C-METHYLATION OF PHLOROGLUCINOL DERIVATIVES

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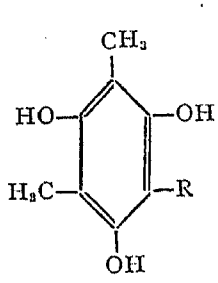
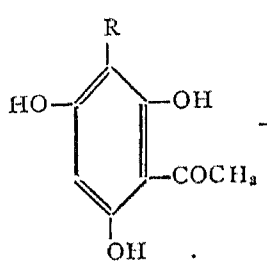
Among naturally occurring C-methyl flavonoids, a few of them are known to have C-methyl groups in both 6- and 8-positions, *e.g.*, matteucinol, desmethoxy-matteucinol and angustifolionol. Their syntheses require 3:5-dimethyl phloracetophenone (I *b*) as the starting material. Though this ketone is readily obtained by the Hoesch reaction on 3:5-dimetyl phloroglucinol (I *a*),[1, 2] the phenol is difficult to obtain and requires a number of steps.[3, 4] The nuclear methylation of C-methyl phloracetophenone (II *a*) which possesses the structural requirements for C-methylation[5] would be more direct. Though it does not take place with methyl iodide and potassium carbonate in acetone medium,[6] in view of the resemblance in structure to resacetophenone, the reaction was carried out using excess of methanolic potash or sodium methoxide. It however yielded a different product which was a low melting solid, gave an intense orange-red ferric reaction and was soluble in aqueous sodium bicarbonate. It did not couple with diazotised *p*-nitraniline and also did not undergo any change when heated with aluminium chloride in benzene solution showing that it was not a methyl ether. These properties and analytical data can only be explained on the basis that it is 5-acetyl-1:1:3:3-tetramethylcyclohexen-(4)-ol-(4)-dione (2 : 6) (III). The same product was obtained when phloracetophenone (II *b*) itself was subjected to nuclear methylation under the same conditions. The corresponding formyl compound (IV) was reported earlier to be produced by heating under reflux 3:5-dimethyl phloroglucinaldehyde (I *c*) with methyl iodide and methanolic potash.[7] 3:5-Dimethyl compound may therefore be considered to be a possible intermediate stage in the nuclear methylation of carbonyl derivatives of phloroglucinol though the exact conditions for its preparation are not known. This conclusion is also supported by an earlier observation of Herzig *et al.*[8] that silver phloroglucinol carboxylate on heating with excess of methyl iodide in a sealed tube gives methyl-3:5-dimethyl phloroglucinol carboxylate along with other products.

The structure (III) for the nuclear methylation product of C-methyl phloracetophenone has now been further supported by the nuclear methylation of phloroisovalerophenone (V) under the same conditions when lepto-



