198. *Furano-compounds. Part V. The Synthesis of Tetrahydroeuparin and the Structure of Euparin.*

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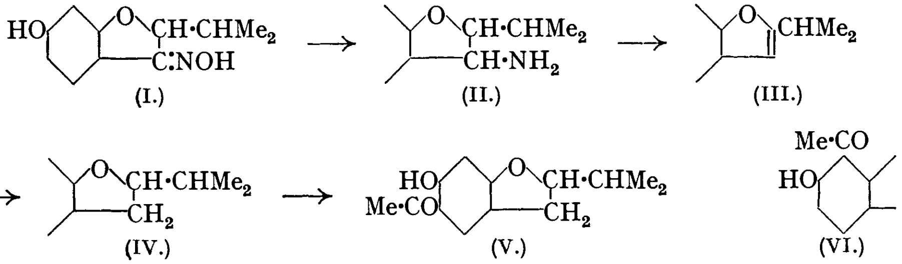
The formation of small amounts of *iso*valeric acid in the course of attempts to obtain deacetyltetrahydroeuparin from tetrahydroeuparin appeared to support the view that the latter was an *iso*propylcoumaran derivative (V). Accordingly the latter has been synthesised from (I) by way of the stages (II), (III), and (IV) and found to be identical with the natural compound. Consequently the expressions (VII) and (VIII, R = H) for euparin and its adduct with maleic anhydride clearly follow.

The preparation of coumarono- and coumarano-γ-pyrones from euparin is described.

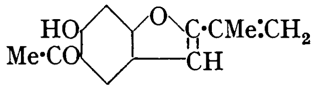
In the course of experiments undertaken to decide between the possible expressions deduced in Part III (this vol., p. 925) for euparin, we investigated the hydrolytic fission of tetrahydroeuparin with a view to preparing deacetyltetrahydroeuparin, the structure of which we hoped to establish by synthesis. Though we were unable to ascertain the conditions required for the formation of the latter substance, we observed that when tetrahydroeuparin was heated with concentrated potassium hydroxide solution at 290° there was formed a small amount of phenolic material along with an acidic fraction which smelt strongly of *iso*valeric acid. Although the amount of the product formed by heating the latter fraction with phenylhydrazine was too small to permit exhaustive purification, the crystalline material isolated from it undoubtedly consisted of the phenylhydrazide of *iso*valeric acid in an almost pure condition. Whilst in agreement with the isoprene skeleton already suggested for the C_5 residue of euparin, the formation of *iso*valeric acid under these conditions is a result which would not normally be expected in the case of the tetrahydro-derivative of a compound having one of the three possible formulæ proposed for euparin in Part III (*loc. cit.*) and must arise from a rearrangement and oxidation of a primary product of hydrolysis. This conversion would appear to be most feasible in the case of the primary fission product formed from a substance having the structure (V), thus $CHMe_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$ or $CHMe_2{\cdot}CH{:}CH{\cdot}OH \longrightarrow CHMe_2{\cdot}CH_2{\cdot}CO_2H$, and consequently, though these experiments failed to give the expected result, they served to indicate that tetrahydroeuparin probably had formula (V), a conclusion which has been substantiated by the synthesis of this compound.

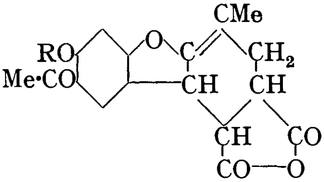
Of the methods available for the synthesis of the required intermediate coumarone (III), the catalytic reduction of 3 : 6-diacetoxy-2-*iso*propylcoumarone had been found to give negative results (Robertson and co-workers, J., **1937**, 1530) and consequently we adopted the procedure of Sonn (*Ber.*, 1925, **58**, 96; compare Späth and co-workers, *ibid.*, 1936, **69**, 1087) whereby a coumarone (type III) is obtained by thermal decomposition of the acetate of a 3-aminocoumaran (type II) formed by reduction of the oxime of the corresponding coumaranone (type I).


(I.) (II.) (III.) (IV.) (V.) (VI.)

