951. *Chromanones Derived from Resorcinol.*

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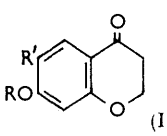
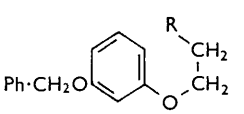
The benzylation of resorcinol has been further examined. 7-Benzyloxychroman-4-one has been prepared and shown to have expected properties.

A compound believed to be 7-benzyloxychroman-4-one (I; R′ = H, R = CH_2Ph) has been reported by Gregory and Tomlinson.[1] It was prepared by a route intended to involve *O*-cyanoethylation of resorcinol monobenzyl ether, followed by hydrolysis of the resulting nitrile (II; R = CN) and subsequent cyclisation of the corresponding β-phenoxypropionic



(I)



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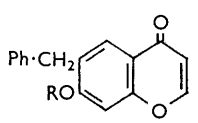


(III)

acid (II; R = CO_2H). Surprisingly, neither the acid obtained nor the chromanone was debenzylated even under vigorous conditions.

Recent work on dihydropyranochromones led to additional routes to 7-hydroxychroman-4-one (I; R = R′ = H) which was readily benzylated with benzyl chloride and potassium carbonate in acetone. The product (I; R′ = H, R = CH_2Ph) was different from that prepared by the earlier authors and, as expected, was readily debenzylated by catalytic reduction or by acid treatment, although the latter was accompanied by rearrangement. 7-Hydroxychromanone was prepared by two independent routes, the first of which was similar to that intended by Gregory and Tomlinson, but involved resorcinol monomethyl ether. Cyanoethylation, followed by cyclisation, gave 7-methoxychroman-4-one (I; R = Me, R′ = H) which was then demethylated.[2] A second, shorter route gave the hydroxychromanone in one stage by the interaction of resorcinol and β-chloropropionyl chloride in the presence of aluminium chloride.[3]

In order to elucidate the anomalous behaviour of the benzyl derivative of the earlier

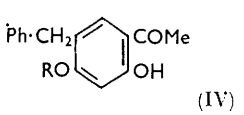
[1] Gregory and Tomlinson, *J.*, 1956, 795.
[2] Loudon and Razdan, *J.*, 1954, 4301.
[3] Naylor, Ramage, and Schofield, *J.*, 1958, 1190.

authors, an examination of the starting material prepared by Klarmann's method from resorcinol and benzyl chloride in boiling xylene [4] was undertaken. It was considered by him, and by Gregory and Tomlinson, to be resorcinol monobenzyl ether but was substantially the same as the substance which was obtained from a Friedel–Crafts reaction in nitrobenzene.[5] This Klarmann correctly formulated as 4-benzylresorcinol but the compound is best obtained pure by Clemmensen reduction of 4-benzoylresorcinol.[5]

On the other hand, resorcinol monobenzyl ether was obtained from resorcinol and benzyl chloride in acetone with anhydrous potassium carbonate, although this method was stated by Klarmann to give the same product as that obtained from benzylation in boiling xylene. This error may have arisen from use of mineral acid in the isolation of the product, since resorcinol monobenzyl ether has recently been shown to rearrange to 4-benzylresorcinol in such conditions.[6] In the present work, rearrangement was avoided by use of carbon dioxide for liberation of the monobenzyl ether from solutions of its sodium salt.

The nuclear benzyl derivative was distinguished by the preparation of the benzoate and *p*-nitrobenzoate, which were shown by analysis to be diesters, whereas the corresponding derivatives of the benzyl ether were clearly monoesters. Infrared spectra of the two benzyl compounds were also quite different.

