195. *Furano-compounds. Part II.*

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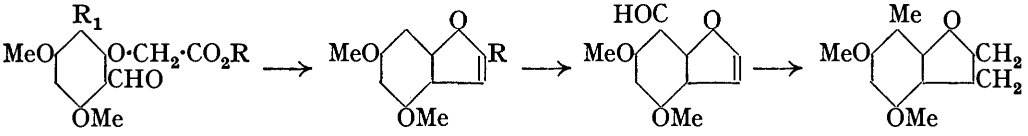
Application of the Gattermann reaction to (II, R = H) gave rise to a poor yield of (III) along with much amorphous material, but when the α-position was occupied by a carbethoxyl group as in (II, R = CO_2Et) an excellent yield of (V) was obtained. The orientation of (III) was established by its conversion into (IV), a specimen of which was prepared by an unambiguous method from (I; R = Et, R_1 = Me). In the course of this work it has been observed also that the presence of the carbethoxy-group in the α-position (*e.g.*, as in VI, R = CO_2Et) inhibits hydrogenation of the coumarone to the coumaran by a palladium catalyst.

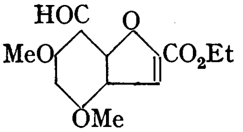
THE synthesis of *O*-dimethylpyrousnic acid followed upon the discovery that application of the Gattermann reaction to β-methylcoumarones, *e.g.*, 4 : 6-dimethoxy-3-methyl- and 4 : 6-dimethoxy-3 : 5-dimethyl-coumarone, gave rise to the α-formyl derivatives (Birch and Robertson, J., 1938, 306), and in the course of experiments which were primarily undertaken during exploratory work on the rational synthesis of furocoumarins of the bergapten type it seemed of interest to investigate the application of this reaction to an analogous coumarone unsubstituted in the αβ-positions.

Prepared by cyclisation of 3 : *5-dimethoxy-2-formylphenoxyacetic acid* (I; R = H, R_1 = H) and simultaneous decarboxylation of the resulting acid (II, R = CO_2H) with boiling acetic anhydride and sodium acetate according to the general method, 4 : *6-dimethoxycoumarone* (II, R = H) gave by Gattermann's procedure an amorphous product, from which only a small yield of the *formylcoumarone* (III) was isolated. Although the expected α-formyl derivative (II, R = CHO) could not be prepared by this procedure, it may well be, since unchanged coumarone (II, R = H) could not be isolated from the reaction mixture, that polymerisation and resinification accompanied the formation of the α-aldimine or its subsequent hydrolysis (compare the behaviour of thiophen; Barger and Easson, J., 1938, 2100). In the course of unsuccessful attempts to discover the conditions essential to the preparation of (II, R = CHO) it was found that the use of zinc chloride (added as zinc cyanide) as an auxiliary condensing agent in the Gattermann reaction gave rise to intractable products.

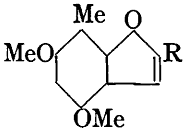
The orientation of the aldehyde (III) was established by the fact that on catalytic hydrogenation with the aid of a palladium–charcoal catalyst, involving simultaneous reduction of the formyl group and saturation of the αβ-double bond, it gave rise to the *coumaran* (IV) identical with an authentic specimen. In the synthesis of the latter, cyclisation of the *formylphenoxyacetic ester* (I; R = Et, R_1 = Me) with alcoholic sodium ethoxide furnished the *carbethoxycoumarone* (VI, R = CO_2Et), which on hydrolysis and subsequent decarboxylation of the resulting *acid* (VI, R = CO_2H) yielded the coumarone (VI, R = H). Hydrogenation of the last substance gave a quantitative yield of (IV), and the isomeric 4 : 6-*dimethoxy*-3-*methylcoumaran* (VIII) was obtained from 4 : 6-dimethoxy-3-methylcoumarone by the same method.



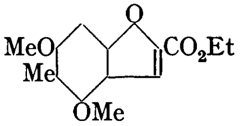
(I.) (II.) (III.) (IV.)



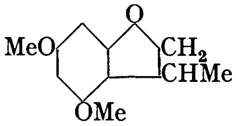
(V.)



(VI.)



(VII.)



(VIII.)