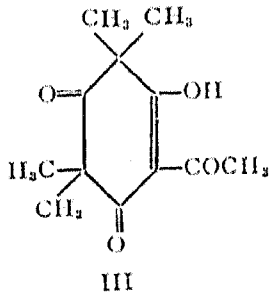
I

a, R=H
b, R=$COCH_3$
c, R=CHO

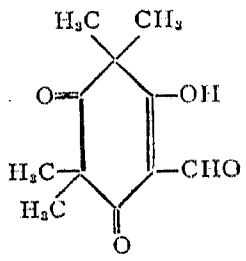


II

a, R=CH_3
b, R=H

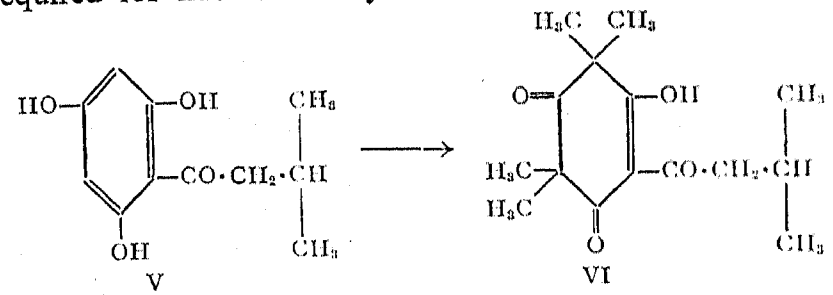


III



IV

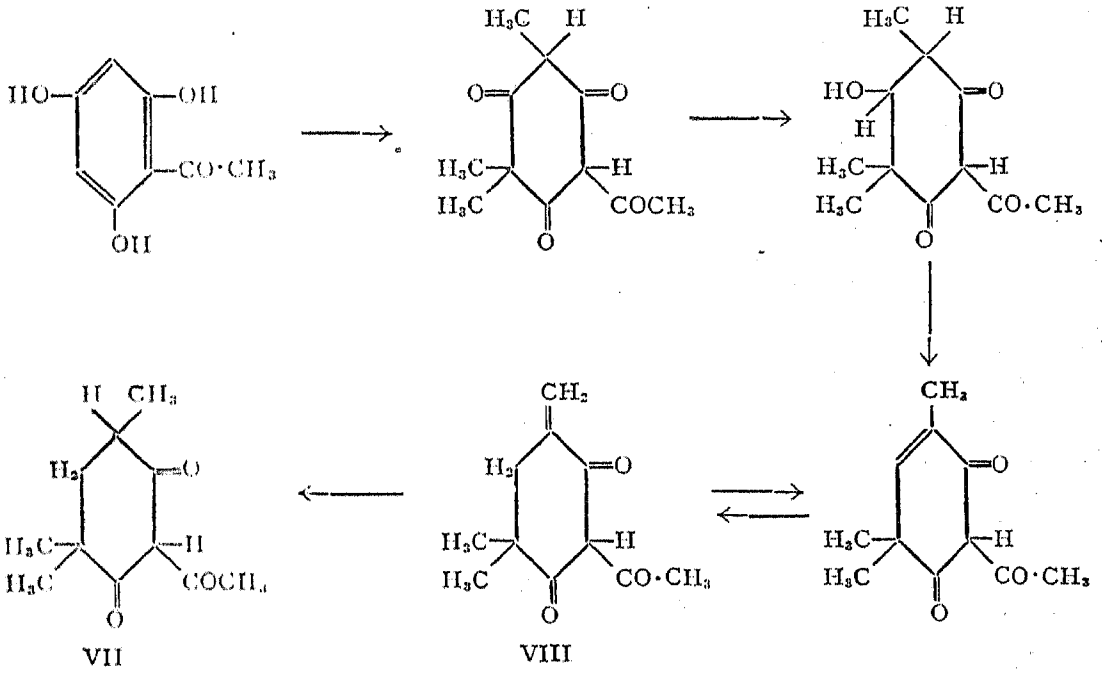
spermone which occurs in the oil of *Leptospermum flavescens*[9] and possesses an analogous structure (VI)[10, 11] could be obtained in 65% yield. It was earlier synthesised by Briggs *et al.*[12] using rather vigorous conditions. They heated a mixture of the phloroisovalerophenone (V), methyl iodide and aqueous potash in a sealed tube at 70° for 3 days and obtained a comparatively less yield (32%) of leptospermone (VI). Thus it is clear that carbonyl derivatives of phloroglucinol differ markedly from those of resorcinol which uniformly give the 3-C-methyl-4-O-methyl derivatives under similar conditions of nuclear methylation (see Ref. 5). This difference in behaviour seems to lie in their difference in capacity to assume the ketonic form required for nuclear methylation.



V VI

C-Polymethylation in a phloroglucinol derivative seems to be a natural process as a number of C-polymethylated β-triketones are known to occur in nature. Important examples are: leptospermone (VI), protokosin, α-kosin and β-kosin found in the anthelmintic drug, kousso (*Hagenia abyssinica*)[13, 14] and a number of substances from male and female ferns

(*Aspidium filix*) among which aspidin,[14] aspidinol,[15] albaspidin[14] and flavaspidic acid[15] are more important. There are two other C-polymethylated compounds but they are β-diketones; angustione (VII) and dehydroangustione (VIII) occurring in admixture in the oil of *Backhousia angustifolia*.[16–19] These two also seem to be evolved in nature from a phloroglucinol derivative, phloracetophenone (the dimethyl ether of which is found in nature).[20] The various stages in the evolution may be C-trimethylation, reduction, elimination of water (dehydroangustione VIII) and further reduction of the double bond (angustione VII) as shown below:



VII VIII

On the expectation that milder conditions may give appreciable yields of 3 : 5-dimethyl phloracetophenone, experiments using lesser proportions of methanolic potash have been conducted. From the resulting mixtures it could be isolated in 2% yield when 2 moles of alkali and in 5% yield when 3 moles of alkali are used. The use of 1 mole of alkali gives rise to a 50% yield of 3-methyl-phloracetophenone (II *a*) and 3 moles of alkali yields mainly 5-acetyl-1 : 3 : 3-trimethyl cyclohexen-(4)-ol-(4)-dione (2 : 6).

Experimental

5-Acetyl-1 : 1 : 3 : 3-tetramethyl-cyclohexen-(4)-(ol)-4-dione-(2 : 6) (III) :

(i) *By the nuclear methylation of 3-methyl phloracetophenone*

With methanolic potash.—To an ice-cooled solution of the ketone (2 g.) in methanolic potash (3 g. in 20 c.c.) methyl iodide (5 c.c.) was added in

one lot and the whole solution well shaken and kept overnight at room temperature. It was then refluxed with more of methanolic potash (1·5 g. in 10 c.c.) and methyl iodide (2·5 c.c.) for 6 hours. The solvent was removed under vacuum and dilute hydrochloric acid added to acidify the mixture. On cooling a soid separated. It was filtered, washed with water and triturated with aqueous sodium bicarbonate. Most of it dissolved, leaving behind a small amount of fluffy material. The bicarbonate solution was acidified and the colourless solid so obtained crystallised from aqueous methanol, yielding colourless needles, m.p. 52–53°. Yield, 1·8 g. It gave an intense orange-red colour with alcoholic ferric chloride, did not couple with diazotised *p*-nitraniline and also did not undergo any change when heated with aluminium chloride in benzene solution for two hours (Found: C, 64·3; H, 7·2; $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%).

