Usnic Acid. Part XI. A Synthesis of 7-Acetyl-4 : 6-dihydroxy-3 : 5-dimethylcoumaran-2-one.*

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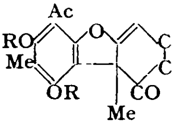
7-Acetyl-4 : 6-dihydroxy-3 : 5-dimethylcoumaran-2-one (II; R = H), identical with the ozonolysis product from usnic acid (Schöpf and Ross, *Annalen*, 1941, **546**, 1), has been synthesised from methyl 4 : 6-dimethoxy-3 : 7-dimethylcoumarilate.

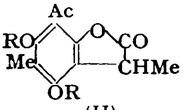
In exploratory experiments dihydropyran was found to react at the 6-position of 5 : 7-dihydroxy-4 : 8-dimethylcoumarin and did not form the expected ether.

Phloroglucinol trimethyl ether and *C*-methylphloracetophenone respectively condense with ethyl α-chloro-α-ethoxyacetate to give only diphenylacetates with the simultaneous elimination of alcohol and hydrogen chloride.

The observation by Schöpf and Ross (*Annalen*, 1941, **546**, 1) that ozonolysis of di-*O*-acetylusnic acid (I; R = Ac) gives rise to the lactone (II; R = Ac) serves to substantiate the structure (I; R = H) for usnic acid proposed by Curd and Robertson (*J.*, 1937, 894). Whilst the mode of formation and the properties of the diacetate (II; R = Ac) described by Schöpf and Ross (*loc. cit.*), Asahina and Okazaki (*J. Pharm. Soc. Japan*, 1943, **63**, 618), and Barton and Bruun (*J.*, 1953, 603) place its constitution beyond doubt, a synthesis of this compound has not hitherto been described. The dihydric phenol formed by deacetylation of this diacetate (II; R = Ac) was considered by the German authors to be the rearranged product (III; R = H) rather than the direct product (II; R = H) because on reacetylation it furnished a diacetate different from the original. Asahina and Okazaki (*loc. cit.*), however, showed that the compounds were dimorphic and hence the phenol (II; R = H) is apparently formed preferentially to its isomer (III; R = H) when the acid (IV) lactonises.



(I)



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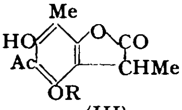

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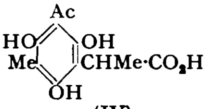

(IV)

Although slow in boiling alcohol or toluene, the formation of the hydrazide (V; R = NH·NH$_2$) from methyl 4 : 6-dimethoxy-3 : 7-dimethylcourmarilate (V; R = OMe) was rapid in hot Carbitol (diethylene glycol monomethyl ether). This hydrazide was converted by the Curtius method into the urethane (VI) for which the alternative structure (VII) is also possible. In support of formula (VI) the infrared spectrum of the compound showed absorption at 3360 cm.$^{-1}$, characteristic of amidic :NH group. On vigorous alkaline hydrolysis or selective dealkylation with hydriodic acid this comparatively stable urethane gave 4 : 6-dimethoxy-3 : 7-dimethylcoumaran-2-one (VIII) exhibiting the strong absorption at 1802 cm.$^{-1}$, typical of βγ-unsaturated five-membered lactones; the corresponding hydroxy-acid was not isolated.

C-Acetylation of the lactone (VIII) with acetic anhydride and boron trifluoride gave a lactone which had the properties of an *o*-hydroxy-ketone, showing that monodemethylation had occurred (cf. Part VIII, *J.*, 1953, 1241) but it was not obvious which methoxyl group had survived. In keeping with the fact that it is not identical with the phenol (X; R = Me) formed by the partial methylation of the phenol (II; R = H) and is not isomerised on hydrolysis this lactone is provisionally regarded as having formula (III; R = Me). The other possible structure (IX) for this compound might be expected to permit the isomerisation in view of the tendency of the acid (IV) to regenerate the phenol (II; R = H)