In view of the results obtaining when the Gattermann reaction is applied to (II, R = H) and to coumarones having an alkyl group in the β-position (Birch and Robertson, *loc. cit.*) it seemed of interest to investigate the behaviour of an α-substituted coumarone of the type (II) and, since α-alkylcoumarones, *e.g.*, (II, R = Me), are not readily accessible, we employed the α-*carbethoxy*-derivative (II, R = CO_2Et). By Gattermann's procedure with the aid of aluminium chloride an excellent yield of the *ethyl* 4 : 6-*dimethoxy*-7-*formylcoumarone*-2-*carboxylate* (V) was obtained (the use of zinc chloride gave a considerably smaller yield along with unchanged material), the orientation of which was conclusively established by the fact that on catalytic reduction it gave rise to (VI, R = CO_2Et). In the course of the identification of this reduction product the *isomeride* (VII) was synthesised from 2-hydroxy-4 : 6-dimethoxy-5-methylbenzaldehyde by the method employed for (II, R = CO_2Et).

On the basis of these results it seems clear that the carbethoxy-group in the α-position can be used to protect the furano-residue in the application of the Gattermann reaction to the synthesis of aldehydo-coumarones having the formyl group in the benzene nucleus and, further, it seems reasonable to expect that, in general, replacement of the carbethoxy-group with alkyl groups would yield similar results. Moreover, in the reduction of (V) to (VI, R = CO_2Et), the presence of the carbethoxy-group in the α-position appears to inhibit the conversion of the coumarone into the coumaran by means of hydrogen and a palladium–charcoal catalyst under the usual conditions. This inhibitory effect, which has also been observed in the course of attempts to hydrogenate (VII), ethyl 6-hydroxy-, ethyl 6-methoxy-, and ethyl 6-methoxy-3-methyl-coumarone-2-carboxylate, even when pressures of 40—42 lb./sq. in. were employed, appears to be removed when the α-carbethoxy-residue is replaced by an alkyl group, because, *e.g.*, *iso*tubanol, 6-hydroxy-2-*iso*propylcoumarone (unpublished work), and usnetol (Schöpf and Heuck, *Annalen*, 1927, **459**, 233; Curd and Robertson, J., 1933, 1173) can be hydrogenated under these conditions, giving rise to the corresponding coumarans.

In their experiments on catechin Dean and Nierenstein (*J. Amer. Chem. Soc.*, 1924,

46, 2798) claim to have prepared 4 : 6-dimethoxycoumaran, m. p. 109°, by heating the hydrazone of 4 : 6-dimethoxy-3-coumaranone with sodium ethoxide at 160°, but their product is not identical with the coumaran, m. p. 52°, prepared in the course of the present work by hydrogenation of 4 : 6-dimethoxycoumarone under conditions which do not reduce the benzene residue. These authors state that, when suspended in concentrated sulphuric acid, their substance and a number of its derivatives gave a violet coloration on the addition of ferric chloride, a reaction which was extensively employed by Kostanecki and his co-workers (*Ber.*, 1908, **41**, 1330; 1909, **42**, 901, 911) to characterise coumarones. 4 : 6-Dimethoxycoumaran and its analogues, (IV) and (VIII), do not give this reaction and when warmed with concentrated sulphuric acid do not give the bright colorations which are characteristic of coumarones. On the other hand all the coumarone derivatives described in this communication give colorations by Kostanecki's procedure which are identical or almost identical with those given when the substances are warmed with sulphuric acid.

EXPERIMENTAL.

3 : 5-*Dimethoxy-2-formylphenoxyacetic Acid* (I; R = H, R_1 = H).—Interaction of *O*-dimethylphloroglucinolaldehyde (3 g.) and ethyl bromoacetate (3 g.) in boiling acetone (30 c.c.), containing potassium carbonate (5 g.), during 3 hours gave rise to the *ethyl* ester, which formed colourless rectangular prisms (3·6 g.), m. p. 105°, from ethyl acetate, having a negative ferric reaction (Found: C, 58·3; H, 6·0. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* of this substance separated from alcohol or ethyl acetate in red needles, m. p. 197° (Found: N, 12·6. $C_{19}H_{20}O_9N_4$ requires N, 12·5%).

Hydrolysis of the ester (10 g.) with 4% aqueous sodium hydroxide (200 c.c.) for 10 minutes furnished the *acid*, which formed colourless needles (8 g.), m. p. 177°, from water or benzene [Found: C, 55·2; H, 5·0; OMe, 25·5. $C_9H_6O_4(OMe)_2$ requires C, 55·0; H, 5·0; OMe, 25·8%].