The sequence of reactions used by Gregory and Tomlinson has been repeated from pure resorcinol monobenzyl ether and from 4-benzylresorcinol. The former reacted with acrylonitrile to give a monocyanoethyl derivative (II; R = CN) which could not be hydrolysed to the corresponding carboxylic acid (II; R = CO_2H) without debenzylation under acid conditions or complete removal of the cyanoethyl side-chain under alkaline conditions. The desired carboxylic acid was, however, obtained from the monobenzyl ether by condensation with β-chloropropionic acid, and was also found to be readily debenzylated. Cyclisation of the acid (II; R = CO_2H) in polyphosphoric acid was accompanied by rearrangement, giving mainly 6-benzyl-7-hydroxychroman-4-one (I; R = H, R′ = CH_2Ph). This chromanone was also obtained by treatment of 7-benzyloxychroman-4-one with hydrochloric acid and its structure confirmed in the following way. It was dehydrogenated by triphenylmethyl perchlorate in a mixture of acetic acid and acetic anhydride to the corresponding 7-acetoxy-6-benzylchromone (III; R = Ac), which was degraded by sodium hydroxide to 5-benzylresacetophenone (IV; R = H). Acid hydrolysis gave 6-benzyl-7-hydroxychromone (III; R = H), which also underwent alkaline hydrolysis to 5-benzylresacetophenone. 6-Benzyl-7-hydroxychroman-4-one formed a methyl ether which was similarly dehydrogenated and degraded, giving 5-benzyl-2-hydroxy-4-methoxyacetophenone (IV; R = Me).



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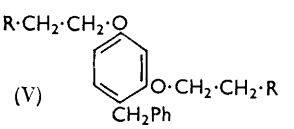

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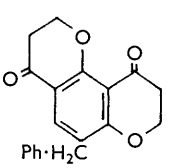

(VI)

The compounds obtained in the sequence from 4-benzylresorcinol are probably described by Gregory and Tomlinson with different formulations. Condensations of 4-benzylresorcinol with acrylonitrile clearly gave a dicyanoethyl derivative (V; R = CN), which was hydrolysed by acetic and hydrochloric acids to a dicarboxylic acid (V; R = CO_2H). Cyclisation of this acid in polyphosphoric acid gave a diketone, considered to be the compound (VI).

[4] Klarmann, Gatyas, and Shternov, *J. Amer. Chem. Soc.*, 1931, **53**, 3404.
[5] Klarmann, *J. Amer. Chem. Soc.*, 1926, **48**, 792.
[6] Freudenberg and Alonso, *Annalen*, 1958, **612**, 78.

Experimental

Resorcinol Monobenzyl Ether.—A mixture of resorcinol (36·6 g.) and benzyl chloride (42 g.) was stirred and heated under reflux with anhydrous potassium carbonate (46·6 g.) in dry acetone (250 ml.) during 10 hr., then cooled and filtered. The filtrate was evaporated, water (500 ml.) was added to the residue, and the mixture extracted with ether. The ethereal layer was washed with water, and then the phenol was removed by repeated extraction with 10% aqueous sodium hydroxide. Passage of an excess of carbon dioxide liberated the crude product as a light brown oil which was extracted with ether. Evaporation of the dried ($MgSO_4$) solution followed by distillation of the residue gave resorcinol monobenzyl ether (18 g.) as a pale yellow oil, b. p. 202—210°/11 mm., solidifying to a wax. It crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 50—51° (Found: C, 78·0; H, 6·0. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·0%). It formed a benzoate, plates (from ethanol), m. p. 81—82° (Found: C, 78·6; H, 5·2. Calc. for $C_{20}H_{16}O_3$: C, 79·0; H, 5·3%), and a p-*nitrobenzoate*, needles (from ethanol), m. p. 94—95° (Found: C, 68·7; H, 4·5; N, 4·1. $C_{20}H_{15}NO_5$ requires C, 68·8; H, 4·3; N, 4·0%).

β-m-*Benzyloxyphenoxypropionitrile* (II; R = CN).—A solution of resorcinol monobenzyl ether (10 g.) in acrylonitrile (20 ml.) was refluxed with dry sodium methoxide (0·75 g.) during 7 hr. The excess of acrylonitrile was distilled off and the residue thoroughly extracted with ether. The ethereal extract was washed successively with aqueous sodium hydroxide and water, and the dried ($MgSO_4$) solution evaporated. The residue was distilled and gave the product (5 g.), b. p. 236—248°/14 mm., that solidified on cooling and scratching. Further purification by successive crystallisations from carbon tetrachloride and methanol gave β-m-*benzyloxyphenoxypropionitrile* as prisms, m. p. 64—65° (Found: C, 75·8; H, 5·9; N, 5·5. $C_{16}H_{15}NO_2$ requires C, 75·9; H, 6·0; N, 5·5%).