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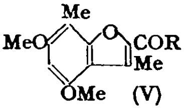
* Part X, *J.*, 1954, 4565.

under similar conditions (cf. Asahina and Okazaki, *loc. cit.*). With the common demethylating agents, *e.g.*, hydriodic and hydrobromic acid or aluminium chloride, the lactone (III; R = Me) was completely destroyed but on being heated with magnesium iodide (cf. Schönberg and Sina, *J. Amer. Chem. Soc.*, 1950, **72**, 3396) it gave a small yield of a demethylation product which was identical with the lactone (II; R = H) from usnic acid,


(V)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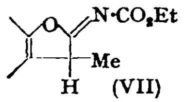
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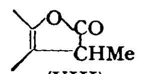
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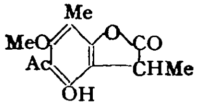
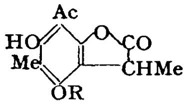
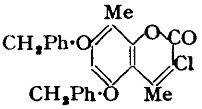
(IX)



(X)

having the same infrared absorption spectrum. As the method employed to isolate the synthetic lactone (II; R = H) was of a hydrolytic nature this would clearly allow the formation of the acid (IV) and consequently the production of the lactone (II; R = H).

Acetylation of the natural or the synthetic lactone (II; R = H) by the method of Schöpf and Ross (*loc. cit.*) gave only the monoacetate (X; R = Ac) and not the expected diacetate (II; R = Ac), a result which seems to be due to the ease with which the diacetate is partially hydrolysed in the isolation process. Shibata, Asahina, and Takahaski (*J. Pharm. Soc. Japan*, 1952, **72**, 255) obtained this monoacetate * by pyrolysis of (+)-diacetyldihydrousnic acid and identified it with the product formed by the partial deacetylation of the diacetate (II; R = Ac).

In attempts to avoid the unsatisfactory demethylation process other routes to the phenol (II; R = H) were explored which, however, did not appear promising. With sodium hydroxide the dibenzyl ether (XI) gave 4 : 6-dibenzyloxy-3 : 7-dimethylcoumarilic acid (XII; R = OH). The hydrazide (XII; R = NH·NH$_2$) was obtained from the methyl ester (XII; R = OMe) of this acid, and on treatment with nitrous acid and then with the appropriate alcohol furnished the urethanes (XIII; R = Et) and (XIII; R = CH$_2$Ph) which on attempted hydrolysis gave only resins.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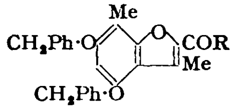
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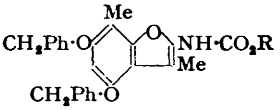
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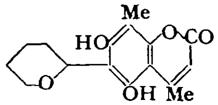


(XV)

The formation of 2-tetrahydropyranyl ethers has been employed by Parker and Anderson (*J. Amer. Chem. Soc.*, 1948, **70**, 4187) and Geissman (*ibid.*, 1951, **73**, 3514) (cf. Woods and Kramer, *ibid.*, 1947, **69**, 2246) for the protection of phenolic hydroxyl groups but under the conditions described 5 : 7-dihydroxy-4 : 8-dimethylcoumarin failed to react with dihyropyran. With more drastic conditions a phenolic adduct was obtained which, since it did not react with diazonium salts and formed a dimethyl ether stable to acid hydrolysis, is considered to have the formula (XIV). This type of addition to dihydropyran does not appear to have been observed previously but may be regarded as an extension of the well-established Friedel–Crafts reaction with simpler olefins here facilitated by the strongly anionoid nature of the phloroglucinol residue. Because the active intermediate is presumably (XV) the 2- rather than the 3-position of the pyran system is believed to be involved.

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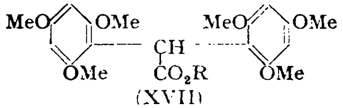
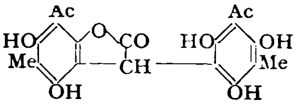
* The Japanese authors attribute the isolation of this monoacetate to Schöpf and Ross (*loc. cit.*) who, however, do not refer to it in their communication.

