A New Synthesis of Walker's Colupulone Degradation Products

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The by-product in the reaction of ββ-dimethylacrylyl chloride with phloroglucinol has been shown to be 5-hydroxy-2,2,8,8-tetramethylbenzo[1,2-*b*:3,4-*b*′]dipyran-4(3*H*),10(9*H*)-dione. Sodium borohydride reduction gave 3,4,9,10-tetrahydro-2,2,8,8-tetramethylbenzo[1,2-*b*:3,4-*b*′]dipyran-5-ol, which was acylated to 3,4,9,10-tetrahydro-6-isobutyryl-2,2,8,8-tetramethylbenzo[1,2-*b*:3,4-*b*′]dipyran-5-ol and then isomerised to its linear isomer, 3,4,6,7-tetrahydro-10-isobutyryl-2,2,8,8-tetramethylbenzo[1,2-*b*:5,4-*b*′]dipyran-5-ol. The last-mentioned compounds were identical with authentic specimens obtained by degradation of colupulone with acid.

In 1937, Robertson and his associates,[1] in the reaction of ββ-dimethylacrylyl chloride with phloroglucinol, obtained, in addition to the chromanone (I), an uncharacterised minor by-product which could not be obtained pure. However, analysis of the mono-2,4-dinitrophenylhydrazone indicated the formula $C_{16}H_{18}O_5$ for the parent ketone. In repeating this reaction we have isolated the pure by-product and characterised it as (II) by using the compound in the synthesis of the two chromans (III) and (IV). These chromans, which we required for our work on hop compounds, were first obtained by Walker[2] in 1924 by acid degradation of colupulone (V),[2] but were not characterised until 1955.[3]

Repetition of the Friedel–Crafts acylation conditions of Robertson[1] gave (I) and (II) in the approximate ratio 20 : 1, and the two compounds were easily separated by chromatography on silicic acid of the mother liquors from the crystallisation of the main product (I). The minor product (II) gave a satisfactory analysis for $C_{16}H_{18}O_5$, showed a molecular ion at *m/e* 290 in its mass spectrum, and in its n.m.r. spectrum (deuterioacetone) showed singlet signals at τ 8·57 and 8·52 (O·CMe$_2$), 7·2 and 7·37 (CH$_2$·CO), 4·17 (·C:CH·), and —3·26 (OH). T.l.c. showed no evidence of the linear tricyclic isomer of (II). As expected, the yield of (II) could be improved by treating the chromanone (I) with ββ-dimethylacrylyl chloride (1 mol.) in which case the ratio of unchanged chromanone (I) to the product (II) was 5 : 2.

Reduction of (II) with sodium borohydride in buffered solution[4] gave, unexpectedly, the chroman (VI), directly, in 70% yield. Compound (VI) showed three main peaks in its mass spectrum, at *m/e* 262 (60%, M^+), 207 (100%), and 151 (70%). Production of the latter two ions is ascribed to cleavage of one dihydropyran ring with hydrogen rearrangement and subsequent retro-Diels–Alder-type fission of the remaining ring with loss of isobutene. In its n.m.r. spectrum (deuteriochloroform) (VI) showed signals at τ 8·68 (12H, s, O·CMe$_2$), 8·27 and 8·24 (each 2H, t, *J* 7 Hz, C*H*$_2$·CMe$_2$), 7·46 and 7·40 (each 2H, t *J* 7 Hz, CH$_2$·C=), 5·19 (1H, s, OH), and 4·12 (1H, s, HC=). The chromanone (I), on reduction with borohydride, similarly gave the chroman (VII), but in smaller yield. This reaction had advantages in speed and convenience over the conventional Clemmensen reduction. Acylation of (VI) with isobutyryl chloride and aluminium chloride then gave the angular chroman (III), which was identical in all respects (m.p., mixed m.p. u.v., i.r., t.l.c., and g.l.c.) with a sample prepared by

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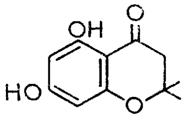
[1] W. Bridge, R. G. Heyes, and A. Robertson, *J. Chem. Soc.*, 1937, 279.

[2] T. K. Walker, *J. Inst. Brewing*, 1924, 712; 1949, 266.

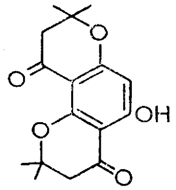
[3] G. A. Howard, J. R. A. Pollock, and A. R. Tatchell, *J. Chem. Soc.*, 1955, 174.

[4] J. Nickl, *Chem. Ber.*, 1959, **92**, 1989.

