536. *Pristimerin. Part IV.*[1] *Total Structure.*

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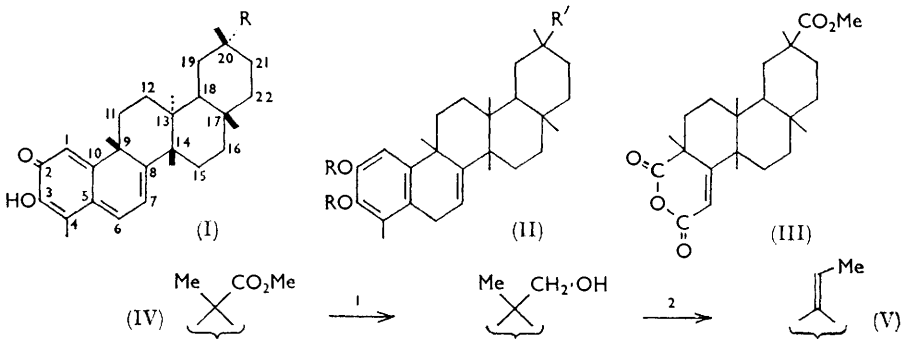
Chemical properties and biogenetic analogy lead to the formulation of pristimerin as (I; R = CO_2Me). The alcohol (II; R = Me, R′ = CH_2·OH) formed by reduction of pristimerol dimethyl ether (II; R = Me, R′ = CO_2Me) with lithium aluminium hydride is converted by phosphorus pentachloride into a substance containing an ethylidene group. Structures are suggested for three acid-rearrangement products of pristimerin.

A RECENT note [2] gives convincing reasons for assigning the complete structure (I; R = CO_2Me) to pristimerin, the pigment of the root bark of *Maytenus dispermus*. The assumption implicit in this and other recent papers that pristimerin possesses a hydrogenated



Reagents: 1, $LiAlH_4$; 2, PCl_5.

picene skeleton related to that of certain triterpenes, and in particular to that of cerin, is justified almost entirely on biogenetic grounds and analogy. Experimental support for the assumption comes only from the isolation by Nakanishi and his co-workers [3] of a very small amount of an alkylpicene from the zinc-dust fusion of pristimerin, which we have confirmed, and from the isolation of a phenanthrene,[2] again in minute yield, by dehydrogenation of the anhydride (III) obtained by oxidative removal of rings A and B of pristimerin.[1]

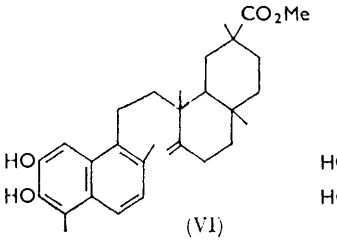
We have obtained independent evidence to support the formulation (I; R = CO_2Me) of pristimerin. The proton magnetic resonance spectrum of pristimerol dimethyl ether (II; R = Me, R′ = CO_2Me) has served to confirm the structure of its A and B rings and hence also that of the A and B rings of pristimerin as we had suggested previously.[1] *Inter alia*, the spectrum showed the presence of a single aromatic proton, an aromatic methyl group, a single olefinic proton appearing as a quadruplet justified by coupling with non-equivalent protons at C-6, and a complex multiplet assigned to these two non-equivalent protons.

The alcohol (II; R = Me, R′ = CH_2·OH) with phosphorus pentachloride gave an amorphous product which, on ozonolysis, produced acetaldehyde in 15% yield. Such a result can only be rationalised, on the basis of a triterpene skeleton, if primisterol contains the partial structure (IV), which by reduction and rearrangement would give (V) together with its double-bond isomers. Such a reaction sequence is common in diterpene chemistry and has provided the basis for the determination of the structure of many diterpene acids,

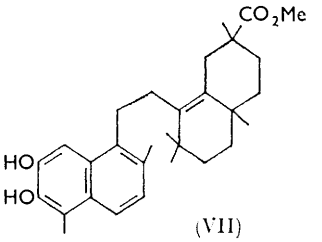
[1] Part III, Grant, Johnson, Juby, and King, *J.*, 1960, 549.
[2] Hadreda, Kakisawa, Kobayashi, Musya, Nakanishi, and Takahashi, *Tetrahedron Letters*, 1962, 603.
[3] Nakanishi, Kakisawa, and Hirata, *J. Amer. Chem. Soc.*, 1955, **77**, 3169, 6729; *Bull. Chem. Soc. Japan*, 1956, **29**, 7.

including abietic acid.[4] The partial structure (IV) can only occur in pristimerin if this has the methoxycarbonyl group at position 20 as in (I; R = CO_2Me).