Quelet and Gavarret (*Compt. rend.*, 1950, **250**, 394) have shown that the interaction of ethyl α-chloro-α-ethoxyacetate (XVI; R = H) and the methyl ethers of phenols gives the α-chloro-α-arylacetates, Ar·CHCl·CO_2Et, along with small amounts of diarylacetates, Ar_2CH·CO_2Et, by a secondary reaction. Hydrogenolysis of the chloro-esters Ar·CHCl·CO_2Et furnished good yields of the corresponding arylacetates and accordingly a synthesis of the phenol (II; R = H) from *C*-methylphloracetophenone and ethyl α-chloro-α-ethoxyacetate (XVI; R = H) in two steps was envisaged. With phloroglucinol derivatives, however, the secondary reaction (formation of diarylacetates) supervened. Thus in acetic acid, ethyl chloroethoxyacetate and phloroglucinol trimethyl ether gave only ethyl di-(2 : 4 : 6-trimethoxyphenyl)acetate (XVII; R = Et) whereas in methanol a slower reaction was accompanied by trans-esterification, giving the analogous ester (XVII; R = Me). In ether, in which the condensation was very slow, the required product, Ar·CHCl·CO_2Et, was not obtained even when the reaction was interrupted whilst much unchanged phloroglucinol trimethyl ether was still present. With *C*-methylphloracetophenone and the ester (XVI; R = H) a diaryl derivative was obtained which was devoid of a methoxyl group and formed a penta-acetate. This compound is considered to have a structure of type (XVIII), where the orientation of the lactone system conforms with the behaviour of the simpler diphenol (II; R = H). Phloroglucinol triacetate and the ester (XVI; R = H) did not react at room temperature and on being heated gave a resin.

EtO·CRCl·CO_2Et
(XVI)



(XVII)



(XVIII)

EXPERIMENTAL

2-Ethoxycarbonylamino-4 : 6-dimethoxy-3 : 7-dimethylcoumarone (VI).—A mixture of methyl 4 : 6-dimethoxy-3 : 7-dimethylcoumarilate (Part X, *J.*, 1954, 4565) (1 g.), 90% hydrazine hydrate (1·5 ml.), and Carbitol (10 ml.) was heated under reflux for 1 hr., cooled, and diluted with water (50 ml.). The resulting *hydrazide* (V; R = NH·NH_2) crystallised from alcohol in needles (1·7 g.), m. p. 208—210°, which reduced Fehling's solution [Found : N, 10·7; OMe, 24·0. $C_{11}H_{10}O_2N_2(OMe)_2$ requires N, 10·6; OMe, 23·5%]. A solution of sodium nitrite (1·5 g.) in water (5 ml.) was added dropwise to a well-stirred mixture of this hydrazide (5·3 g.) in acetic acid (80 ml.) and the fawn azide, which began to separate immediately, was collected 2 hr. later, washed, dried, and heated in boiling alcohol (50 ml.) for 2 hr. The resulting hot solution was treated with charcoal, filtered, cooled, and diluted with water, giving *2-ethoxycarbonylamino-4 : 6-dimethoxy-3 : 7-dimethylcoumarone* (VI) which separated from alcohol or benzene in colourless needles (4 g.), m. p. 150—151° (Found : C, 61·0; H, 6·6; N, 5·0. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·6; N, 4·8%).

4 : 6-Dimethoxy-3 : 7-dimethylcoumaran-2-one (VIII).—(*A*) A solution of the aforementioned urethane (VI) (1 g.) in a mixture of acetic acid (20 ml.) and hydriodic acid (10 ml.; *d* 1·7) was boiled for 1·5 hr. On cooling, the mixture deposited a crystalline solid (0·5 g.) which on purification from alcohol gave *4 : 6-dimethoxy-3 : 7-dimethylcoumaran-2-one* in prisms, m. p. 125° [Found : C, 64·6; H, 6·3; OMe, 27·9. $C_{10}H_8O_2(OMe)_2$ requires C, 64·9; H, 6·4; OMe, 27·9%]. This compound, which was insoluble in cold aqueous 2N-sodium hydroxide, dissolved in the hot reagent and the solution gave an intense blue colour with Gibbs's reagent.