4 : 6-*Dimethoxycoumarone* (II, R = H).—A mixture of the foregoing acid (10 g.), acetic anhydride (100 c.c.), and sodium acetate (28 g.) was boiled for ½ hour, diluted with water and neutralised next day with sodium bicarbonate. On isolation with ether the *coumarone* was obtained as an almost colourless, mobile oil, b. p. 108—110°/0·15 mm., giving a yellow coloration with concentrated sulphuric acid which on warming or on addition of a drop of ferric chloride became brown and then purple (Found: C, 67·3; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The *picrate* separated from methyl alcohol in scarlet, elongated, rectangular prisms, m. p. 95° (Found: C, 47·3; H, 3·4; N, 10·0. $C_{10}H_{10}O_3,C_6H_3O_7N_3$ requires C, 47·2; H, 3·2; N, 10·3%).

Hydrogenation of the coumarone (1 g.), dissolved in acetic acid (25 c.c.), with hydrogen (approx. 1 mol. absorbed) and a palladium–charcoal catalyst was complete in 10 minutes. The filtered solution was neutralised with aqueous sodium bicarbonate and, after isolation with ether, 4 : 6-dimethoxycoumaran was crystallised from methyl alcohol, forming irregular prisms (0·75 g.), m. p. 52°, which sublimed unchanged in a high vacuum, were soluble in benzene alcohol, or light petroleum, and had a negative sulphuric acid reaction [Found: C, 66·6; H, 6·8; OMe, 34·1. Calc. for $C_8H_6O(OMe)_2$: C, 66·7; H, 6·7; OMe, 34·1%].

4 : 6-*Dimethoxy-7-formylcoumarone* (III).—On being saturated with hydrogen chloride, a well-cooled solution of the afore-mentioned coumarone (4 g.) in ether (100 c.c.), containing hydrogen cyanide (5 c.c.), gradually deposited a dark brown oil. Next day the solvent was decanted, and the residual oil well washed with ether and heated with water (100 c.c.) on the steam-bath for 20 minutes. Trituration of the oily product with cold water finally gave a yellow solid (3·5 g.), which did not yield crystalline material on treatment with solvents but, on being heated at 130—140°/0·1 mm., gave a small amount of the *aldehyde* as a crystalline sublimate (0·4 g.), which formed colourless rectangular plates (0·3 g.), m. p. 180°, from methyl alcohol [Found: C, 64·0; H, 5·0; OMe, 29·2; *M*, 195. $C_9H_4O_2(OMe)_2$ requires C, 64·1; H. 4·9; OMe, 29·6%; *M*, 206]. This substance, which had the typical properties of an aldehyde, was moderately soluble in benzene, alcohol, or ethyl acetate and insoluble in light petroleum.

Reduction of this aldehyde (0·5 g.), dissolved in acetic acid (50 c.c.), with hydrogen (approx. 3 mols. absorbed) and a palladium–charcoal catalyst was complete in 5 minutes and on isolation the resulting 4 : 6-dimethoxy-7-methylcoumaran (IV), m. p. 68°, crystallised from dilute alcohol in diamond-shaped plates, m. p. 73°, identical in every way with an authentic specimen.

Ethyl 4 : 6-*Dimethoxy-7-formylcoumarone-2-carboxylate* (V).—Cyclisation of ethyl 3 : 5-dimethoxy-2-formylphenoxyacetate (I; R = Et, R_1 = H) (2 g.), dissolved in alcohol (20 c.c.), with sodium ethoxide (from 0·2 g. of sodium) gave *ethyl* 4 : 6-*dimethoxycoumarone*-2-*carboxylate* (II, R = CO_2Et), which was precipitated by addition of water. Crystallised from aqueous alcohol, the ester formed needles (0·8 g.) m. p. 96·5°, soluble in benzene or ethyl acetate and giving a purple coloration, changing to ruby-red, with warm sulphuric acid (Found : C, 62·4; H, 5·6. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%).

Acidification of the alkaline liquors gave an oily product, from which a small amount of 3 : 5-dimethoxy-2-formylphenoxyacetic acid, m. p. 177°, was isolated by extraction with boiling water.