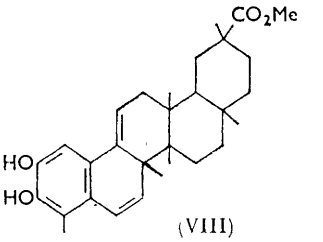
The chemistry of pristimerin is notable for the variety of rearrangement products produced from it by acids. We have previously described three of these and structures for two of them have been suggested [2] as being (VI) and (VII) named isopristimerin-I and isopristimerin-II (the diol corresponding to our Thiele product [1,5]), respectively. We accept these formulations which are in agreement with the nuclear magnetic resonance spectra of the respective compounds; thus only isopristimerin-I shows a two-proton doublet at 4·82 and 5·00 τ attributable to the protons on a terminal methylene group, which is absent in isopristimerin-II.



(VI)

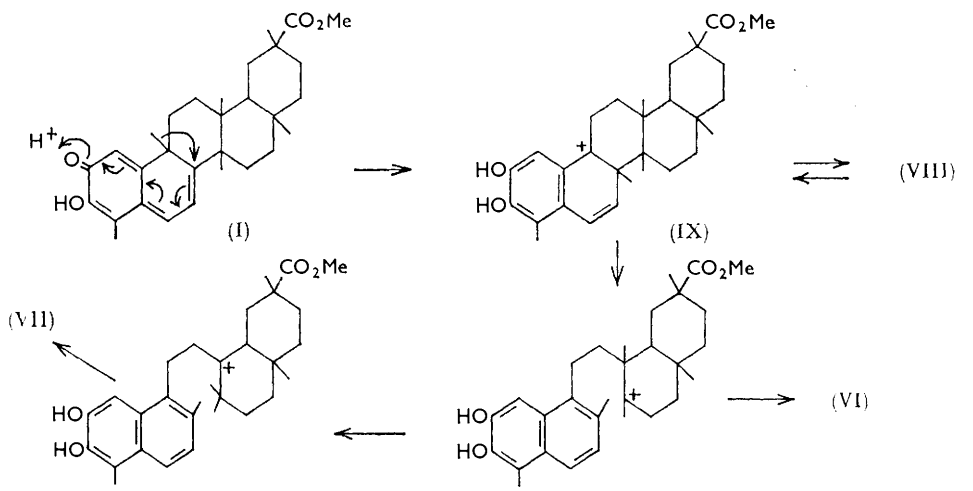


(VII)



(VIII)

The product formed from primisterin by use of methanolic sulphuric acid rearrangement has now also been obtained by ultraviolet irradiation. This aromatic diol is a substituted styrene rather than a naphthalene derivative.[1] Nuclear magnetic resonance measurements of the derived dimethyl ether enable us to formulate it (now named isopristimerin-III) as the *o*-divinylbenzene derivative (VIII). The spectrum shows nine singlet methyl peaks, five from aliphatic tertiary *C*-methyl groups, one from an aromatic methyl group, one from an ester methyl group, and two from aromatic methoxy-groups. Only one aromatic proton resonance is observed (as a singlet at 3·24 τ), and in addition there are a pair of doublets centred at 3·51 and 3·70 τ (*J* 8·6 c./sec.) attributable to the AB system of the two vinyl protons at C-6 and C-7, and a single proton quartet at 4·32 τ



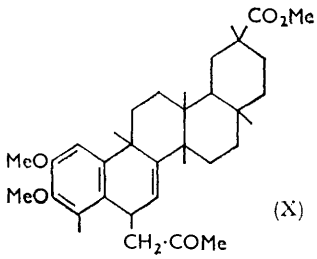
attributable to the proton at C-11 split by the two non-equivalent allylic protons at C-12, which themselves are revealed as a broad envelope at 7·55 τ. The formulation of isopristimerin-III as a divinylbenzene is supported by the high intensity of the ultraviolet absorption [$\lambda_{max.}$ 309 and 256 mμ (ε 5500 and 38,000)].