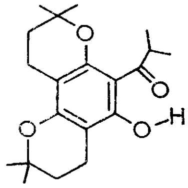
acid degradation of colupulone (V).[3] T.l.c. showed that the reaction mixture contained none of the linear isomer (IV), into which (III) was subsequently partially converted by treatment with concentrated sulphuric acid.[3]



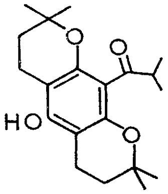
(I)



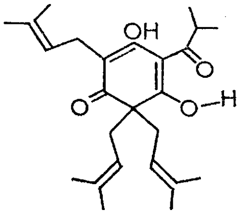
(II)



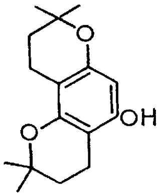
(III)



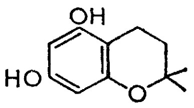
(IV)



(V)



(VI)



(VII)

The natural and synthetic compounds were again identical in all respects.

EXPERIMENTAL

Light petroleum used had b.p. 40—50°. Silicic acid used for chromatography was Mallinckrodt, 100 mesh. M.p.s are corrected. N.m.r. spectra were measured with a Perkin-Elmer R10 spectrometer at 60 MHz. I.r. spectra were measured for solutions in chloroform, unless otherwise stated, with a Unicam SP 200 spectrophotometer, and u.v. spectra with a Beckman DB spectrophotometer. G.l.c. was carried out with a Pye series 104 chromatograph on a silylated glass column (1·5 m.) packed with 1% D.C. 560 (formerly called F.60) on gas chrom. P (mesh size 100—120) which had previously been acid-washed and silylated. The column was temperature-programmed from 150 to 250° at 3°/min. Nitrogen flow-rate was 45 c.c./min. Trimethylsilylation was achieved by dissolving the compound (*ca.* 1 mg.) in dimethylformamide (0·5 c.c.). Hexamethyldisilazane (0·5 c.c.) was added and the solution was kept at 50° for 30 min.

5,7-*Dihydroxy*-2,2-*dimethylchromanone* (I).—The conditions of Robertson [1] were followed; phloroglucinol (16·2 g.) dried overnight at 100° was used. After steam distillation, to remove nitrobenzene, the crude solid product was chromatographed on silicic acid (column 25 × 4 cm.) and the partially purified product, eluted with light petroleum–ether (6 : 4), was crystallised from chloroform to give the chromanone (I). M.p. 198—199° (lit.,[1] 198°), M^+ 208, $\lambda_{max.}$ (EtOH) 290 (ε 16,850) and 325sh nm., $\lambda_{max.}$ (alkaline EtOH) 240sh and 324 nm., τ [$(CD_3)_2CO$] 8·57 (6H, s, $O\cdot CMe_2$), 7·27 (2H, s, $CH_2\cdot CO$), 4·15 (2H, s, C:CH), 0·65 (1H, s, non-hydrogen-bonded enol), and −2·22 (1H, s, hydrogen-bonded enol). The combined mother-liquors of five such preparations were chromatographed on a column (25 × 4 cm.) of silicic acid. Further quantities of the chromanone (I) were eluted with ether–light petroleum (4 : 6), and the crude chromanone (II) (*ca.* 2·2 g.) with ether–light petroleum 55 : 45. Recrystallisation from ether gave (II) (1·7 g.), m.p. 135—137°; further recrystallisation gave pure 5-*hydroxy*-2,2,8,8-*tetramethylbenzo*[1,2-b:3,4-b′]*dipyran*-4(3H),10(9H)-*dione* (II), m.p. 138·5—139·5°, M^+ 290, $\lambda_{max.}$ (EtOH) 268 (ε 42,200), nm., $\lambda_{max.}$ (alkaline EtOH) 283 and 317 nm., $\nu_{max.}$ (Nujol) 1640 and 1676 cm.$^{-1}$ (Found: C, 66·5; H, 6·2. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%).

In a further preparation, the same conditions were used with the quantities: chromanone (I) (3·25 g.), aluminium chloride (1·6 g.), and ββ-dimethylacrylyl chloride (1·2 c.c.). After 5 days stirring, the mixture was worked up as before. Chromatography and crystallisation gave starting material (I) (650 mg.), m.p. 196—198°, eluted with ether–light petroleum (6 : 4), and the crude chromanone (II) (253 mg.) eluted with ether–light petroleum (7 : 3). Recrystallisation from ether gave the pure chromanone (II), m.p. 137—139°, mixed m.p. 138—139° with the previously described sample.