(*B*) On being heated with potassium hydroxide (0·8 g.) in boiling Carbitol (40 ml.) the urethane (VI) rapidly liberated ammonia and 10 min. later the mixture was cooled, diluted with water (200 ml.), and acidified with concentrated hydrochloric acid. The resulting precipitate of coumaran-2-one (VIII) crystallised from acetic acid in prisms (0·5 g.), m. p. and mixed m. p. 125°.

5-Acetyl-6-hydroxy-4-methoxy-3 : 7-dimethylcoumaran-2-one (III; R = Me).—A rapid stream of boron trifluoride (from 40 g. of potassium fluoroborate) was led into a solution of 4 : 6-dimethoxy-3 : 7-dimethylcoumaran-2-one (1 g.) in acetic acid (10 ml.) containing acetic anhydride (10 ml.). After 40 min. the addition of water (200 ml.) to the cooled mixture precipitated a sticky yellow mass which was dissolved in ether. This solution was washed with much water and on evaporation gave 5-*acetyl*-4-*methoxy*-6-*hydroxy*-3 : 7-*dimethylcoumaran*-2-*one* which formed pale yellow prisms (0·4 g.), m. p. 127°, from alcohol, with a dark violet ferric reaction; the yellow solution of the coumaran-2-one in aqueous sodium hydroxide gave a negative Gibbs's reaction (Found: C, 62·3; H, 5·6; OMe, 12·6. $C_{12}H_{11}O_4{\cdot}OMe$ requires C, 62·4; H, 5·6; OMe, 12·4%). This compound was not affected by aqueous N-sodium hydroxide at 90° for 1·5 hr.

7-*Acetyl*-6-*hydroxy*-4-*methoxy*-3 : 5-*dimethylcoumaran*-2-*one* (X; R = Me).—7-Acetyl-4 : 6-dihydroxy-3 : 5-dimethylcoumaran-2-one (Schöpf and Ross, *loc. cit.*) (0·2 g.) was heated with methyl iodide (0·1 ml.) and potassium carbonate (0·5 g.) in boiling acetone (50 ml.) for 4 hr. On isolation the resulting 7-*acetyl*-6-*hydroxy*-4-*methoxy*-3 : 5-*dimethylcoumaran*-2-*one* separated from methanol in prisms, m. p. 178°, with a greenish-red ferric reaction in dilute alcohol (Found: C, 62·2; H, 5·4; OMe, 12·0. $C_{12}H_{11}O_4{\cdot}OMe$ requires C, 62·4; H, 5·6; OMe, 12·4%).

7-*Acetyl*-4 : 6-*dihydroxy*-3 : 5-*dimethylcoumaran*-2-*one* (II; R = H).—A solution of 5-acetyl-6-hydroxy-4-methoxy-3 : 7-dimethylcoumaran-2-one (0·2 g.) in benzene, containing magnesium iodide (0·5 g.), was evaporated and the residue kept at 180° for 40 min. The red mass was extracted several times with hot dilute sulphuric acid and, on cooling, the extracts deposited the crude coumaranone (II; R = H); a further quantity was isolated from the residual red resin with methanol. From methanol, 7-acetyl-4 : 6-dihydroxy-3 : 5-dimethylcoumaran-2-one formed pinkish prisms (*ca.* 10 mg.), m. p. 212°, undepressed on admixture with a natural specimen (Schöpf and Ross, *loc. cit.*) and having a dark blue ferric reaction. Acetylation of this coumaran-2-one (synthetic or natural) by the method of Schöpf and Ross (*loc. cit.*) gave 4-acetoxy-7-acetyl-6-hydroxy-3 : 5-dimethylcoumaran-2-one which separated from methanol in pale yellow needles, m. p. 189—190° having a greenish-red ferric reaction and giving a yellow solution with dilute aqueous sodium hydroxide (Found: C, 60·4; H, 5·2. Calc. for $C_{14}H_{14}O_6$: C, 60·4; H, 5·0%).