[4] Ruzicka, de Graaff, and Müller, *Helv. Chim. Acta*, 1932, **15**, 1300; Haworth, *J.*, 1932, 2717.
[5] Grant and Johnson, *J.*, 1957, 4079.

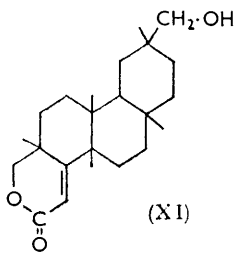
The formation of all three acid-rearrangement products can be rationalised as shown on p. 2885 in which the indicated reversibility of the change from the carbonium ion (IX) to isopristimerin-III (VIII) is justified by the conversion of the latter by strong acids into isopristimerin-II (VII).

We have previousyl commented on the marked shift of the infrared carbonyl absorption frequency shown by isopristimerin-I (VI) compared with its diacetate and the other two rearrangement products. A study of models shows that it is possible for the methoxycarbonyl group of isopristimerin-I to form a hydrogen bond with the 2-hydroxyl group and that this is easier if the ester group has the β-configuration, as suggested by the Japanese workers,[2] but it is not clear why isopristimerin-II does not appear to form such a bond.

The reduction of pristimerin by lithium aluminium hydride has been reported [6] by Indian workers to give two products. We have repeated this reduction but obtained only one product, a hydroxycatechol (spectra; ferric reaction) which, by methylation, was converted into the dimethyl ether (II; R = Me, R′ = CH_2·OH) and the hydroxycatechol must therefore be (II; R = H, R′ = CH_2·OH). It is easily oxidised by air to an orange compound which has light absorption similar to that of pristimerin and is thus formulated as (I; R = CH_2·OH). The alcoholic product (II; R = Me, R′ = CH_2·OH) from the reduction of pristimerol dimethyl ether by lithium aluminium hydride afforded a crystalline toluene-*p*-sulphonate which on further reduction by hydride gave an amorphous product, presumably (II; R = R′ = Me). Similar reduction of the acetone addition product [7,8] of pristimerol dimethyl ether produced a diol (infrared) $C_{34}H_{52}O_4$, confirming the structure (X) previously [7] assigned to the acetone adduct. Reduction of pristimerol dimethyl ether by sodium or lithium in ammonia gave intractable products from which the only compound isolated, in very low yield, was the alcohol (II; R = Me, R′ = CH_2·OH).



(X)



(XI)

The main permanganate oxidation product of pristimerin is now formulated as (III) and the structure is supported by nuclear magnetic resonance which shows six singlet methyl peaks and one singlet olefinic proton. This anhydride (III) has been characterised as the benzylimide and, from the unstable parent acid, diazomethane forms the corresponding trimethyl ester. Lithium aluminium hydride reduces the anhydride to a slightly impure unsaturated hydroxy-lactone, which because of its spectral properties is formulated as (XI).

Experimental

M. p.s were determined on a Kofler block and are uncorrected. Ultraviolet and visible spectra refer to ethanolic solutions and were determined with a Unicam S.P. 700 spectrophotometer; infrared spectra refer to carbon tetrachloride solutions except where otherwise stated and were determined with a Unicam S.P. 100 spectrophotometer. Nuclear magnetic resonance spectra were determined by using a A.E.I. RS2 instrument (60 Mc./sec.) and tetramethylsilane as an internal reference.

Ozonolysis of the Phosphorus Pentachloride Rearrangement Product of Reduced Pristimerol

[6] Seshadri, Mhaskar, Kulkarni, and Shah, *J. Sci. Ind. Res., India*, 1958, **17**, *B*, 111.
[7] Grant and Johnson, *J.*, 1957, 4669.
[8] Shah, Kulkarni, and Thakore, *J.*, 1955, 2515.

