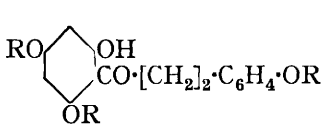
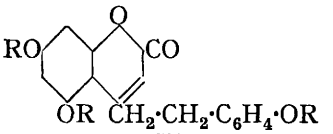
93. *Hydroxy-carbonyl Compounds. Part IX. Benzopyrones related to Phloretin.*

By Frederick E. King and Alexander Robertson.

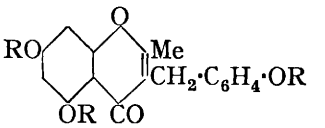
By the vigorous acetylation of phloretin (I, R = H) (Kostanecki reaction) Ciamician and Silber (*Ber.*, 1894, **27**, 1627; 1895, **28**, 1393) obtained a product (isolated as the triacetate) which they believed to be the coumarin (II, R = H). Using phloretin trimethyl ether (I, R = Me), Wesseley and Sturm (*Monatsh.*, 1929, **53**, 554) by the same procedure prepared the trimethyl ether of a benzopyrone which they found to be identical with the trimethyl ether of Ciamician and Silber's product and for which they retained the coumarin structure. The same trimethyl ether was independently described by Johnson and Robertson (J., 1930, 21), who, however, preferred the chromone structure (III, R = Me) and, although Shinoda and Sato (*J. Pharm. Soc. Japan*, 1930, **50**, 265) have shown that the general properties of Ciamician and Silber's product are those of the chromone group, it seemed clearly desirable to establish the constitution of this compound beyond doubt, if possible by an unambiguous synthesis, more especially since it has been shown in certain cases that the Kostanecki reaction gives anomalous results (Wittig, *Annalen*, 1926, **446**, 155; Heilbron and co-workers, J., 1933, 1263).



(I.)



(II.)



(III.)

A synthesis of compounds of the type (III) was originally attempted early in 1930 by the method of Simonis from phloroglucinol dimethyl ether and the appropriate ketones, but it was found that the products were coumarins, *viz.*, 5 : 7-*dimethoxy*-3-*benzyl*- and 5 : 7 : 4′-*trimethoxy*-3-*benzyl*-4-*methylcoumarin*, and not the expected chromones, and this has since been shown to be the normal type of reaction for phloroglucinol and its derivatives (Robertson *et al.*, J., 1931, 1245, 1255; Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 407). Eventually the validity of the chromone structure (III) was established by the method of Heilbron, Barnes, and Morton (J., 1923, **123**, 2559), who have shown that the 2-methyl group in chromones of this type can react with aldehydes, giving rise to styryl derivatives (compare Chakravarti, *loc. cit.*). By this means also it has been proved that the ring closure of 2 : 4-dihydroxy-β-phenylpropiophenone (Crabtree and Robinson, J., 1918, **113**, 859; compare Shinoda and Sato, *loc. cit.*) and of 2-*hydroxy*-4 : 6-*dimethoxy*-β-*phenylpropiophenone* with acetic anhydride and sodium acetate gives rise to chromones.

The ring closure of phloretin with acetic anhydride and sodium acetate has been reinvestigated and is found to occur with unique facility, a good yield of the triacetate (III, R = Ac) being obtained even at 100°; the trimethyl ether (I, R = Me), however, does not undergo chromone formation under the same mild conditions.

Experimental.

5 : 7 : 4′-*Triacetoxy*-3-*benzyl*-2-*methylchromone* (III, R = Ac).—Acetylation of phloretin (6 g.) with acetic anhydride (40 c.c.) and fused sodium acetate (10 g.) on the steam-bath during 10—12 hours gave rise to the *O*-triacetyl chromone, m. p. 167—168° after one crystallisation

from alcohol. Repeated crystallisation finally gave a product, m. p. 170°, identical with a specimen prepared under the more drastic conditions prescribed by Ciamician and Silber (*loc. cit.*), who give m. p. 173° (Shinoda and Sato, *loc. cit.*, give m. p. 170—171°).