Methyl 5 : 7-*Dibenzyloxy*-3 : 7-*dimethylcoumarilate* (XII; R = OMe).—3-Chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (Part X, *loc. cit.*) was dried in a vacuum at 150° for 4 hr. and then heated with benzyl bromide (7 g.) and potassium carbonate (6 g.) in boiling acetone (150 ml.) for 10 hr. The resulting 5 : 7-*dibenzyloxy*-3-*chloro*-4 : 8-*dimethylcoumarin* (XI) crystallised from alcohol in prisms (7 g.), m. p. 220—221° (Found: C, 71·4; H, 4·9; Cl, 8·6. $C_{25}H_{21}O_4Cl$ requires C, 71·3; H, 5·0; Cl, 8·4%).

On being heated with potassium hydroxide (1·2 g.) in boiling Carbitol (30 ml.) for 5 min. this coumarin (4 g.) was converted into the *hydrate* of 4 : 6-dibenzyloxy-3 : 7-dimethylcoumarilic acid (XII; R = OH) which was precipitated from the cooled hydrolysate by hydrochloric acid and purified from dioxan, forming diamond-shaped plates (3 g.), m. p. 210° (decomp.), with a deep red sulphuric acid (warm) reaction (Found: C, 71·4; H, 6·0. $C_{25}H_{22}O_5,H_2O$ requires C, 71·4; H, 6·2%). Formed by use of diazomethane, the *methyl ester* (XII; R = OMe) separated from methanol in prisms, m. p. 116—118° (Found: C, 75·6; H, 6·2; OMe, 7·8. $C_{25}H_{21}O_4{\cdot}OMe$ requires C, 75·0; H, 5·8; OMe, 7·5%).

4 : 6-*Dibenzyloxy*-2-*ethoxycarbonylamino*-3 : 7-*dimethylcoumarone* (XIII; R = Et).—On being heated in boiling Carbitol (100 ml.) with 90% hydrazine hydrate (6 ml.) for 2 hr. methyl 4 : 6-dibenzyloxy-3 : 7-dimethylcoumarilate (13 g.) gave the *hydrazide* (XII; R = NH·NH$_2$) which separated from alcohol in long prisms (12 g.), m. p. 170°, darkening on exposure to light (Found: N, 6·7. $C_{25}H_{24}O_4N_2$ requires N, 6·7%). Treatment of this hydrazide (4 g.) in acetic acid (70 ml.) with sodium nitrite (0·7 g.) in water (10 ml.) gave the azide which was washed and air-dried. This azide (2 g.) was decomposed with boiling alcohol (15 ml.), the resulting hot solution was treated with charcoal and evaporated, and the residue was chromatographed from benzene on aluminium oxide, giving 4 : 6-*dibenzyloxy*-2-*ethoxycarbonylamino*-3 : 7-*dimethylcoumarone* which formed needles (0·9 g.), m. p. 144°, from alcohol (Found: N, 3·0; OEt, 11·1. $C_{25}H_{22}O_4N{\cdot}OEt$ requires N, 3·2; OEt, 11·1%).

The crude azide (4 g.) was gently heated with benzyl alcohol (1·1 g.) in toluene (40 ml.) to maintain a steady effervescence and when this had ceased the mixture was boiled for 2 hr., filtered, and evaporated in a vacuum. Crystallised from alcohol, the residue gave the *urethane* (XIII; R = CH$_2$Ph) in prisms (2·9 g.), which melted at 136° and then on solidification had m. p. 144° (Found: C, 76·0; H, 5·6; N, 3·3. $C_{33}H_{29}O_5N$ requires C, 75·7; H, 5·7; N, 2·8%).