Dimethyl Ether.—The reduction product[1] (II; R = Me, R′ = CH_2·OH) of pristimerol dimethyl ether (100 mg.), and lithium aluminium hydride, in dry ether (25 ml.) was treated with phosphorus pentachloride (100 mg.) and kept for 2 hr. with occasional shaking, the phosphorus pentachloride dissolving. The mixture was kept overnight and the clear solution then heated under reflux for 2 hr. Water was added and the ethereal layer washed free from acid with aqueous sodium hydrogen carbonate and then water. Removal of the solvent from the dried ethereal solution gave a brownish-yellow amorphous product which was dissolved in methylene dichloride (20 c.c.) and cooled to −5°. A stream of ozonised oxygen was passed through the solution for 2½ hr. and the whole kept overnight at −5°. The mixture was distilled in steam and the distillate treated with solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid; the derivative (15·6%), m. p. and mixed m. p. 147—147·5°, of acetaldehyde was obtained.

Rearrangement of Isopristimerin-III Dimethyl Ether to Isopristimerin-II Dimethyl Ester.—A solution of isopristimerin-III dimethyl ether[1] (25 mg.) in acetic acid (2·5 ml.) was treated with perchloric acid (1 drop). The colourless solution immediately became orange and then red, and it was heated on the steam-bath for 2 hr. Addition of water precipitated a grey solid which was dissolved in methanol and reprecipitated with water. Crystallisation of the solid from methanol gave colourless needles (6 mg.), m. p. 92—93°, of isopristimerin-II dimethyl ether.[1] The ultraviolet and infrared spectra were identical with those of an authentic specimen.

Isocelastrol-III Dimethyl Ether.—Isopristimerin-III dimethyl ether (100 mg.) was heated in 25% methanolic potassium hydroxide (50 ml.) for 1 hr. The hot solution was filtered and the cooled filtrate acidified with concentrated hydrochloric acid. The precipitated white solid was separated and extracted in ether, and after removal of the solvent the residue (50 mg.) was crystallised from aqueous methanol, to give *isocelastrol-III dimethyl ether* [Me_2 ether of the acid from (VIII)] as colourless needles, m. p. 253—254° (Found: C, 77·9; H, 9·25. $C_{31}H_{42}O_4$ requires C, 77·8; H, 8·85%), $\lambda_{max.}$ 249, 255, and 301 mμ (ε 39,300, 38,000, and 6460, respectively), inflection at 283 mμ (ε 4860), $\nu_{max.}$ 1701 (carboxyl C=O), 1597, 1482 (aromatic), and 849 (tri-substituted olefin) cm.$^{-1}$.

The acid was treated with diazomethane and the product crystallised from methanol; colourless needles, m. p. and mixed m. p. 197—198°, of isopristimerin-III dimethyl ether were obtained, with the correct ultraviolet and infrared spectra.

Rearrangement of Isocelastrol-III Dimethyl Ether to Isocelastrol-II Dimethyl Ether.—Isocelastrol-III dimethyl ether (20 mg.) in acetic acid (2 ml.) was treated with perchloric acid (1 drop) in the manner described above for isopristimerin-III dimethyl ether. The product was crystallised from light petroleum as needles, m. p. 114—118° alone and mixed with an authentic specimen.[1] The ultraviolet and infrared spectra of the two samples were identical.

Photochemical Conversion of Pristimerin into Isopristimerin-III.—A solution of pristimerin (100 mg.) in 95% ethanol contained in a quartz vessel was heated under reflux and irradiated with ultraviolet light for 7 days. No change in colour occurred. After removal of the solvent the residue crystallised from ether–light petroleum as needles, m. p. 230—235°, not depressed on admixture with isopristimerin-III. The corresponding dimethyl ether had m. p. 197—198° and was identical with isopristimerin-III dimethyl ether.[1] In a control experiment an ethanolic solution of pristimerin was heated under reflux for 7 days but without irradiation: unchanged pristimerin was recovered.