β-m-*Benzyloxyphenoxypropionic Acid* (II; R = CO_2H).—A solution of β-chloropropionic acid (4·36 g.) and potassium carbonate (5·52 g.) in water (40 ml.) was added to a solution of resorcinol monobenzyl ether (12 g.) and potassium hydroxide (4 g.) in water (40 ml.), and the whole heated under reflux during 15 min., then cooled and acidified with concentrated hydrochloric acid. The mixture was extracted with ether and, after being washed with water, the ethereal solution was extracted with saturated aqueous sodium hydrogen carbonate. The crude product was precipitated on acidification of the alkaline extract with concentrated hydrochloric acid. Filtration and crystallisation of the residue from aqueous ethanol gave β-m-*benzyloxyphenoxypropionic acid* (1·0 g.) as flakes, m. p. 109—110° (Found: C, 70·3; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

7-*Benzyloxychroman-4-one* (I; R = CH_2Ph, R′ = H).—A mixture of 7-hydroxychroman-4-one (1·64 g.), benzyl chloride (1·3 g.), and sodium iodide (1·5 g.) was stirred and heated under reflux with anhydrous potassium carbonate (1·4 g.) in dry acetone (40 ml.) during 9 hr., then cooled and filtered. The filtrate was evaporated and the residue extracted with ether (50 ml.). The ethereal extract was washed successively with 10% aqueous sodium hydroxide and water, and the dried ($MgSO_4$) solution evaporated to dryness. Crystallisation of the residue from methanol (charcoal) gave 7-*benzyloxychroman-4-one* (1·2 g.) as prisms, m. p. 103—104° (Found: C, 75·9; H, 6·0. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

4-*Benzylresorcinol.*—4-Benzoylresorcinol (4·0 g.) was heated under reflux with a mixture of amalgamated zinc (20 g.) and constant-boiling hydrochloric acid (50 ml.) during 8 hr. The cooled liquid was decanted from excess of zinc and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residue gave an opaque gel, b. p. 222—228°/13 mm., which crystallised from carbon tetrachloride to yield 4-benzylresorcinol (2·6 g.) as prisms, m. p. 77—78°. It formed a *benzoate*, prismatic needles (from ethanol), m. p. 104—105° (Found: C, 79·5; H, 5·2. $C_{27}H_{20}O_4$ requires C, 79·4; H, 4·9%), and a *di*-p-*nitrobenzoate*, prismatic needles (from ethanol), m. p. 150° (Found: C, 65·0; H, 3·6; N, 5·3. $C_{27}H_{18}N_2O_8$ requires C, 65·0; H, 3·6; N, 5·6%).

4-*Benzylresorcinol Di*-(2-*cyanoethyl*) *Ether* (V; R = CN).—A mixture of 4-benzylresorcinol (5 g.) and acrylonitrile (30 ml.) was heated under reflux with sodium (0·1 g.) during 15 hr. The excess of acrylonitrile was removed by distillation and the residue extracted with ether. The extract was washed successively with 10% aqueous sodium hydroxide and water, then dried ($MgSO_4$) and evaporated. Crystallisation of the residue from methanol gave 4-*benzylresorcinol*

di-(2-cyanoethyl) ether (1·95 g.) as prismatic needles, m. p. 85·5—87° (Found: C, 74·5; H, 5·9; N, 9·4. $C_{19}H_{18}N_2O_2$ requires C, 74·5; H, 5·9; N, 9·2%).

4-Benzylresorcinol Di-(2-carboxyethyl) Ether (V; R = CO_2H).—A mixture of 4-benzylresorcinol di-(2-cyanoethyl) ether (1·5 g.), concentrated hydrochloric acid (20 ml.), and glacial acetic acid (15 ml.) was heated under reflux during 3 hr., then left overnight. The precipitate was filtered off, and successive crystallisations from acetic acid and ethanol gave *4-benzylresorcinol di-(2-carboxyethyl) ether* (0·9 g.) as prismatic needles, m. p. 169—170° (Found: C, 66·3; H, 5·9. $C_{19}H_{20}O_6$ requires C, 66·2; H, 5·9%).

