1019. *Synthesis of* 3-O-p-*Coumaroylquinic Acid.*

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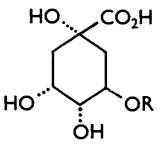
A substance previously isolated from cider apples is shown by synthesis to be 3-*O*-*p*-coumaroylquinic acid. Its biogenetic relationship to chlorogenic acid is briefly discussed.

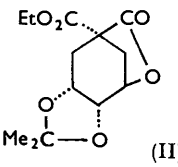
Chlorogenic acid was first isolated from coffee beans by Gorter [1] who showed it to be a derivative of quinic acid (Ia). Freundenberg [2] showed that the enzyme tannase hydrolysed chlorogenic acid to equimolar amounts of quinic and caffeic acid, and its structure as the 3-caffeic ester (Ib) of quinic acid was later deduced by Fischer and Dangschat [3] from its methylation and subsequent hydrolysis to 3,4-di-*O*-methylcaffeic acid and 1,4,5-tri-*O*-methylquinic acid (isolated as the 1,3-lactone). A synthesis of chlorogenic acid by Panizzi, Scarpati, and Oriente [4] has recently confirmed this structure. Since its initial isolation from coffee beans, chlorogenic acid has been found in other plant species [5] and the advent of modern methods of plant analysis, notably paper chromatography, has shown its widespread distribution in the fruit, leaves, and other tissues of a variety of dicotyledenous plants.[6] Paper-chromatographic analysis of the chemical constituents of plant tissues has also enabled additional related phenolic compounds to be identified and later isolated. Thus in 1958 Williams [7] isolated from cider apples a compound which

[1] Gorter, *Annalen*, 1907, **358**, 328.
[2] Freudenberg, *Ber.*, 1920, **53**, 232.
[3] Fischer and Dangschat, *Ber.*, 1932, **65**, 1037.
[4] Panizzi, Scarpati, and Oriente, *Experientia*, 1955, **11**, 383.
[5] Paech and Tracey, "Moderne Methoden der Pflanzenanalyse," Springer-Verlag, Berlin, 1955, Vol. III, p. 427.
[6] Bate-Smith, *Chem. and Ind.*, 1954, 1457; Hermann, *Pharmazie*, 1956, **11**, 433.
[7] Williams, *Chem. and Ind.*, 1958, 1200.

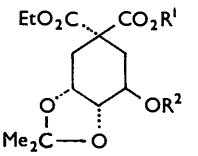
was shown to be a *p*-coumaric ester of quinic acid and Schütte, Langenbeck, and Böhme [8] described the isolation of a similar but not identical substance from *Antirrhinum majus*. Since the amount isolated did not allow a complete structural proof by chemical degradation, Williams,[7] on the basis of its paper-chromatographic similarity and probable biogenetic relation to chlorogenic acid, tentatively assigned to the compound from cider apples the structure of 3-*O*-*p*-coumaroylquinic acid (Ic). Paper chromatography has been used to show that this substance occurs also in tea, cacao, and quebracho leaves, and in apples and pears,[9] and its presence in other plant species, *e.g.*, *Cratageus*, *Betulaceae*, *Vaccinia*, has been established by similar techniques during this present work.



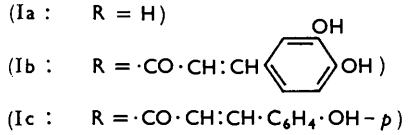
(Ia : R = H)



(II)



(IIIa : $R^1 = R^2 = H$)
(IIIb : $R^1 = Me$; $R^2 = H$)
(IIIc : $R^1 = CHPh_2$; $R^2 = H$)
(IIId : $R^1 = CHPh_2$;



(Ib : R = ·CO·CH:CH OH)

(Ic : R = ·CO·CH:CH·C_6H_4·OH-*p*)

R^2 = CO·CH:CH·C_6H_4·O·CO·OEt-*p*)

(IIIe : $R^1 = CHPh_2$; R^2 = CO·CH:CH·C_6H_4·OH-*p*)

Panizzi *et al.*[4] synthesised chlorogenic acid by esterification of the unsubstituted 3 position in the ester (IIIb) with 3,4-oxomethylenedioxycinnamoyl chloride, followed by removal of the isopropylidene group in acid and hydrolysis of the cyclic carbonate, ethoxycarbonyl, and methyl ester groups with barium hydroxide. In modifying this synthesis for the preparation of 3-*O*-*p*-coumaroylquinic acid it was sought in particular to protect the carboxyl group of quinic acid in such a way that it would be regenerated by acid; the diphenylmethyl group was chosen for this purpose.

