656. *Lignans. Part IV.*[1] *Structural Changes Accompanying the Acylation of Alcohols*

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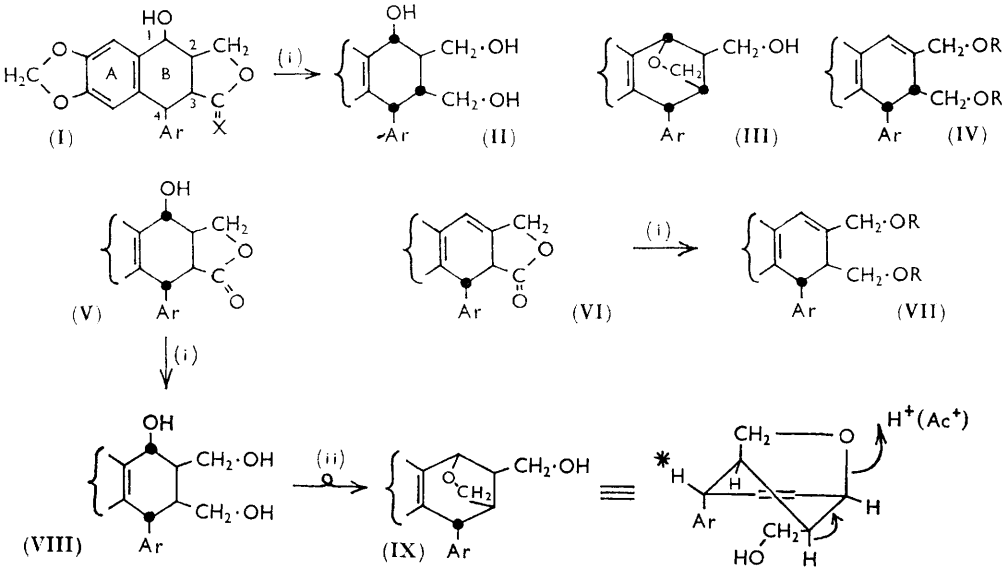
Isopropenyl acetate is an effective acetylating agent for lignan alcohols, but reaction is attended by an elimination whose course is only consistent with the structures previously assigned to anhydropodophyllol (III) and anhydropicropodophyllol (IX). The products were α-apo-compounds, including those not hitherto described, with the podophyllotoxin configuration retained at C-3 and C-4.

The location of the hydroxyl group in anhydropodophyllol, and hence an assignment of structure, was originally approached by nuclear magnetic resonance spectroscopy but the necessary resolution from resonances due to ether functions could not be obtained with the hydroxyl group free.[2] In an effort to overcome this, acetylation was attempted with a number of reagents but ill-characterised products were obtained. Since isolated crude materials had very different optical rotations from starting material, it seemed probable that structural changes, possibly involving elimination were occurring; accordingly, reaction was attempted with isopropenyl acetate, a reagent [3] which is useful for the acetylation of hindered alcohols liable to undergo elimination.

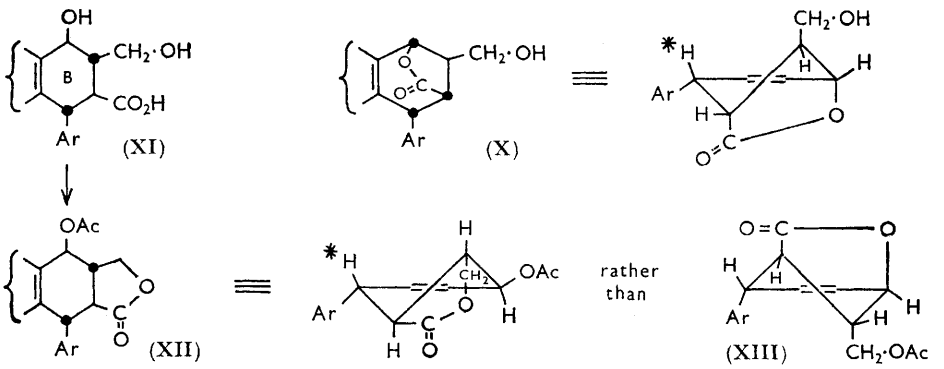


Reagents: (i) $LiAlH_4$, (ii) TsCl/xylene. Ar = 3,4,5-trimethoxyphenyl

Podophyllotoxin (I; X = O), α_D −119° ($CHCl_3$), was smoothly converted into acetylpodophyllotoxin, α_D −146° ($CHCl_3$), and it was expected that anhydropodophyllol, α_D 0° ($CHCl_3$), would behave similarly if its structure included a *trans*-fused tetrahydrofuran ring at C-2,3, *i.e.*, (I; X = H_2), since in the lactone this geometry has been shown [4] to preclude the formation of a 1,2-double bond by elimination. The product obtained was acetylated (infrared spectrum) but a substantial change in rotation, α_D +73° ($CHCl_3$), had occurred and treatment of the acetyl derivative with lithium aluminium hydride or alkali afforded an alcohol, α_D +90° ($CHCl_3$), different from the starting anhydropodophyllol.

[1] Part III, Ayres, Carpenter, and Denney, preceding Paper.
[2] L. M. Jackman, private communication.
[3] Hagemeyer and Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920.
[4] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1954, **76**, 752.