Ethyl 4 : 6-dimethoxycoumarone-2-carboxylate (3 g.) and then hydrogen cyanide (3 c.c.) were added to a solution of aluminium chloride (3 g.) in ether (100 c.c.), the mixture was saturated with hydrogen chloride, next day the solvent was decanted, and the residual pale green product (washed with ether) was heated with water (50 c.c.) on the steam-bath for ½ hour. The resulting *aldehyde* separated from alcohol in colourless rods, m. p. 201° (Found : C, 60·3; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%). On being warmed on the steam-bath, a dilute hydrochloric acid extract (50 c.c.) of the ethereal liquor yielded a further quantity of the aldehyde, m. p. 201° after purification; total yield, 3 g.

When the aluminium chloride was replaced with zinc chloride (added as zinc cyanide), 3 g. of the original ester gave 0·8 g. of aldehyde and 2 g. of unchanged material.

Reduction of this aldehyde (1 g.) with hydrogen (approx. 2 mols. absorbed) and a palladium catalyst was effected in 15 minutes, giving ethyl 4 : 6-dimethoxy-7-methylcoumarone-2-carboxylate (0·75 g.), which formed rectangular prisms, m. p. 127°, from alcohol, identical with an authentic specimen.

Ethyl 4 : 6-*Dimethoxy*-5-*methylcoumarone*-2-*carboxylate* (VII).—Prepared by the interaction of 2-hydroxy-4 : 6-dimethoxy-5-methylbenzaldehyde (Robertson and Subramaniam, J., 1937, 288) (3 g.) and ethyl bromoacetate (3 g.) in boiling acetone (40 c.c.), containing potassium carbonate (4 g.), for 2½ hours, *ethyl* 3 : 5-*dimethoxy*-2-*formyl*-4-*methylphenoxyacetate* formed rectangular prisms (3 g.), m. p. 92°, from light petroleum (b. p. 60—80°) (Found : C, 59·4 H, 6·4. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in red needles, m. p. 218° (Found : N, 12·3. $C_{20}H_{22}O_9N_4$ requires N, 12·1%).

Cyclisation of this compound (2 g.) with potassium ethoxide (from 0·32 g. of potassium in alcohol (20 c.c.) in the course of 3 minutes and subsequent dilution of the mixture with water gave a crystalline precipitate of the *coumaronecarboxylate* (VII) (1 g.). Recrystallised from alcohol, this compound formed colourless rectangular prisms, m. p. 115°, which gave a red-purple and then deep violet sulphuric acid reaction (Found : C, 63·7; H, 6·1; OAlkyl, 19·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1; OAlkyl, 18·2%).

Acidification of the alkaline liquors gave 3 : 5-*dimethoxy*-2-*formyl*-4-*methylphenoxyacetic acid*, which separated from warm water in plates, m. p. 172° (Found : C, 56·7; H, 5·5. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%).

Ethyl 4 : 6-*Dimethoxy*-7-*methylcoumarone*-2-*carboxylate* (VI, R = CO_2Et).—Absorption of hydrogen by 6-hydroxy-2 : 4-dimethoxybenzaldehyde (3 g.), dissolved in acetic acid (50 c.c.) containing a palladium–charcoal catalyst (from 4 g. of charcoal and 0·4 g. of palladium chloride), ceased in 1 hour and after evaporation of the greater part of the solvent in a vacuum and addition of water to the residue a crystalline precipitate separated. This compound, which could not be further hydrogenated with a palladium–charcoal catalyst, appeared to be s.-2 : 2′-*dihydroxy*-4 : 4′ : 6 : 6′-*tetramethoxydiphenylethane*, forming squat, rectangular prisms (0·5 g.), m. p. 218°, from alcohol or aqueous acetone (Found : C, 65·0; H, 6·5. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%). From the aqueous liquors, which had been neutralised with sodium bicarbonate, *C*-methylphloroglucinol-α-dimethyl ether (1·5 g.) was isolated with ether, m. p. 67° after purification from light petroleum, and converted into 2-hydroxy-4 : 6-dimethoxy-3-methylbenzaldehyde, m. p. 169° (Curd and Robertson, J., 1933, 442). Prepared from this compound (2 g.) by the potassium carbonate–acetone method, ethyl 3 : 5-dimethoxy-2-formyl-6-methylphenoxyacetate (1·5 g.) could not be economically purified. On being recrystallised from ethyl acetate–light petroleum, it had m. p. 137° and gave a 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate in orange-red rectangular prisms, m. p. 198° (Found : N, 12·3. $C_{20}H_{22}O_9N_4$ requires N, 12·1%).