Reduction of Pristimerin with Lithium Aluminium Hydride.—A solution of pristimerin (200 mg.) in tetrahydrofuran (40 ml.) was added to a suspension of a slight excess of lithium aluminium hydride in tetrahydrofuran (20 ml.). The colour of the solution changed from orange to light yellow and the suspension was heated under reflux for 3 hr. The excess of hydride was decomposed with water, and the solution acidified with dilute sulphuric acid and then extracted with ether. The ethereal extract was washed and dried. Removal of the solvent gave the triol (II; R = H, R′ = CH_2·OH) (126 mg.) which was crystallised from carbon tetrachloride to give a *solvate*, m. p. 165—166°, as needles (Found: C, 71·6; H, 8·15. $3C_{29}H_{42}O_3,CCl_4$ requires C, 71·9; H, 8·45%). Recrystallisation from benzene gave the *triol* as colourless needles, m. p. 186—187·5° (Found: C, 79·0; H, 9·65. $C_{29}H_{42}O_3$ requires C, 79·4; H, 9·65%), $\lambda_{max.}$ 284 mμ (ε 3090), $\nu_{max.}$ (in $CHCl_3$) 3570 (free OH), 3365, 3310 (bonded OH) cm.$^{-1}$.

The triol (50 mg.) in methanol (30 ml.) was heated under reflux with dimethyl sulphate (1 ml.) and potassium carbonate (1 g.) for 30 min. A further quantity (1 ml.) of dimethyl sulphate was added and the solution heated for 2 hr. Water was added to dissolve the salts, and the solution extracted exhaustively with ether. The dried ethereal solution was filtered

through a short column of alumina, the solvent removed from the eluate, and the residue (12 mg.) crystallised from aqueous ethanol to form colourless needles, m. p. 109—114°, identical with the reduction product [1] of pristimerol dimethyl ether.

The *toluene*-p-*sulphonate* formed colourless prisms (from methanol), m. p. 147—148° (Found: C, 73·7; H, 8·7; S, 4·8; OMe, 8·75. $C_{38}H_{52}O_5S$ requires C, 73·5; H, 8·45; S, 5·15; 2OMe, 10·0%), $\nu_{max.}$ 1176, 1186, 1479, 1587, 1645, and 2933 cm.$^{-1}$.

Aerial Oxidation of the Triol (II; R = H, R′ = CH_2·OH).—The solid triol slowly (*ca.* 10 weeks) became orange and the m. p. was then 198—204°. Crystallisation from benzene gave orange needles, m. p. 211—213° which were also obtained in following manner. A solution of the triol (25 mg.) in benzene (25 ml.) was heated on the steam-bath in an open flask for 3 hr. The volume of benzene was maintained by the addition of fresh solvent. Concentration of the solution gave orange needles of (I; R = CH_2·OH), m. p. 211—213°, identical with the sample obtained as above (Found: C, 79·5; H, 9·35. $C_{29}H_{40}O_3$ requires C, 79·75; H, 9·25%) and having $\lambda_{max.}$ 425 mμ (ε 5470), inflections at 258 and 284 mμ (ε 5880 and 2260), and $\nu_{max.}$ 1609 (quinone C=O; cf. ref. 5), 3389 (bonded OH), and 3556 (non-bonded OH) cm.$^{-1}$.

Reduction of Pristimerol Dimethyl Ether with Lithium in Liquid Ammonia.—A solution of pristimerol dimethyl ether (170 mg.) in tetrahydrofuran (3 ml.) was added dropwise to the blue solution of lithium (0·5 g.) in liquid ammonia (50 ml.) with stirring in a flask fitted with a carbon dioxide–acetone-cooled condenser. Then ethanol (1·5 ml.) was added dropwise to the stirred mixture. Stirring was continued for 4 hr., after which the mixture was treated with ice and then water. The product was stirred for an hour and then extracted with ether. The ethereal extract was dried and the solvent removed, leaving a yellow oil which slowly crystallised. This recrystallised from methanol as colourless rosettes (7 mg.), m. p. 109—114°, $\lambda_{max.}$ 283 mμ (ε 2190), identical (infrared and ultraviolet spectra) with the product of reduction of pristimerol dimethyl ether by lithium aluminium hydride. No crystalline organic product could be isolated from the aqueous layer after the ether-extraction.

Alkaline Hydrolysis of Pristimerol Dimethyl Ether.—Pristimerol dimethyl ether (200 mg.) was hydrolysed with 20% methanolic potassium hydroxide (50 ml.) for 16 hr. as described above for isopristimerin-III dimethyl ether. The acidic *product* (160 mg.) crystallised from ether as colourless needles, m. p. 238—239° (Found: C, 77·8; H, 9·25. $C_{31}H_{44}O_4$ requires C, 77·45; H, 9·25%), $\lambda_{max.}$ 281 mμ (ε 1970), inflection at 224 mμ (ε 8570), $\nu_{max.}$ (KBr disc) 849 (trisubstituted olefin), 1494, 1598 (aromatic), and 1693 (carboxyl C=O) cm.$^{-1}$.