6-Benzyl-3,4,9,10-tetrahydro-4,10-dioxo-2H,8H-benzo[1,2-b : 3,4-b′]*dipyran* (VI).—4-Benzyl resorcinol di-(2-carboxyethyl) ether (0·75 g.) was stirred with polyphosphoric acid (10 g.) at room temperature during 3 hr. The mixture was poured into water (50 ml.), stirred, and extracted with benzene. The extract was washed successively with aqueous sodium hydroxide and water and dried ($MgSO_4$), and the solvent was distilled off. Crystallisation of the residue from ethanol gave the *benzodipyran* (0·35 g.) as pale yellow prismatic needles, m. p. 161·5—163° (Found: C, 73·8; H, 5·0%; *M*, 308. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%; *M*, 308). The diketone formed a *di-2,4-dinitrophenylhydrazone*, bright orange needles (from dioxan), m. p. 273—274° (Found: C, 55·9; H, 3·9. $C_{31}H_{24}N_8O_{10}$ requires C, 55·7; H, 3·6%).

6-Benzyl-7-hydroxychroman-4-one (I; R = H, R′ = CH_2Ph).—(*a*) β-*m*-Benzyloxyphenoxypropionic acid (9 g.) was stirred with polyphosphoric acid (90 g.) for 3 hr. at >50°. The mixture was poured into water (500 ml.), giving an oily suspension which was extracted with ether. The ethereal solution was repeatedly extracted with 10% aqueous sodium hydroxide, to remove the phenolic product, which was then liberated from the combined alkaline extracts by acidification with concentrated hydrochloric acid. Extraction with ether and evaporation of the dried ($MgSO_4$) extract produced a dark green residue which crystallised from benzene (carbon) to yield *6-benzyl-7-hydroxychroman-4-one* (2·15 g.) as prisms, m. p. 189·5—191° (Found: C, 75·5; H, 5·7. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

(*b*) 7-Benzyloxychroman-4-one (0·4 g.) was heated under reflux with constant-boiling hydrochloric acid (15 ml.) during 2 hr., then the mixture was cooled and extracted with ether. The ethereal layer was extracted with 10% aqueous sodium hydroxide, and acidification of this extract with concentrated hydrochloric acid liberated an oil which was re-extracted with ether. Evaporation of the extract gave a residue which crystallised from aqueous ethanol as prisms (0·1 g.), identical with the above material.

6-Benzyl-7-hydroxychroman-4-one formed a *2,4-dinitrophenylhydrazone*, deep red needles (from acetic acid) m. p. 260—261° (Found: C, 60·7; H, 4·1. $C_{22}H_{18}N_4O_6$ requires C, 60·9; H, 4·1%).

7-Acetoxy-6-benzylchromone (III; R = Ac).—To a solution of 7-benzyl-6-hydroxychromanone (1 g.) in acetic acid (28 ml.) and acetic anhydride (4 ml.), was added freshly prepared triphenylmethyl perchlorate (1·34 g.) and the temperature of the whole raised to 100° in 30 min. The resulting solution was evaporated to dryness under reduced pressure and the residue ground with ether until solid. The pink oxonium salt was filtered off and treated with an excess of sodium hydrogen carbonate solution. Filtration and crystallisation of the residue from ethanol gave *7-acetoxy-6-benzylchromone* (0·35 g.) as cream leaflets, m. p. 126—127° (Found: C, 73·5; H, 4·7. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

6-Benzyl-7-hydroxychromone (III; R = H).—A suspension of 7-acetoxy-6-benzylchromone (0·25 g.) in 2N-hydrochloric acid (10 ml.) was heated under reflux during 30 min., then cooled and filtered. Crystallisation of the dried residue from ethyl acetate gave *6-benzyl-7-hydroxychromone* (0·13 g.) as colourless prismatic needles, m. p. 215—216° (Found: C, 76·5; H, 4·7. $C_{10}H_{12}O_3$ requires C, 76·1; H, 4·8%).

5-Benzylresacetophenone (IV; R = H).—(*a*) 7-Acetoxy-6-benzylchromone (0·35 g.) was heated under reflux with 5% sodium hydroxide solution (15 ml.) during 1 hr., then cooled and acidified with concentrated hydrochloric acid. The precipitate was filtered off, dried, and crystallised from benzene, to yield 5-benzylresacetophenone (0·1 g.) as hexagonal plates, m. p. 149—150° (Found: C, 74·1; H, 5·6. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%).

5-Benzylresacetophenone also resulted from identical sodium hydroxide treatment of 6-benzyl-7-hydroxychromone.