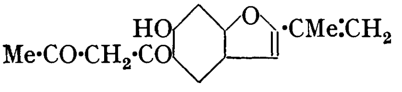
Accordingly, reduction of the *oxime* (I) was effected with sodium amalgam in the presence of acetic acid, but owing to the intractable nature of the product we did not attempt to isolate the intermediate amine (II) or its acetate. On being heated in a high vacuum, however, the light brown solid, which was isolated from the crude product with the aid of light petroleum, furnished a 10% yield of the *coumarone* (III), which on hydrogenation with a palladium catalyst yielded the *coumaran* (IV). Condensation of the latter compound with acetonitrile according to the method of Hoesch gave rise to (V), identical in every way with tetrahydroeuparin. That the substance (V) has the *C*-acetyl group in the 5-position follows upon the formation of 4-hydroxy-2-methoxyacetophenone-5-carboxylic acid from *O*-methyleuparin by means of potassium permanganate (Part III, *loc. cit.*), and consequently the isomeric *C*-acetylcoumaran resulting from the application of the Fries reaction to the acetate of (IV) must have formula (VI).

(VII.)

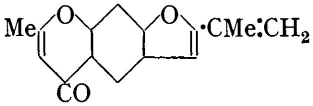




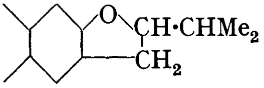
(VIII.)



(IX.)



(X.)



(XI.)

As a consequence of evidence described in Part III and the established structure for tetrahydroeuparin it is now clear that euparin has formula (VII) and hence the adducts formed by condensation of euparin and of *O*-methyleuparin with maleic anhydride (Part III) must be represented by the expressions (VIII, R = H) and (VIII, R = Me) respectively.

The syntheses of (X) and (XI) by way of the corresponding diketones (type IX), which are included in the present communication, were undertaken at an earlier stage in the work on euparin in order to demonstrate that in euparin and tetrahydroeuparin the hydroxyl group is in the *o*-position to the *C*-acetyl group. These compounds constitute examples of furo- and dihydrofuro-chromones (compare Curd and Robertson, J., 1933, 1173), analogous to kellin (*Ber.*, 1938, **71**, 106).

In the course of experiments on the constitution and synthesis of chroman derivatives evidence has been advanced in support of the view that the reduction product of, *e.g.*, 7-hydroxy-2 : 2-dimethylchromanone is the corresponding chroman and not the isomeric 6-hydroxy-2-*iso*propylcoumaran (IV) (Robertson and co-workers, J., 1937, 279, 1530). The present synthesis of the latter compound by an unambiguous method affords confirmatory evidence for the structure of the isomeric 6-hydroxy-2 : 2-dimethylchroman and hence of xanthyletin (J., 1937, 1542).

EXPERIMENTAL.

Fission of Tetrahydroeuparin with Potassium Hydroxide.—A solution of tetrahydroeuparin (1 g.) in alcohol (10 c.c.) and 50% aqueous potassium hydroxide (50 c.c.) was heated (oil-bath) in an atmosphere of nitrogen at 290° for 4 hours, and the cooled mixture treated with ice-water (100 g.), neutralised with sulphuric acid and aqueous sodium bicarbonate, and extracted with ether. Evaporation of the dried extracts left a small amount of a viscous oil, having a red ferric reaction, which after distillation in a high vacuum gave, on treatment with *p*-nitrobenzoyl chloride in pyridine, a small yield of a product, forming colourless prisms, m. p. 182—183°, from alcohol. The amount of this material was insufficient for further investigation.

From the aqueous liquors which had been acidified with dilute sulphuric acid a brown oil (0·32 g.) was isolated with ether and treated with aqueous ammonia containing calcium chloride; the mixture was filtered from a small precipitate, acidified with sulphuric acid, and extracted several times with ether. The residue left on evaporation of the combined, dried extracts was heated with phenylhydrazine (2 c.c.) at 120—130° for 2 hours, and the product (0·12 g.), b. p. 110—130°/2 mm., isolated by distillation in a vacuum and repeatedly crystallised from ether–light petroleum (b. p. 40—60°), giving a small amount of a substance in colourless plates, m. p. 105—106°, undepressed by authentic *iso*valerophenylhydrazide, m. p. 110°, prepared by the same method (*Ber.*, 1901, **34**, 179).

