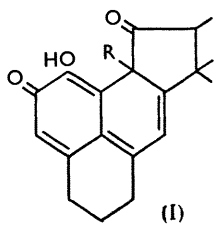
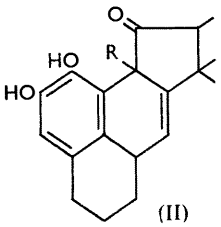
937. *Pristimerin. Part II.*[1] *Further Reactions involving the Chromophore.*

By P. K. Grant and A. W. Johnson.

Methylation of pristimerin by dimethyl sulphate, potassium carbonate, and acetone is shown to involve an addition of acetone to the pristimerin chromophore, a reaction which is catalysed by acid as well as by alkali. The product of addition of hydrogen chloride to pristimerin is also formulated.

In an earlier paper,[1] it was suggested that the wood pigment pristimerin, $C_{30}H_{40}O_4$, isolated from *Celastrus dispermus* and *Denhamia pittosporoides* (Celastraceae), contained the partial structure (I; R = OMe or Me), and that the related compound, celastrol, contained the unit (I; R = OH or Me). On the basis of structure (I), we formulated dihydropristimerin (pristimerol) as (II; R = OMe or Me), a rearrangement product obtained by the action of hot dilute sulphuric acid on pristimerin, as (III; R = OMe or Me), and the Thiele acetylation product as (IV; R = OMe or Me).


(I)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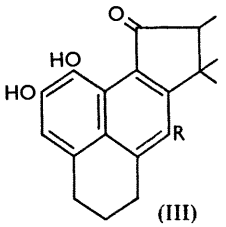
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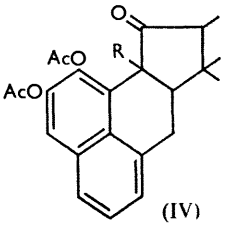

(IV)

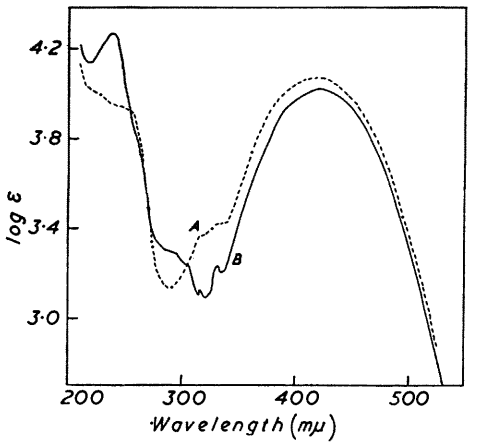
Shah, Kulkarni, and Thakore [2] prepared " methylated pristimerin," $C_{30}H_{42}O_4$, by using dimethyl sulphate in acetone in presence of potassium carbonate. They recognised that the product was benzenoid from its ultraviolet absorption spectrum, that it also contained an aliphatic double bond (perbenzoic titration; positive tetranitromethane test), and that it formed a 2 : 4-dinitrophenylhydrazone by a condensation assumed to involve the original inert carbonyl group of pristimerin. Reduction of the methylated product by lithium aluminium hydride gave a secondary alcohol, which was also assumed to be derived from the inert keto-group. Re-examination of this compound has led us to amend the molecular formula to $C_{35}H_{50}O_5$ although we agree with the Indian workers that it contains three methoxy-groups, a benzene ring, and an isolated double bond. The additional oxygen atom is contained in an aliphatic ketone group (band in infrared spectrum at 1713 cm.$^{-1}$), and the inert carbonyl group of pristimerin (band at 1724 or 1718 cm.$^{-1}$ in chloroform solution) is retained. The 2 : 4-dinitrophenylhydrazone, $C_{41}H_{54}O_8N_4$, which is yellow, still shows the band (1718 cm.$^{-1}$ in chloroform) corresponding to the inert carbonyl group in the infrared spectrum, and the visible and ultraviolet absorption spectrum corresponds to a derivative of a saturated ketone. The reaction is therefore interpreted as the addition of acetone across the activated methylene-quinone system of pristimerin to give structure (V; R = OMe or Me, R′ = H), an acetonylpristimerol which is converted by dimethyl sulphate into the corresponding dimethyl ether (V; R = OMe or Me, R′ = Me).

The view expressed by the Indian workers that the active ketonic group of (V; R = OMe or Me, R′ = Me) corresponds to the inert ketone of pristimerin is therefore erroneous and is attributable to their use of an incorrect molecular formula. The alcohol formed by reduction of the derivative (V; R = OMe or Me, R′ = Me) should be formulated as $C_{35}H_{52}O_5$ rather than $C_{30}H_{44}O_4$,[2] and is produced by reduction of the acetonyl group.

