrogen bromide in acetic acid) was left at room temperature in the dark for 5 days. The acidic product, extracted with sodium carbonate solution, was very soluble in all solvents. It was characterised by methylation with diazomethane, to give methyl dibromodiketopyroquinovate acetate (57 mg.) (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +48° (*c*, 0·51)}. In a parallel experiment with 50 mg. of the diketo-acid acetate the acidic product was treated with silver nitrate and pyridine as above. The product gave the phenol (X; R = Ac, R′ = H) (20 mg.), identified by m. p., mixed m. p., and absorption spectrum.

Diketopyroquinovic acid acetate was recovered unchanged [confirmed by conversion into the methyl ester acetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +29° (*c*, 1·73)}] on treatment with hydrogen bromide in acetic acid as under the conditions of the bromination.

Methyl Dihydrodiketopyroquinovate Acetate (VII; R = Ac).—Methyl diketopyroquinovate acetate (200 mg.) in 10 ml. of 1 : 1 ether–methanol was shaken overnight at room temperature with zinc dust (1 g.), which had been activated by hot acetic acid and washed with methanol. The product afforded colourless *methyl dihydrodiketopyroquinovate acetate* (from methanol), m. p. 262—264°, $[\alpha]_D$ +47° (*c*, 1·71), with no high-intensity absorption in the ultra-violet (Found: C, 72·8; H, 9·2. $C_{32}H_{48}O_6$ requires, C, 72·7; H, 9·15%). This diketone (100 mg.) was refluxed with 5% methanolic potassium hydroxide (10 ml.) on the steam-bath for 2 hr. The product was methylated with diazomethane and reacetylated and crystallised from methanol, to give yellow methyl diketopyroquinovate acetate, identified by m. p. and absorption spectrum ($\lambda_{max.}$ 270 mμ; ε 7200).

When methyl dibromodiketopyroquinovate acetate (50 mg.) was similarly reduced and oxidised, methyl diketopyroquinovate acetate, identified by m. p., mixed m. p., and absorption spectrum, was likewise obtained.

Methyl Novate Oxide (XXI; R = Me).—Novic acid (Schmitt and Wieland, *Annalen*, 1945/47, **557**, 1) was converted into the methyl ester (Wieland and Erlenbach, *ibid.*, 1927, **453**, 83), m. p. 207—208°, $[\alpha]_D$ +132° (*c*, 0·52). The latter (100 mg.) in carbon tetrachloride (3 ml.) was treated with ozonised oxygen until it gave no colour with tetranitromethane. Crystallisation of the product from methanol gave *methyl novate oxide*, m. p. 246—247°, $[\alpha]_D$ +80° (*c*, 1·90) (Found: C, 74·6; H, 9·1. $C_{31}H_{46}O_5$ requires, C, 74·65; H, 9·3%).

Anhydroquinovic Acid (XXII).—Novic acid (200 mg.) was heated with methanolic 3N-potassium hydroxide (2 ml.) at 170° for 3 hr. (cf. Wieland and Erlenbach, *loc. cit.*). Recrystallisation of the product from acetic acid gave "anhydroquinovic acid," m. p. 222—224° (decomp.), $[\alpha]_D$ +310° (*c*, 0·25), $\lambda_{max.}$ 294 mμ (ε 6000). This (20 mg.) was pyrolysed *in vacuo* at 245° as described by Wieland and Erlenbach (*loc. cit.*). The product "pyroanhydroquinovic acid" had no selective absorption in the ultra-violet (at 220—350 mμ, ε <3000).

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