6-*Hydroxy*-2-iso*propylcoumarone* (III).—On being refluxed with hydroxylamine hydrochloride (9 g.) and sodium acetate (10 g.) on the steam-bath for 4 hours, a solution of 6-hydroxy-2-*iso*propyl-3-coumaranone (20 g.) (Robertson and co-workers, *loc. cit.*) in alcohol (200 c.c.) gave the *oxime* (I), which separated from dilute alcohol in colourless needles (19·5 g.), m. p. 165—166° (Found: N, 7·0. $C_{11}H_{13}O_3N$ requires N, 6·8%). Sodium amalgam (650 g., containing 2½% of sodium) was added gradually in the course of 3 hours to a solution of the oxime (13 g.) in a mixture of absolute alcohol (150 c.c.) and acetic acid (60 c.c.) at 0°; after 1 hour a further quantity of acetic acid was added. After separation of the mercury the greater part of the alcohol was distilled in a vacuum, the residue neutralised with sodium bicarbonate and extracted with ether, and the brown resinous product left on evaporation of the solvent repeatedly extracted with light petroleum (b. p. 80—100°). The volume of the combined extracts was reduced to about 100 c.c. and, after having been filtered to remove a small amount of a brown semi-solid which had separated, the solution was diluted with an equal volume of ether and extracted several times with 4% aqueous sodium hydroxide. Acidification of the combined alkaline extracts with acetic acid gave a light brown precipitate, from which 6-*hydroxy*-2-iso*propylcoumarone* was isolated by sublimation in a high vacuum at 110—120°/2 mm.; it formed colourless prisms (1·6 g.), m. p. 75—76°, from light petroleum (b. p. 60—80°) (Found: C, 75·3; H, 7·2. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). In a similar manner a further quantity (0·2 g.) of the coumarone was obtained from the brown product which separated from the concentrated light petroleum extracts. On being warmed, the yellow solution of this substance in concentrated sulphuric acid became red.

A diminished yield of the coumarone resulted when the reduction was carried out at 40—50°.

6-*Hydroxy*-2-iso*propylcoumaran* (IV).—Hydrogenation of the foregoing coumarone (1 g.), dissolved in ethyl acetate (100 c.c.), with hydrogen (approx. 1 mol. absorbed) at atmospheric pressure and a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) in the course of 1½ hours gave rise to the *dihydro*-derivative, which formed colourless prisms (0·6 g.), m. p. 79—80°, from light petroleum (b. p. 60—80°) (Found: C, 74·0; H, 7·7. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%).

6-*Hydroxy*-5-*acetyl*-2-iso*propylcoumaran* (*Tetrahydroeuparin*) (V).—The condensation of the foregoing compound (1 g.) and excess of acetonitrile in ether (50 c.c.) was effected with zinc chloride (2 g.) and excess of hydrogen chloride in the course of 3 days. After the addition of more ether (200 c.c.) the solvent was decanted, the residual brown oil was washed with ether and heated with water (50 c.c.) on the steam-bath for 20 minutes, and next day the resulting tetrahydroeuparin was collected, washed, and crystallised from light petroleum (b. p. 60—80°), forming rhombic prisms, m. p. 70—71°, identical in every way with a natural specimen (Found: C, 71·0; H, 7·3. Calc. for $C_{13}H_{16}O_3$: C, 70·9; H, 7·3%). The 2:4-dinitrophenylhydrazone separated from benzene in scarlet prisms, m. p. 240—241°, alone or mixed with the natural derivative (Found: N, 14·3. Calc. for $C_{19}H_{20}O_6N_4$: N, 14·0%).

6-*Hydroxy*-7-*acetyl*-2-iso*propylcoumaran* (VI).—A solution of the acetate of 6-hydroxy-2-*iso*propylcoumaran (0·9 g.), m. p. 47—48° (prepared by means of pyridine and acetic anhydride) in nitrobenzene (10 c.c.) containing aluminium chloride (1·4 g.) was kept for 24 hours and then treated with ice-water and dilute hydrochloric acid. The nitrobenzene was removed from an ethereal extract of the reaction mixture with steam and on isolation with ether the ketone (0·4 g.) was purified by means of 5% aqueous sodium hydroxide and then by crystallisation from light petroleum, forming colourless needles, m. p. 115—116°, which gave a red-brown ferric reaction in alcohol and a 2 : 4-*dinitrophenylhydrazone*, separating in dark orange needles, m. p. 295—297°, from much alcohol (Found : N, 14·3. $C_{19}H_{20}O_6N_4$ requires N, 14·0%).