The triacetate (5 g.) was dissolved in boiling 8% methyl-alcoholic sodium hydroxide (36 c.c.) and 2 hours later the solution was acidified with dilute acetic acid, and the greater part of the methyl alcohol evaporated, thereby affording a precipitate of 5 : 7 : 4′-trihydroxy-3-benzyl-2-methylchromone (III, R = H) which separated from 50% methyl alcohol in needles, m. p. 204—207°. The partially purified product (2·5 g.) was methylated with methyl iodide (3 c.c.) and potassium carbonate (8—10 g.) in boiling acetone during 16—18 hours; after 8 hours more iodide (2 c.c.) was added. On isolation the trimethyl ether separated from methyl alcohol in colourless needles, m. p. 166°, identical with a specimen prepared by Johnson and Robertson (*loc. cit.*). Deacetylation of the triacetate obtained by Ciamician and Silber's method and methylation of the resulting trihydroxychromone gave the same trimethyl ether, m. p. and mixed m. p. 166°.

5 : 7 : 4′-*Trimethoxy-2-styryl-3-benzylchromone.*—A solution of the chromone (0·75 g.) and benzaldehyde (0·3 g.) in alcohol (17 c.c.) containing sodium ethoxide (from 0·07 g. of sodium) was refluxed for 2 hours; the *styryl* derivative (0·7 g.), which separated from the cooled mixture, crystallised from a small volume of alcohol in pale yellow needles, m. p. 165° (Found : C, 75·5; H, 5·7. $C_{27}H_{24}O_5$ requires C, 75·7; H, 5·6%). Mixed with the original pyrone, it melted at 140—145°. The deep yellow solution of the substance in sulphuric acid has a green fluorescence.

Condensation of β-*Phenylpropionitrile and Phloroglucinol Dimethyl Ether.*—β-Phenylpropionyl chloride was prepared from the acid with thionyl chloride and converted into the amide by means of aqueous ammonia, the recrystallised amide (70 g.) dehydrated with boiling thionyl chloride (80 c.c.) in the course of 1·5 hours, and the resulting nitrile on isolation and purification by distillation in a vacuum obtained as a colourless oil, b. p. 137°/18 mm.; yield, 50 g. or 81% of the theoretical, whereas Klarmann (*J. Amer. Chem. Soc.*, 1926, **48**, 2358), using phosphoric oxide in the dehydration process, obtained a 40% yield (Found : N, 10·8. Calc. for C_9H_9N : N, 10·7%).

The nitrile (12 g.) and phloroglucinol dimethyl ether (14 g.) were condensed in dry ether (75 c.c.) by means of zinc chloride (5 g.) and excess of hydrogen chloride and 30 hours later the precipitation of the ketimine salts was completed by addition of ether (150 c.c.). The product was boiled with water (110 c.c.) for 15 minutes and, after cooling, the oil which had separated was collected and dissolved in boiling alcohol (35 c.c.). The cooled solution deposited 2-*hydroxy*-4 : 6-*dimethoxy*-β-*phenylpropiophenone* (5·2—6 g.) in glistening hexagonal plates, m. p. 105° after recrystallisation, having a deep red-violet ferric chloride reaction in alcohol (Found : C, 71·0; H, 6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

Addition of ethyl acetate (300 c.c.) to the alcoholic filtrate from the foregoing crude ketone precipitated the zinc chloride–imine double compound of 4-*hydroxy*-2 : 6-*dimethoxy*-β-*phenylpropiophenone*. This salt crystallised from warm alcohol in stout yellow prisms, m. p. 206—208° (decomp.), and on hydrolysis by boiling with water (30 c.c.) for 15 minutes gave rise to the ketone, which separated from 50% alcohol as a *hemihydrate* in colourless plates, m. p. 73—74°, and m. p. 104—105° after having been dried in a vacuum (Found : loss on drying at 110°, 3·4. $C_{17}H_{18}O_4$,0·5H_2O requires H_2O, 3·1%. Found in dried material : C, 71·0; H, 6·3%). This ketone, unlike the isomeride described above, does not give a ferric chloride reaction and is soluble in 1% aqueous sodium hydroxide.