[1] Part I, Grant and Johnson, *J.*, 1957, 4079.
[2] Shah, Kulkarni, and Thakore, *J.*, 1955, 2515.

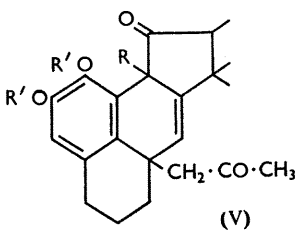
Examples of the direct addition of acetone to an unsaturated system are not common [3] and the high yield of adduct obtained in the present instance is evidence of the pronounced reactivity of the methylene-quinone system in pristimerin.

The dihydroxy-compound (V; R = OMe or Me, R′ = H), $C_{33}H_{46}O_5$, was obtained by the action of potassium carbonate, or better, dilute sulphuric acid, on an acetone solution of pristimerin. The product contained one methoxyl group, two active hydrogen atoms, and three *C*-methyl groups. On the basis of its absorption spectrum (log $\varepsilon_{max.}$ 3·48 at 285 mμ, and log $\varepsilon_{min.}$ 2·73 at 257 mμ), the compound was formulated as a substituted catechol. It gave a green ferric reaction and a negative Gibbs reaction, an alkaline solution darkened rapidly in air, and the R_F value of the product on paper was markedly decreased in the presence of borate.[4] The infrared spectrum (Nujol) showed bands at 3460 (OH),



Absorption spectra of pristimerin (A) and its hydrogen chloride adduct (B).

3340 (bonded OH), 1715 (bonded inert >CO), and 1701 cm.$^{-1}$ (the acetonyl-carbonyl group). In chloroform solution, a carbonyl band at 1705 cm.$^{-1}$ was obtained with a shoulder at 1724 cm.$^{-1}$. It will be evident that the presence of the acetonyl group prevents the migration of the angular methoxyl or methyl group and the double-bond rearrangements which are involved in the formation of compound (III) from pristimerin by the action of dilute sulphuric acid in the absence of acetone.



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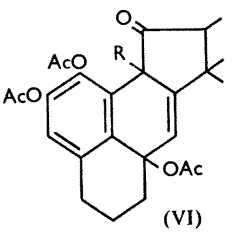

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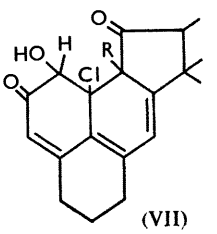

(VII)

The dual reaction of pristimerin with dilute sulphuric acid in the presence or absence of acetone is somewhat paralleled by its reactions with acetylating agents. It has been shown in the previous paper that the naphthalene derivative (IV) is the product obtained on Thiele acetylation. With acetic anhydride in pyridine a pale yellow amorphous acetate is formed which is a benzenoid derivative (log $\varepsilon_{max.}$ 2·92 at 265 mμ) and which shows maxima in its infrared spectrum at 1776 (>CO of aromatic acetate) and 1730 cm.$^{-1}$ (inert >CO group together with >CO of aliphatic acetate). The product possibly contains some

[3] Cairns, Carboni, Coffman, Engelhardt, Heckart, Little, McGeer, McKusick, and Middleton, *J. Amer. Chem. Soc.*, 1957, **79**, 2340.
[4] Swain, *Biochem. J.*, 1953, **53**, 200.

of the triacetate (VI; R = OMe or Me), but further speculation must await the isolation of a crystalline compound.

Another type of addition has been encountered in the action of dry hydrogen chloride on pristimerin. This was originally carried out when the possibility of pristimerin's being an anhydro-base was under consideration, but the red adduct obtained, $C_{30}H_{41}O_4Cl$, contained no ionic chlorine. It was insoluble in water and gave a green ferric reaction similar to that of pristimerin, which compound it re-formed after treatment with alkali. No ketonic derivatives could be obtained and the ultraviolet and visible absorption spectrum was sufficiently close to that of pristimerin (see Figure) to suggest that the chromophore had undergone little change.

The infrared spectrum of the hydrogen chloride adduct showed strong bands at 3400 (OH), 1724 (inert >CO; chloroform solution), and 1624 cm.$^{-1}$ (unsaturated >CO of the chromophore). In view of the modified positions of the bands associated with the functional groups of the quinonoid ring, the adduct is formulated as (VII; R = OMe or Me) in which the main conjugated system of the chromophore has been maintained but the strong interaction between the hydroxyl group and the adjacent carbonyl group is apparently diminished.