With diazomethane the acid gave pristimerol dimethyl ether [5] as colourless needles (from chloroform–methanol), m. p. and mixed m. p. 214—215°. The infrared spectrum of the product was identical with that of an authentic sample of pristimerol dimethyl ether.

Reduction of Acetonylpristimerol Dimethyl Ether (X) *by Lithium Aluminium Hydride.*—Acetonylpristimerol dimethyl ether [7] (112 mg.) in ether was added to a suspension of lithium aluminium hydride (excess) in ether (25 ml.), and the mixture kept with occasional stirring at room temperature for 35 min. The excess of hydride was decomposed with water, and the solution was acidified with 10% sulphuric acid. The ether layer was washed with aqueous sodium carbonate and then with water, and after removal of the solvent the product (51 mg.) was obtained which crystallised from ethanol as colourless rods, m. p. 157—158°, resolidifying and remelting at 198—199° [lit.,[8] 162° (decomp.)] (Found, on a sample dried at 150° *in vacuo*: C, 77·7; H, 9·7; OMe, 12·5. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0; 2OMe, 11·8%), $\lambda_{max.}$ 280 mμ (ε 2090), $\nu_{max.}$ (in $CHCl_3$) 1493, 1599 (aromatic), and 3472 and 3624 (OH) cm.$^{-1}$.

Dimethyl Ester of the Parent Acid of Anhydride A (III).—A solution of anhydride A (100 mg.) in methanol (2 ml.) was treated with 20% methanolic potassium hydroxide (1 ml.) and kept for 1 hr., then diluted with water (50 ml.) and acidified with concentrated hydrochloric acid. The precipitated acid was separated, dried, and treated with diazomethane. The *methyl ester* so obtained sublimed at 150°/0·5 mm. as colourless needles (86 mg.), m. p. 164—165° (Found: C, 69·2; H, 8·55; OMe, 20·6. $C_{26}H_{40}O_6$ requires C, 69·6; H, 8·9; 3OMe, 20·8%), $\lambda_{max.}$ 225 mμ (ε 11,500). The ester carbonyl band in the infrared spectrum was at 1733 cm.$^{-1}$.

Benzylimine of Anhydride A.—A solution of anhydride A (50 mg.) in benzylamine (0·5 ml.) was heated at 160° for 3¼ hr. The yellow solution was cooled, then poured into 10% hydrochloric acid (30 ml.), and the precipitated off-white solid was collected. After crystallisation from methanol the *benzylimine* formed colourless rods, m. p. 184—185° (Found: C, 75·7; H, 8·35; N, 3·0; OMe, 7·7. $C_{31}H_{41}NO_4$ requires C, 75·7; H, 8·4; N, 2·85; 1OMe, 6·3%), $\lambda_{max.}$ 209 mμ (ε 18,200), $\nu_{max.}$ 1678, 1718 (imine C=O), and 1737 (ester C=O) cm.$^{-1}$.

Reduction of Anhydride A by Lithium Aluminium Hydride.—Anhydride A (90 mg.) was reduced with an excess of lithium aluminium hydride; the *product* (XI) (16 mg.) crystallised from aqueous methanol as colourless prisms, m. p. 243—245° (Found: C, 75·9; H, 9·65; OMe, 0·0. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·05%), $\lambda_{max.}$ 225 mμ (ε 11,750), $\nu_{max.}$ (KBr disc) 3508 (OH) and 1695 (αβ-unsaturated δ-lactone) cm.$^{-1}$.

We are grateful to Dr. J. R. Price, C.S.I.R.O., Melbourne, for generous supplies of the root bark of *Maytenus dispermus* and to Professor L. M. Jackman who determined the nuclear magnetic resonance spectrum of pristimerol dimethyl ether. We also acknowledge the award of a maintenance grant from D.S.I.R. (to P. F. J.) and a Commonwealth Scholarship from the Commission in the United Kingdom (to S. W. T.).

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