5 : 7-*Dihydroxy*-4 : 8-*dimethyl*-6-2′-*tetrahydropyranylcoumarin* (XIV).—A mixture of 5 : 7-dihydroxy-4 : 8-dimethylcoumarin (Part X, *loc. cit.*) (1·0 g.), dihydropyran (1·4 ml.), and chloroform (8 ml.), containing a trace of sulphuric acid, was kept for 5 days. The grey solid was collected, washed with alcohol, and crystallised from dioxan, giving the *coumarin* (XIV) in colourless prisms (0·3 g.), m. p. 222° (decomp), which formed a yellow solution in aqueous sodium

hydroxide, unchanged on the addition of diazotised sulphanilic acid (Found: C, 66·0; H, 6·6. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%). The ***dimethyl ether***, formed by the methyl iodide–potassium carbonate method, had m. p. 150—151° [Found: C, 68·2; H, 7·1; OMe, 18·9%; *M* (Rast), 333. $C_{16}H_{16}O_3(OMe)_2$ requires C, 67·9; H, 7·0; OMe, 19·5%; *M*, 318]. On being boiled with a mixture of alcohol (5 ml.) and 4N-hydrochloric acid (5 ml.) for 1 hr. this dimethyl ether was recovered unchanged.

Ethyl Di-(2 : 4 : 6-*trimethoxyphenyl*)*acetate* (XVII; R = Et).—A mixture of ethyl α-chloro-α-ethoxyacetate (2 g.), phloroglucinol trimethyl ether (2 g.), and acetic acid (10 ml.) was kept at 100° for 12 hr.; hydrogen chloride was evolved and the solution became pink. Precipitation with water and purification from alcohol gave ***ethyl di***-(2 : 4 : 6-***trimethoxyphenyl***)-***acetate*** in irregular prisms (1·1 g.), m. p. 158—159·5°, with a negative test for halogen (Found: C, 62·8; H, 6·8. $C_{22}H_{28}O_8$ requires C, 62·9; H, 6·7%).

When the aforementioned mixture was kept at room temperature reaction did not take place but boiling it for 16 hr. gave a product, which was precipitated with water and contained the acetate (XVII; R = Et) (0·2 g.).

Interaction of phloroglucinol trimethyl ether (2 g.) and ethyl α-chloro-α-ethoxyacetate (2 g.) in boiling methanol for 16 hr. gave ***methyl di***-(2 : 4 : 6-***trimethoxyphenyl***)***acetate*** (XVII; R = Me) which separated from light petroleum (b. p. 60—80°) in irregular prisms (1·3 g.), m. p. 147—148° [Found: C, 62·0; H, 6·5; OMe, 53·0. $C_{18}H_{17}O_5(OMe)_3$ requires C, 62·1; H, 6·5; OMe, 53·4%].

7-*Acetyl*-4 : 6-*dihydroxy*-5-*methyl*-3-(3-*acetyl*-2 : 4 : 6-*trihydroxy*-5-*methylphenyl*)-*coumar*-2-*one* (XVIII).—On being kept at room temperature for 5 hr. a mixture of *C*-methylphloracetophenone (1·8 g.), ethyl α-chloro-α-ethoxyacetate (1·5 g.), and acetic acid (10 ml.) deposited a yellow solid which could not be recrystallised but which on being washed with ether and triturated with warm alcohol gave the ***hydrate*** of (XVIII) in fawn-yellow hexagonal prisms (0·9 g.), m. p. 262° (decomp.) (Found: C, 57·3; H, 4·9. $C_{20}H_{18}O_9,H_2O$ requires C, 57·1; H, 4·8%). This compound gives a dark purple ferric reaction and forms a yellow solution in dilute sodium hydroxide solution. The ***penta-acetate***, prepared by acetic anhydride–pyridine, formed prisms, m. p. 233° (decomp.), from dilute acetic acid (Found: C, 59·0; H, 4·5. $C_{30}H_{28}O_{14}$ requires C, 58·8; H, 4·6%).

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