Oxidative degradations of pristimerin have given further support to the proposed pristimerin structure and will be reported later.

Experimental

Methylation of Pristimerin in the Presence of Acetone.—A solution of pristimerin (700 mg.) in acetone (80 c.c.) was heated under reflux with dimethyl sulphate (2·5 c.c.) and potassium carbonate (1 g.) for 4 hr. Additional dimethyl sulphate (2 c.c.) and potassium carbonate were added, and heating was continued until there was no further reduction in the colour of the solution. The mixture was diluted with water, the acetone removed under reduced pressure, and the solution shaken with aqueous 10% sodium hydroxide to destroy the excess of dimethyl sulphate. A concentrate of an ethereal extract of the reaction product was chromatographed on alumina (grade I), and the crude methyl ether (80 mg.) crystallised from the ether eluate. Recrystallisation from aqueous methanol gave colourless needles of " methylated pristimerin," [2] m. p. 185—186° (lit., 186°) (Found: C, 76·0, 76·0, 76·65; H, 8·8, 8·9, 8·9; OMe, 18·6. Calc. for $C_{35}H_{50}O_5$: C, 76·3; H, 9·15; OMe, 16·9%), $\lambda_{max.}$ 281—282 mμ (log ε 3·35), $\lambda_{min.}$ 254—255 mμ (log ε 2·76), infrared absorption bands (in Nujol) at 1732(s), 1713(s) [1708(s) with a shoulder at 1720 in $CHCl_3$ solution], 1588, 1376(s), 1328(w), 1316, 1257, 1221, 1195, 1158(s), 1123(w), 1100(s), 1067, 1038, 1000, 861, 845, and 771 cm.$^{-1}$. The 2 : 4-dinitrophenylhydrone formed yellow needles, m. p. 204° (lit.,[2] 206°) (with previous shrinking) from ethanol (Found: C, 67·4; H, 7·7; N, 7·75. Calc. for $C_{41}H_{54}O_8N_4$: C, 67·4; H, 7·45; N, 7·7%), $\lambda_{max.}$ 362—366 and 266—268 mμ (log ε 4·34 and 4·07), $\lambda_{min.}$ 296—297 and 248—249 mμ (log ε 3·33 and 4·03), infrared bands (in Nujol) at 3330(w), 1735(s) and 1718(s) [single band at 1718(s) in $CHCl_3$ solution], 1618(s), 1600(s), 1513, 1333(s), 1314, 1284, 1270, 1240, 1205, 1137, 1093(s), 1025(w), 1005, 977, 920, and 830 cm.$^{-1}$.

Rearrangement of Pristimerin with Dilute Sulphuric Acid in the Presence of Acetone.—A solution of pristimerin (1·01 g.) in acetone (80 c.c.) was heated under reflux with 2N-sulphuric acid (30 c.c.) for 40 min. in an atmosphere of nitrogen. The initial deep red solution formed after addition of the acid was rapidly discharged to give a final straw-coloured solution. The acetone was removed under reduced pressure and the resulting precipitate was extracted with ether. The washed ethereal extracts were evaporated and the residue (1·1 g.) crystallised on trituration with ether. Repeated crystallisation from ether and finally ether–light petroleum (b. p. 40—60°) gave colourless needles (400 mg.) of the rearrangement *product*, m. p. 250° (Found: C, 75·7, 75·8, 76·0, 75·5; H, 8·5, 8·5, 8·55, 8·9; OMe, 7·2; *C*-Me, 8·7; active H, 0·43. $C_{33}H_{46}O_5$ requires C, 75·8; H, 8·9; 1OMe, 5·9; 3*C*-Me, 8·4; 2H, 0·38%), $\lambda_{max.}$ 285 mμ (log ε 3·49), $\lambda_{min.}$ 257 mμ (log ε 2·83), infrared bands (in Nujol) at 3540, 3420(s), 1715(s), and 1701(s) [band at 1705(s) with a shoulder at 1720 in $CHCl_3$ solution], 1623, 1513, 1345, 1295, 1265(w), 1219, 1163, 1094, 1060, 1027, 1000, 958(w), 861(s), and 773 cm.$^{-1}$. Paper chromatography with the butan-1-ol–water system on Whatman No. 1 paper gave R_F 0·89, and on Whatman No. 1 borate-buffered paper R_F 0·71. The product was detected with tetrazotised benzidine.

The reaction was repeated several times with methanol, dioxan, and ethyl methyl ketone as solvent in place of acetone, but in no case was the above rearrangement product isolated.