Cyclisation of the crude phenoxy-ester (1 g.) in alcohol (13 c.c.) with potassium ethoxide (from 0·16 g. of potassium) in the course of 15 minutes furnished *ethyl* 4 : 6-*dimethoxy*-7-*methylcoumarone*-2-*carboxylate*, which separated from alcohol in rectangular prisms (0·5 g.), m. p. 127°, soluble in benzene or ethyl acetate and giving a red-violet and then blue-violet sulphuric acid reaction (Found : C, 63·7; H, 5·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

Acidification of the alkaline liquors left on separation of this ester gave 3 : 5-*dimethoxy*-2-*formyl*-6-*methylphenoxyacetic acid*, which formed clusters of needles, m. p. 163°, from warm water [Found : C, 56·6; H, 5·5; OMe, 24·6. $C_{10}H_8O_4(OMe)_2$ requires C, 56·7; H, 5·5; OMe, 24·8%].

Hydrolysis of ethyl 4 : 6-dimethoxy-7-methylcoumarone-2-carboxylate (2 g.) with 5% aqueous-alcoholic potassium hydroxide (50 c.c.) during 1 hour yielded the *acid*, which separated from alcohol in clusters of needles (1·3 g.), m. p. 242° (decomp.), giving a brown ferric reaction in alcohol [Found : C, 60·6; H, 5·0; OMe, 25·8. $C_{10}H_6O_3(OMe)_2$ requires C, 61·0; H, 5·1; OMe, 26·3%].

4 : 6-*Dimethoxy*-7-*methylcoumaran.*—4 : 6-Dimethoxy-7-methylcoumarone was prepared by decarboxylation of the aforementioned acid (1 g.) with boiling quinoline (5 c.c.) containing copper-bronze during 5 minutes and on isolation was purified by distillation in a vacuum; colourless solid, b. p. 70—71°/0·3 mm., m. p. 38°, readily soluble in all organic solvents. The *picrate* formed rectangular, chocolate-brown prisms from methyl alcohol, m. p. 110° (Found : C, 48·6; H, 3·6. $C_{11}H_{12}O_3,C_6H_3O_7N_3$ requires C, 48·5; H, 3·6%).

Hydrogenation of the coumarone (0·4 g.) in acetic acid (25 c.c.) with hydrogen (approx. 1 mol. absorbed) and a palladium–charcoal catalyst (1 g.) was complete in 5 minutes, giving rise to the *coumaran*, which separated from aqueous alcohol in diamond-shaped plates, m. p. 73°; these did not give a coloration with sulphuric acid and were readily soluble in light petroleum or benzene [Found : C, 68·1; H, 7·1; OMe, 31·9. $C_9H_8O(OMe)_2$ requires C, 68·0; H, 7·2; OMe, 32·0%]. The isomeride, 4 : 6-*dimethoxy*-3-*methylcoumaran* (VIII), was prepared by hydrogenation of 4 : 6-dimethoxy-3-methylcoumarone (*loc. cit.*) (1 g.), dissolved in acetic acid (30 c.c.) with hydrogen (1 mol. absorbed) and a palladium catalyst in the course of 10 minutes and obtained as a colourless mobile oil, b. p. 91—92°/0·05 mm., having, like the foregoing coumaran, a negative sulphuric acid reaction (Found : C, 68·0; H, 7·4; OMe, 31·7%).

In attempting to prepare 4 : 6-dimethoxy-2-methylcoumarone we obtained 4 : 6-*dimethoxy*-3-*acetoxy*-2-*methylcoumarone* by acetylation of 4 : 6-dimethoxy-2-methyl-3-coumaranone (J., 1936, 1834) (2 g.) with boiling acetic anhydride (15 c.c.) and sodium acetate (1 g.) during ½ hour, which on distillation in a vacuum formed colourless prisms, b. p. 110°/0·1 mm., m. p. 69° [Found : C, 62·5; H, 5·4; OMe, 24·8. $C_{11}H_8O_3(OMe)_2$ requires C, 62·4; H, 5·6; OMe, 24·8%], but were unable to hydrogenate this substance with a platinum oxide catalyst or in acetic acid with a palladium–charcoal catalyst. We likewise failed to reduce the parent coumaranone.

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