Equal amounts of *p*-toluidine and the above product were heated on a boiling water-bath for half an hour and then refluxed for 5 minutes. The product was poured into ice-water, extracted with ether and the ether solution washed with dilute hydrochloric acid, followed by aqueous sodium hydroxide and water. The ether was removed and the residue was crystallised from 50% alcohol when the *p*-toluidino compound separated as pale yellow needles melting at 134° (Found: C, 73·1; H, 7·4; $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·3%).

With sodium methoxide.—C-Methyl phloracetophenone (2 g.) was dissolved in methanolic sodium methoxide (2 g. sodium in 30 c.c.) and refluxed for 3 hours with excess of methyl iodide (10 c.c.). The solvent was distilled off and the product was worked up as described in the above experiment. It melted at 52–53° and was identical with the sample obtained by using alcoholic potash (1·3 g.).

(ii) *By the nuclear methylation of phloracetophenone*

Phloracetophenone (2 g.) was methylated by both methods and the same product was formed melting at 52–53° and identical in all respects with the nuclear methylation product of C-methyl phloracetophenone. Yield, 1·6 g.

Leptospermone (*Nuclear methylation of phloroisovalerophenone*).—Phloroisovalerophenone[21] (2 g.) was dissolved in methanolic sodium methoxide (1·5 g. of sodium in 20 c.c.) and then refluxed for 3 hours with excess of methyl iodide (10 c.c.) . The solvent was distilled off under vacuum and dilute hydrochloric acid added. The product was extracted with ether and the ether solution washed with a dilute aqueous solution of sodium sulphite (5 g.). It was dried over anhydrous sodium sulphate. The residue left

after evaporation of ether was distilled under 10 mm. pressure (bath temp. 120–40°). Yield, 1·6 g. It was soluble in aqueous sodium carbonate and gave an orange-red colour with alcoholic ferric chloride. The *p*-toluidino compound prepared in the same way as described for an earlier case crystallised from aqueous alcohol in the form of colourless needles melting at 100–01° (Found: C, 74·6; H, 8·4; $C_{22}H_{29}O_3$ requires C, 74·4; H, 8·2%). In all these properties the product agreed with leptospermone described by Briggs *et al.*[11, 12].

Partial Methylation of Phloracetophenone.—(i) To a boiling solution of phloracetophenone (3 g.) in methanol (10 c.c.) was added methyl iodide (6 c.c., excess) in one lot and methanolic potash (10%, 10 c.c.; 1 mole) gradually in the course of 3 hours. The product was taken up in ether as described earlier and extracted successively with 5% aqueous solutions of sodium bicarbonate (*a*), sodium carbonate (*b*) and sodium hydroxide (*c*). The remaining ether solution contained no substance; (*a*) was negligible; (*b*) gave C-methyl-phloracetophenone (50%), m.p. 210–11° after crystallisation from boiling water, acetate, m.p. 111°; (*c*) yielded 2·5% of C-methyl-phloracetophenone dimethyl ether, m.p. 140–41°.

(ii) Same as above using 20 c.c. (2 moles) of methanolic potash: (*a*) gave 10% of 5-acetyl-1 : 3 : 3-trimethyl cyclohexen-(4)-ol-(4)-dione (2 : 6), m.p. 161–62° (from 30% methanol) which underwent deacetylation on boiling with 7% hydrochloric acid for four hours to 3-methyl filicinic acid, m.p. 180–81°; (*b*) 3 : 5-dimethyl-phloracetophenone (2%), m.p. 220–22° from 30% methanol and 3-methyl-phloracetophenone (20%) from boiling water.

(iii) Same as above using 30 c.c. (3 moles) of methanolic potash: (*a*) yielded on fractional crystallisation from 30% methanol, 5-acetyl-1 : 3 : 3-trimethyl-cyclohexen-(4)-ol-(4)-dione (2 : 6) (25%), m.p. 161–62°; (*b*) gave 3 : 5-dimethyl phloracetophenone (5%) from 30% methanol and C-methyl phloracetophenone (15%) from boiling water.

Summary

Nuclear methylation of phloracetophenone and 3-C-methyl phloracetophenone, under vigorous conditions yields 5-acetyl-1 : 1 : 3 : 3-tetramethyl cyclohexen-(4)-ol-(4)-dione (2 : 6) (III); the intermediate 3 : 5-dimethyl compound could not be obtained. This method is convenient for the preparation of leptospermone (VI). Many natural products seem to be formed by the nuclear methylation of the carbonyl derivatives of phloroglucinol. Using lesser proportions of alcoholic potash lower methylation products are obtained; but 3 : 5-dimethyl-phloroacetophenone could be isolated only in small quantities.

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