(*b*) A solution of 4-benzylresorcinol (2 g.) in boron trifluoride–acetic acid (40% w/w; 10 ml.) was heated at 100° during 2 hr., then cooled and added to water (100 ml.). The resulting precipitate was filtered off and crystallised from aqueous ethanol, to yield fawn needles (2·2 g.),

subsequent crystallisation of which from benzene yielded hexagonal plates, identical with the above material and also with a sample of 5-benzylresacetophenone synthesised by a Hoesch reaction (Dhringa *et al.*[7]).

6-Benzyl-7-methoxychroman-4-one (I; R = Me; R′ = CH_2Ph).—6-Benzyl-7-hydroxychroman-4-one (2·54 g.) and dimethyl sulphate (1·9 g.) were stirred and heated under reflux with anhydrous potassium carbonate (1·52 g.) and dry acetone (35 ml.) during 10 hr., cooled, and filtered. The residue obtained on evaporation of the filtrate was dissolved in ether, washed with 10% aqueous sodium hydroxide and water, then dried ($MgSO_4$) and evaporated. Crystallisation of the residue from methanol gave *6-benzyl-7-methoxychroman-4-one* (1·7 g.) as needles, m. p. 90—91° (Found: C, 76·1; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

6-Benzyl-7-methoxychromone (III; R = Me).—To a solution of 6-benzyl-7-methoxychroman-4-one (1·34 g.) in acetic acid (30 ml.) and acetic anhydride (5 ml.), was added freshly prepared triphenylmethyl perchlorate (1·71 g.) and the temperature of the whole raised to 100° during 30 min. The resulting solution was evaporated under reduced pressure and the residue ground with ether until solid. The pink oxonium salt (m. p. 125°) was filtered off and treated with an excess of aqueous sodium hydrogen carbonate. The resulting gum slowly solidified and was ground and filtered off. Crystallisation of the residue from ethanol gave *6-benzyl-7-methoxychromone* (1·0 g.) as prismatic needles, m. p. 143° (Found: C, 76·3; H, 5·0. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%).

5-Benzyl-2-hydroxy-4-methoxyacetophenone (IV; R = Me).—6-Benzyl-7-methoxychromone (0·53 g.) was heated under reflux with 5% sodium hydroxide solution (15 ml.) during 2 hr. The cooled solution was filtered and the residue crystallised from ethanol, to yield *5-benzyl-2-hydroxy-4-methoxyacetophenone* (0·23 g.) as needles, m. p. 110—111° (Found: C, 74·8; H, 6·4. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). It formed a *2,4-dinitrophenylhydrazone*, deep red needles (from dioxan), m. p. 230—231° (Found: C, 60·1; H, 4·4. $C_{22}H_{20}N_4O_6$ requires C, 60·5; H, 4·6%).

β-m-*Hydroxyphenoxypropionic Acid.*—A solution of β-*m*-benzyloxyphenoxypropionic acid (0·54 g.) in methanol (25 ml.) was shaken with 10% palladium–charcoal (0·1 g.) and hydrogen until uptake ceased (*ca.* 1 hr.). The catalyst was filtered off and the filtrate evaporated to dryness. Unchanged starting material was removed as white plates on crystallisation of the residue from aqueous alcohol. The mother-liquors (from the crystallisation) were diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts left a residue which was crystallised from benzene to yield β-m-*hydroxyphenoxypropionic acid* (0·12 g.) as plates, m. p. 103—104° (Found: C, 59·6; H, 5·3. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%).

7-Hydroxychroman-4-one (I; R = R′ = H).—A solution of 7-benzyloxychroman-4-one (0·25 g.) in methanol (35 ml.) was shaken with 10% palladium–charcoal (0·1 g.) and hydrogen until uptake ceased (*ca.* 2 hr.). The catalyst was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ether and extracted with 10% aqueous sodium hydroxide. Addition of concentrated hydrochloric acid to the alkaline extract gave a precipitate which was filtered off and crystallised from aqueous ethanol, to yield 7-hydroxychroman-4-one (0·1 g.) as plates, m. p. 141—143°, undepressed on admixture with an authentic sample of 7-hydroxychroman-4-one synthesised by either of the above routes.[2, 3]

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SALFORD, LANCS. [*Received, June 29th,* 1962.]

[7] Dhringa, Harminder Lal Uppal, and Venkataraman, *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 206.