Action of Potassium Carbonate on Pristimerin in the Presence of Acetone.—Potassium carbonate (2 g.) was added to a solution of pristimerin (300 mg.) in acetone (50 c.c.), and the mixture heated under reflux for 10 hr., then diluted with water. The acetone was removed under reduced pressure, the resulting precipitate extracted into ether, and the ethereal layer washed with water and evaporated to dryness, to leave an almost colourless residue (330 mg.). The product was redissolved in ether and crystallised by slow evaporation of the solvent. Repeated recrystallisation from ether and finally ether–light petroleum (b. p. 40—60°) gave colourless needles (50 mg.) of the rearrangement product, m. p. and mixed m. p. with the compound obtained in the previous experiment, 250°.

Methylation of the Above Rearrangement Product.—A solution in acetone (25 c.c.) of the product (60 mg.) from the foregoing rearrangement was heated under reflux with dimethyl sulphate (1·5 c.c.) and potassium carbonate (1 g.) for 9 hr. Dilution with water and removal of the acetone under reduced pressure precipitated the methyl ether (64 mg.), which crystallised from aqueous methanol as colourless needles, m. p. and mixed m. p. with the direct methylation product of pristimerin, 185—186° (Found: C, 76·4, 76·2; H, 9·0, 8·95. Calc. for $C_{35}H_{50}O_5$: C, 76·3; H, 9·15%). The ultraviolet and infrared absorption spectra were identical with those of the direct methylation product.

Acetylation of Pristimerin.—A solution of pristimerin (100 mg.) in pyridine (2 c.c.) and acetic anhydride (10 c.c.) was heated under reflux for 2 hr., then poured into ice-water (100 c.c.), and the yellow precipitate (80 mg.) separated. This was soluble in light petroleum, benzene, ether, chloroform, and methanol but did not crystallise satisfactorily. Purification was effected by chromatography of an ethereal solution on silica, followed by repeated reprecipitation of the product from the ether eluate from a boiling methanolic solution by the addition of sufficient warm water to produce turbidity. The product was a pale yellow amorphous powder, m. p. 120—123°. Qualitative light absorption: $\lambda_{max.}$ 265—266 mμ; $\lambda_{min.}$ 260 mμ. Infrared absorption (Nujol): 1775(s), 1730(s), 1655(w), 1605, 1307, 1213(s), 1190, 1155, 1096, 1060(s), 975, 913, 894, and 733 cm.$^{-1}$.

Hydrogen Chloride Addition Product of Pristimerin.—Dry hydrogen chloride was passed into pristimerin (120 mg.), suspended in dry ether (15 c.c.). A deep red colour developed immediately and scarlet-red crystals (80 mg.) separated. Crystallisation from dry ethereal hydrogen chloride gave red needles of the *adduct*, m. p. 123—124° (Found: C, 71·0, 70·8; H, 8·5, 8·6; OMe, 8·8; Cl, 7·4. $C_{30}H_{41}O_4Cl$ requires C, 71·9; H, 8·2; 1OMe, 6·2; Cl, 7·1%), $\lambda_{max.}$ 420—430, 333—334, 317—318, and 238—239 mμ (log ε 4·03, 3·24, 3·12, and 4·28 respectively), $\lambda_{infl.}$ 282—283 mμ (log ε 3·32), $\lambda_{min.}$ 338, 315, and 219—220 mμ (log ε 3·21, 3·11, and 4·15), infrared bands (in Nujol): 3400, 2400(w), 1734, and 1701(s) (single band at 1724 in $CHCl_3$ solution), 1625, 1584(w), 1527, 1310, 1250, 1220, 1155, 1096, 990(w), 875(s), 853, and 780 cm.$^{-1}$.

Hydrolysis. The adduct (50 mg.) was suspended in aqueous 10% sodium hydroxide (15 c.c.) and heated under reflux for ½ hr. Acidification gave a yellow precipitate which was extracted into ether. The ethereal layer was washed and evaporated to dryness. The residue did not crystallise and a 56-transfer counter-current distribution was carried out with the solvent system used in the isolation of pristimerin.[1] Colour peaks appeared at tube numbers 0—1 and 22—24. The product isolated from tubes 23 and 24 (K 0·7) crystallised and had m. p. and mixed m. p. with pristimerin, 212°. In view of the low m. p. (pure pristimerin has m. p. 219—220°), the acetate of pristimerol was prepared by reductive acetylation:[1] it had m. p. and mixed m. p. with diacetyldihydropristimerin, 251—252°. Tubes 0—1 contained a red-brown compound, very soluble in methanol, which could not be purified.

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