6-*Hydroxy*-2-n-*propyl*-3-*coumaranone*.—In view of the poor yield of (III) obtained from (I) we investigated the conversion of 6-hydroxy-2-*n*-propyl-3-coumaranone into the corresponding 6-hydroxy-2-*n*-propylcoumarone by the same procedure.

α-Bromo-*n*-valeryl chloride (30 g.) was gradually added to a cooled solution of resorcinol (20 g.) and aluminium chloride (26 g.) in nitrobenzene (335 c.c.) and next day the mixture was heated at 70° for 2 hours. After the addition of ice and dilute hydrochloric acid the product mixed with nitrobenzene was isolated with ether, the nitrobenzene removed with steam, a solution of the residual dark oil in ether extracted several times with 4% aqueous sodium hydroxide, and the combined extracts acidified with acetic acid. The product thus precipitated was repeatedly extracted with much boiling water and on being kept for 7 days the combined extracts deposited the *coumaranone* in colourless prisms (5·4 g.). Recrystallised from benzene, this substance formed rhombic prisms, m. p. 108—109°, having a negative ferric reaction (Found : C, 68·9; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·3%).

Oximation of this coumaranone (10 g.) gave rise to a colourless oily product (10 g.) which did not solidify and was reduced with sodium amalgam according to the method employed in the case of the oxime of 6-hydroxy-2-*iso*propyl-3-coumaranone, yielding a resinous brown oil. From the latter material boiling light petroleum extracted a small amount of a light brown oil, which appeared to consist mainly of 6-hydroxy-2-*n*-propylcoumarone. This product, which gave a red coloration with warm concentrated sulphuric acid, formed a p-*nitrobenzoate*, m. p. 61—62° after purification from alcohol (Found : N, 4·4. $C_{18}H_{15}O_5N$ requires N, 4·3%). Lack of material prevented further examination of the coumarone.

6-*Hydroxy*-5-*acetoacetyl*-2-iso*propylcoumaran*.—To a solution of tetrahydroeuparin (1 g.) in ethyl acetate (2 c.c.), sodium (0·5 g., in small pieces) was gradually added and when the initial reaction had ceased the mixture was heated on the steam-bath for 6 hours; after 4 hours more sodium (0·1 g.) and ethyl acetate (1 c.c.) were added. A little alcohol was then added to dissolve traces of unchanged sodium, and the cooled reaction mixture treated with ice-water and acidified with acetic acid. Next day the resulting *diketone* (0·8 g.) was collected, triturated with a little ethyl acetate, and then crystallised from light petroleum (b. p. 80—100°), forming colourless prisms, m. p. 109—110°, soluble in benzene and alcohol and giving a dark brown ferric reaction in alcohol (Found : C, 68·9; H, 6·8. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

2-*Methyl*-2′-iso*propyl*-2′ : 3′-*dihydrofuro*(4′ : 5′ : 6 : 7)*chromone* (XI) was formed by cyclisation of the foregoing diketone (0·2 g.) with boiling acetic acid (5 c.c.), containing 3 drops of concentrated hydrochloric acid, in the course of 3 minutes and was precipitated (m. p. 114—118°) by the addition of water to the reaction mixture. Recrystallised from light petroleum, it formed colourless needles, m. p. 119—120°, soluble in benzene and alcohol and giving in concentrated sulphuric acid a colourless solution which exhibited a blue fluorescence (Found : C, 73·6; H, 6·4. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%).

2-*Methyl*-2′-iso*propenylfuro*(4′ : 5′ : 6 : 7)*chromone* (X).—Interaction of euparin (0·8 g.), ethyl acetate (5 c.c.), and sodium (0·4 g.) on the steam-bath for 5 hours gave rise to 6-*hydroxy*-5-*acetoacetyl*-2-iso*propenylcoumarone* (IX) (0·65 g.), which separated from alcohol in yellow prisms, m. p. 139—140°, readily soluble in ethyl acetate or benzene and having a red-brown ferric reaction (Found : C, 70·0; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%). Cyclisation of this diketone (0·3 g.) by boiling acetic acid (10 c.c.) containing 3 drops of concentrated hydrochloric acid during 2 minutes gave rise to the *furochromone* (X) (0·26 g.), which formed stellate aggregates of slender needles, m. p. 220°, from alcohol (Found : C, 74·8; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The colourless solutions of the compound in alcohol and in sulphuric acid exhibited a faint purple fluorescence.

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