The calculated amount of barium hydroxide converted the lactone (II) into 1-*O*-ethoxycarbonyl-4,5-*O*-isopropylidenequinic acid (IIIa) and this on treatment with diphenyldiazomethane [10] gave the diphenylmethyl ester (IIIc). Acylation of the unsubstituted 3-hydroxyl group with 4-*O*-ethoxycarbonylcinnamoyl chloride gave the ester (IIId), but removal of the protecting groups from this compound to give 3-*O*-*p*-coumaroylquinic acid was not achieved as planned. Treatment with aqueous acetic acid, in order to remove the acid labile isopropylidene and diphenylmethyl groups, gave an intractable gum which on the subsequent action of barium hydroxide gave small yields (2%) of the required 3-*O*-*p*-coumaroylquinic acid and appreciable quantities of *p*-coumaric acid, the former being isolated by counter-current distribution between ethyl acetate and water. In an attempt to reduce the amount of *p*-coumaric acid formed the ester (IIId) was treated with exactly two equivalents of sodium hydroxide, but under these conditions the 1-*O*-ethoxycarbonyl group was unusually stable and selective hydrolysis occurred with the formation of the ester (IIIe). This compound had a chromophore and fluorescence in ultraviolet light typical of esters of *p*-coumaric acid, and with diazomethane it gave a monomethyl ether. However, acid removed the isopropylidene, diphenylmethyl, and 1-*O*-ethoxycarbonyl groups, and 3-*O*-*p*-coumaroylquinic acid (Ic) was isolated. The product was identical with the natural sample (kindly supplied by Dr. A. H. Williams),

[8] Schütte, Langenbeck, and Böhme, *Naturwiss.*, 1957, **44**, 63.
[9] Cartwright, Flood, Roberts, and Williams, *Chem. and Ind.*, 1955, 1062; White and King, *Proc. Chem. Soc.*, 1957, 341; Griffiths, *Biochem. J.*, 1958, **70**, 120.
[10] Staudinger, Anthes, and Pfenninger, *Ber.*, 1916, **49**, 1932.

thus proving the tentative structure suggested in 1958. Hydrogenation of 3-*O*-*p*-coumaroylquinic acid gave the corresponding 3-*O*-*p*-hydroxyphenylpropionylquinic acid.

The biogenetic relation of 3-*O*-*p*-coumarylquinic acid to chlorogenic acid is fairly evident,[7] and the identification in potato tuber [11] of these two substances and a suggested 3-cinnamoyl derivative of quinic acid indicated that the last substance might give rise to the *p*-coumaroyl and caffeoyl derivatives by successive hydroxylation of the aromatic nucleus. Neisch [12] has similarly proposed the existence of a C_6—C_3 pool in which lignin precursors are derived from cinnamic acid by similar processes. Accordingly we attempted to convert 3-*O*-*p*-coumaroylquinic acid into chlorogenic acid by the action of the enzyme tyrosinase,[13] which it is believed can in certain cases convert monohydric into *o*-dihydric phenols, but so far we have been unable to bring about this transformation. Further experiments towards the elucidation of this relationship are in progress.

Experimental

1-O-*Ethoxycarbonyl*-4,5-O-*isopropylidenequinic Acid* (IIIa) [with D. A. Lawton].—Considerable difficulty was experienced in the preparation of this compound as described [4] and the following method was used. 1-*O*-Ethoxycarbonyl-4,5-*O*-isopropylidenequinide [4] (II) (5·7 g.) was heated in ethanol (50 c.c.) containing acetone (15 c.c.) at 50° in an atmosphere of nitrogen. 0·23N-Barium hydroxide (85 c.c.) was added dropwise and then the mixture was heated at 60° for ½ hr., cooled to 5°, and treated with 2N-sulphuric acid until neutral. Removal of the barium sulphate, extraction of the aqueous solution with ethyl acetate (5 × 50 c.c.), and evaporation gave 1-*O*-ethoxycarbonyl-4,5-*O*-isopropylidenequinic acid which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as plates (4·5 g.), m. p. 150—152° (Panizzi *et al.*[4] give this m. p.), $\nu_{max.}$ 1747 cm.$^{-1}$ (KBr disc).

Diphenylmethyl 1-O-*Ethoxycarbonyl*-4,5-O-*isopropylidenequinate* (IIIc) [with D. A. Lawton].—A solution of diphenyldiazomethane [10] (4·8 g.) in chloroform (20 c.c.) was added to one of 1-*O*-ethoxycarbonyl-4,5-*O*-isopropylidenequinic acid (IIIa) (5·0 g.) in chloroform (100 c.c.), and the mixture refluxed for 6 hr. Removal of the solvent and crystallisation of the residue from ethyl acetate gave needles (6·7 g.) of *diphenylmethyl* 1-O-*ethoxycarbonyl*-4,5-O-*isopropylidenequinate*, m. p. 163° (Found: C, 66·1; H, 6·4. $C_{26}H_{30}O_8$ requires C, 66·4; H, 6·4%), $\nu_{max.}$ 1751 cm.$^{-1}$ (KBr disc).

4-O-*Ethoxycarbonylcinnamoyl Chloride*.—*p*-Coumaric acid was prepared by slight modifications of Wittmer and Raiford's method.[14] 4-*O*-Ethoxycarbonylcinnamic acid (1·8 g.), prepared from *p*-coumaric acid by Bonn's method,[15] was dissolved in dry benzene (25 c.c.) containing phosphorus pentachloride (1·6 g.) and refluxed for 1 hr. Removal of the solvent and crystallisation of the residue from light petroleum (b. p. 60—80°) gave needles (1·6 g.), m. p. 73—74°. 4-O-*Ethoxycarbonylcinnamoyl chloride* was characterised as its α-*naphthyl ester* (prepared in pyridine), m. p. 89—90° (Found: C, 72·4; H, 5·1. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%).