5 : 7-*Dimethoxy-2-styryl-3-benzylchromone.*—Acetylation of 2-hydroxy-4 : 6-dimethoxy-β-phenylpropiophenone (2 g.) with acetic anhydride (20 c.c.) and sodium acetate (4 g.) at 190° for 20 hours gave rise to 5 : 7-*dimethoxy-3-benzyl-2-methylchromone*, which separated from alcohol in clusters of colourless slender needles, m. p. 168° (Found : C, 73·3; H, 5·9. $C_{19}H_{18}O_4$ requires C, 73·6; H, 5·8%). The colourless solution of the compound in concentrated sulphuric acid has a faint blue fluorescence.

The condensation of this compound (0·5 g.) with benzaldehyde (0·3 g.) was effected in boiling alcohol (13 c.c.) with sodium ethoxide (from 0·06 g. of sodium) during 1·5 hours; the resulting *styryl* derivative (0·55 g.) crystallised from alcohol in slender, pale yellow needles, m. p. 179—181° (Found in material dried at 110° : C, 78·2; H, 5·6. $C_{26}H_{22}O_4$ requires C, 78·4; H, 5·5%).

7-*Methoxy-2-styryl-3-benzylchromone* was prepared from 7-methoxy-3-benzyl-2-methylchromone by the foregoing procedure and on crystallisation from a large volume of alcohol obtained as a voluminous mass of slender, pale buff needles, m. p. 174°, forming an intense yellow solution with a green fluorescence in concentrated sulphuric acid (Found : C, 81·6; H, 5·6. $C_{25}H_{20}O_3$ requires C, 81·5; H, 5·4%).

5 : 7-*Dimethoxy*-3-*benzyl*-4-*methylcoumarin*.—A mixture of phloroglucinol dimethyl ether (3 g.), ethyl α-benzylacetoacetate (5 g.), and phosphoric oxide (4 g.) was heated on the water-bath for 30 minutes and occasionally stirred; at intervals of 10 minutes two further portions of oxide (2 g.) were added. After treatment of the reaction mixture with water and a slight excess of 10% aqueous sodium hydroxide the insoluble *coumarin* (1·1 g.) was collected, washed, and crystallised from alcohol, forming colourless needles, m. p. 172—173°, identical with material prepared by the methylation of an authentic specimen of 5 : 7-dihydroxy-3-benzyl-4-methylcoumarin (Jacobsen and Ghosh, J., 1915, **107**, 433; Baker, J., 1925, **127**, 2349) by the methyl iodide–potassium carbonate method (Found: C, 73·3; H, 5·6. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%). The greenish-yellow solution of the compound in concentrated sulphuric acid has an intense green fluorescence.

5 : 7 : 4′-*Trimethoxy*-3-*benzyl*-4-*methylcoumarin*.—As ethyl α-*p*-methoxybenzylacetoacetate is somewhat easily decomposed by phosphoric oxide at 100°, a mixture of the ester (2·5 g.), phloroglucinol dimethyl ether (1·6 g.), and oxide (3 g.) was kept at room temperature for 48 hours and then, after the addition of more oxide (2 g.), heated at 100° for 3—5 minutes. On isolation with the aid of dilute aqueous sodium hydroxide the *coumarin* crystallised from methyl alcohol in colourless needles (0·4 g.), m. p. 137° (Found: C, 70·6; H, 6·3. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). The behaviour with concentrated sulphuric acid is identical with that of 5 : 7-dimethoxy-3-benzyl-4-methylcoumarin.

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