3,4,9,10-*Tetrahydro*-2,2,8,8-*tetramethylbenzo*[1,2-b:3,4-b′]-*dipyran*-5-*ol* (VI).—The chromanone (II) (1·4 g.) dissolved in 8% sodium hydroxide and pyridine (2·1 c.c.) was heated to 50—60°, and sodium borohydride (4·2 g.) in water (7 c.c.) was added carefully. This was followed by the careful dropwise addition of ammonium chloride (2·1 g.) in the minimum amount of water (vigorous reaction). After the foaming had subsided, heating was continued for a further 1 hr. After cooling and acidification with hydrochloric acid, the products were collected in ether. The ether layer was washed with dilute hydrochloric acid, and then water until neutral, dried (Na_2SO_4), and evaporated to yield a semi-solid product. Chromatography on silicic acid (column 20 × 3·5 cm.) gave crystalline chroman (0·84 g., 70%), m.p. 159—163°, eluted with ether–light petroleum (65 : 35). Recrystallisation from ether gave the *benzodipyran* (VI), m.p. 164—164·5°, M^+ 262, $\lambda_{max.}$ (EtOH) 270 (ε 720), $\lambda_{max.}$ (alkaline EtOH) 282 nm., $\nu_{max.}$ 3600, 3350, 2980, 2930, 1618, 1503, 1443, 1387, 1373, 1346, 1324, 1259, 1240, 1154, 1116, 1063, 1022, 955, 938, 920, 882, and 820 cm.$^{-1}$ (Found: C, 73·1; H, 8·25. $C_{16}H_{22}O_3$ requires C, 73·2; H, 8·45%).

3,4,9,10-*Tetrahydro*-6-*isobutyryl*-2,2,8,8-*tetramethylbenzo*-[1,2-b:3,4-b′]*dipyran*-5-*ol* (III).—The chroman (VI) (600 mg.) was ground with anhydrous aluminium chloride (370 mg.) and the mixture was added to nitrobenzene (3·7 c.c.) in a dried flask fitted with a calcium chloride guard-tube. When the solid had dissolved, the solution was cooled to −5° and isobutyryl chloride (0·21 c.c.; freshly distilled) was added during 10 min. The mixture was stirred at 20° for 4 days before treatment with ice (4 g.) and N-hydrochloric acid (4 c.c.). The ether extracts (6 × 25 c.c.) were washed with water until neutral, the solvent was evaporated off, and the residue was steam distilled. When all the nitrobenzene had been removed, the residue was extracted into ether, washed with water, and dried. G.l.c. of the trimethylsilyl ethers of this mixture indicated that the ratio of (III) to (VI) was *ca.* 1 : 2. Chromatography on silicic acid (column 20 × 2·5 cm.) afforded crude (III) (220 mg.), eluted with ether–light petroleum (15 : 85), contaminated with nitrobenzene. Incomplete removal of the latter under reduced pressure at 20° overnight and crystallisation from methanol gave the isobutyryl derivative (III) (93 mg.), m.p. 83—84° (Found: C, 72·3; H, 8·0. Calc. for $C_{20}H_{28}O_4$: C, 72·3; H, 8·5%), mixed m.p. 83·2—84° with authentic material (m.p. 84°) prepared by acid degradation of colupulone.[3] The i.r. and u.v. spectra and t.l.c. behaviour (5% ethyl acetate in light petroleum; R_F 0·75) of (III) and the g.l.c. behaviour of the trimethylsilyl ether were indistinguishable from those of authentic material. Preparative t.l.c. (10% ethyl acetate in light petroleum) of the mother liquors from the crystallisation gave a further 30 mg. of (III).

Starting material (VI) (220 mg.) was eluted with ether–light petroleum (65 : 35) in the later fractions of the column chromatography.

Isomerisation of (III).—The angular chroman (III) (65 mg.) in concentrated sulphuric acid (0·5 c.c.) was kept at 60° for 5 min. After treatment with ice and extraction with ether (4 × 5 c.c.), the resultant mixture was fractionated as previously described [2] (with sodium hydrogen carbonate and sodium hydroxide), yielding crude starting material (III) (34 mg.) and crude linear chroman (IV) (16 mg.). Repetition of the isomerisation on the recovered (III) (34 mg.) afforded a further 10 mg. of (IV). Crystallisation of the combined samples of (IV) from chloroform–light petroleum gave 3,4,6,7-tetrahydro-10-isobutyryl-2,2,8,8-tetramethylbenzo[1,2-*b*:5,4-*b*′]dipyran-5-ol (IV) (14 mg.), m.p. 169—170·5°, mixed m.p. 169·5—170° with authentic material (m.p. 170—170·5°) obtained from colupulone.[3] The i.r. and u.v. spectra and t.l.c. behaviour (35% ethyl acetate in light petroleum; R_F 0·8) of (IV) and the g.l.c. behaviour of the trimethylsilyl ether were indistinguishable from those of authentic material.

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