Diphenylmethyl 1-O-*Ethoxycarbonyl*-3-(4-O-*ethoxycarbonylcinnamoyl*)-4,5-O-*isopropylidenequinate* (IIId).—To the ester (IIIc) (1·18 g.) in benzene (25 c.c.) was added 4-*O*-ethoxycinnamoyl chloride and pyridine (2·5 c.c.). The mixture was refluxed for 3 hr. and left for 15 hr. at room temperature, after which it was washed with cold 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Removal of the benzene gave a gum which crystallised from benzene–light petroleum to give the *product* (IIId) as prisms (2·4 g.), m. p. 108—109° (Found: C, 66·2; H, 5·8. $C_{38}H_{39}O_{12}$ requires C, 66·3; H, 5·8%), $\nu_{max.}$ (KBr disc) 1726 and 1756 cm.$^{-1}$.

Diphenylmethyl 1-O-*Ethoxycarbonyl*-3-p-*coumaroyl*-4,5-O-*isopropylidenequinate* (IIIe).—N-Sodium hydroxide (1·5 c.c.) was added dropwise with stirring to a solution of the ester (IIId) (1·0 g.) in methanol (25 c.c.). The solution was kept at 30° for ½ hr. and just acidified with N-hydrochloric acid. Water (25 c.c.) was added and the solution extracted with ethyl acetate (75 c.c.), to yield, on removal of the solvent and crystallisation from ethanol, needles (0·5 g.)

[11] Sondheimer, *J. Biol. Chem.*, 1960, **235**, 2418.
[12] Neisch, *Canad. J. Biochem. Physiol.*, 1959, 537.
[13] Mallette, Lewis, Ames, Nelson, and Dawson, *Arch. Biochem.*, 1948, **16**, 288.
[14] Wittmer and Raiford, *J. Org. Chem.*, 1945, **10**, 527.
[15] Bonn, *Ber.*, 1913, **46**, 4052.

of the *product* (IIIe), m. p. 204—205° (Found: C, 68·0; H, 5·8; OEt, 7·0. $C_{35}H_{36}O_{10}$ requires C, 68·2; H, 5·9; OEt, 7·3%). The compound showed a bright blue fluorescence when exposed to ultraviolet light in the presence of ammonia vapour, and its infrared spectrum (KBr disc) showed absorption at 1717 and 1756 cm.$^{-1}$.

Diphenylmethyl 1-O-*Ethoxycarbonyl*-3-(4-O-*methyl*-p-*coumaroyl*)-4,5-O-*isopropylidene-quinate*.—A solution of diazomethane (0·42 g.) in ether (20 c.c.) was added to a suspension of the ester (IIIe) (0·35 g.) in benzene (100 c.c.) and the mixture left at 20° for 16 hr. Removal of the solvents and recrystallisation of the residue from ethanol gave the *methyl ether* as plates (0·25 g.), m. p. 212° (Found: C, 68·2; H, 6·0; OMe, 4·3. $C_{36}H_{38}O_{10}$ requires C, 68·6; H, 6·0; OMe, 4·9%), that do not fluoresce in ammonia vapour under ultraviolet light.

3-O-p-*Coumaroylquinic Acid* (Ic).—The ester (IIIe) (2·5 g.) was refluxed in 80% aqueous acetic acid (25 c.c.) for 6 hr. The solvent was removed at 30°, and the residue dissolved in saturated sodium hydrogen carbonate solution (40 c.c.) and extracted with ethyl acetate (50 c.c.). Acidification of the aqueous layer with 2N-sulphuric acid gave 3-O-p-*coumaroylquinic acid* which after two recrystallisations from water formed needles (0·5 g.), m. p. and mixed m. p. (with the natural product) 247—248° (Found: C, 56·5; H, 5·3. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3%), had $[\alpha]_D^{20}$ −53·6° (*c* 1·04 in MeOH) (Williams gives $[\alpha]_D$ −53·5°). The ultraviolet ($\lambda_{max.}$ 250 mμ, ε 1·4 × 10^4 in 95% EtOH) and infrared spectra (KBr disc, 1600, 1630, and 1710 cm.$^{-1}$) were identical with those of the natural product.

3-O-p-*Hydroxyphenylpropionylquinic Acid*.—3-*O*-*p*-Coumaroylquinic acid (0·13 g.) in ethanol (20 c.c.) was hydrogenated at 25°/1 atm. in the presence of 10% palladium–charcoal (0·1 g.) for 16 hr. Removal of the catalyst and solvent and crystallisation of the product from water gave the *propionyl derivative* as needles (0·1 g.), m. p. 201° (Found: C, 56·2; H, 6·0. $C_{16}H_{20}O_8$ requires C, 56·5; H, 5·9%), $[\alpha]_D^{20}$ −44·0° (*c* 0·32 in EtOH), $\nu_{max.}$ 1610 and 1725 cm.$^{-1}$.

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