A band was detected at 1700 cm.$^{-1}$ in the infrared spectrum of the derived alcohol which was masked in the acetate, and we ascribe this to an olefinic double bond in ring B. The ultraviolet absorption spectrum had a maximum at 310 mμ close to that at 311 mμ in α-apopicropodophyllin (VI) and hence the product is α-apopodophyllol (IV), in accord with structure (III) for anhydropodophyllol. Since α-apo-compounds retaining the podophyllotoxin configuration have not been described previously, a direct structural correlation is not possible here; however, anhydropicropodophyllol (IX),* α_D +78° ($CHCl_3$), undergoes a similar reaction with isopropenyl acetate as shown, (IX) ⟶ (VII), affording the diacetate (VII; R = Ac), α_D −41° ($CHCl_3$), of α-apopicropodophyllol. The corresponding diol (VII; R = H) was obtained by hydrolysis of the diacetate and by lithium aluminium hydride reduction, and proved to be identical with the reduction product of α-apopicropodophyllin. A point of interest was the ease with which picropodophyllin (V), α_D +9° ($CHCl_3$), afforded the α-apo-lactone on treatment with isopropenyl acetate, no acetyl derivative being detected.



The diacetyl α-apo-compounds were also obtained by reaction of the corresponding triols (II) and (VIII) with isopropenyl acetate. The anhydro-compounds may be formed first, and certainly for podophyllol this step is demonstrably the easier, occurring on reflux in xylene [5] or by treatment with iodine–dimethylformamide with no subsequent elimination.

When 1,3-anhydro-compounds were first isolated,[5] attention was drawn to the possibility of 1,3-lactonisation competing with 2,3-cyclisation in the synthesis of podophyllotoxin. This has recently been demonstrated by Kuhn and von Wartburg,[6] who obtained neopodophyllotoxin (X) by methanolysis of podophyllotoxin: this result contrasting with that of Gensler and Johnson,[7] who obtained acetyl isopodophyllotoxin (XII) by treatment of isopodophyllic acid (XI) with acetic anhydride, and with the analogous 2,3-lactonisation demonstrated by Kulkarni and his co-workers [8] in their synthesis of isosikkimotoxin. 1,3-Cyclisation in the internal ethers is to be expected since the acid-catalysed reaction probably proceeds through a carbonium ion at C-1, which is resonance-stabilised; if the hydroxyl groups are *trans*-related, then net inversion will occur at this position.

On the other hand, formation of the lactone (X) probably proceeds by nucleophilic attack by the hydroxyl group on a *cis*-related carboxyl group with retention of configuratio at C-1, this being the normal mode of formation of γ-lactones with acyl-oxygen fission. The alternative of carbonium ion formation at C-1 is unlikely, as there was no evidence of

* The formula given in Part II [5] is incorrect.

[5] Ayres and Pauwels, *J.*, 1962, 5025.
[6] Kuhn and von Wartburg, *Experientia*, 1963, **19**, 391.
[7] Gensler and Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 3670.
[8] Shroff, Diwadkar, and Kulkarni, *Indian J. Chem.*, 1964, **2**, 190.

epimerisation during the methanolysis. Conformational factors favour the formation of (X) by 1,3-cyclisation, for the bulky aryl group adopts a quasi-equatorial conformation; similar closure of the lactone from (XI) will be opposed because a structure (XIII) would result, having all substituents axial, whereas in the isolated 2,3-cyclised product (XII) all substituents are equatorial.

Experimental

Analyses were by Messrs. D. R. Hanks and B. T. Saunderson. Infrared spectra were measured for Nujol mulls.

Typical Acetylation with Isopropenyl Acetate. Preparation of Acetyl Podophyllotoxin.—Concentrated sulphuric acid (1 drop) was added to isopropenyl acetate (6 ml.) in the cold and podophyllotoxin (500 mg.) was dissolved by warming. The solution was heated on a steam-bath for 30 min., cooled, stirred with sodium carbonate solution, and evaporated under reduced pressure. The solid obtained was washed with ether and the residue (380 gm., 70%) identified as acetylpodophyllotoxin,[9] m. p. 211—212° (from ethanol), $[\alpha]_D^{21}$ −146° (*c* 0·8 in $CHCl_3$).

Picropodophyllin and Isopropenyl Acetate.—Picropodophyllin (1·80 g.) was treated as for podophyllotoxin and, on cooling, a solid separated (1·00 g., 55%), m. p. 240—242°, $[\alpha]_D^{20}$ −16°, (*c* 0·9 in $CHCl_3$) after crystallisation from acetic acid containing a little hydrochloric acid. The pure material had an identical infrared spectrum to that of an authentic sample of α-apopicropodophyllin.[10]

α-Apopicropodophyllol (with S. E. Mhasalkar).—α-Apopicropodophyllin (1·00 g.), in tetrahydrofuran (40 ml.), was reduced with lithium aluminium hydride (0·75 g.) in tetrahydrofuran (20 ml.) as previously described.[5] Isolation with hydrochloric acid and chloroform extraction afforded an oil which became solid (725 mg., 72%), m. p. 47—52°, after removal of the last traces of chloroform in a good vacuum and trituration in light petroleum (b. p. 60—80°). An analytical sample was obtained by solution of crude product (75 mg.) in dry ether (6 ml.), filtration from a little insoluble material, and shaking with charcoal (20 mg.) for several hours. On concentration of the solution, *α-apopicropodophyllol* (60 mg.) separated, m. p. 92—93° (softening at 75°), $[\alpha]_D^{20}$ −66° (*c* 1·0 in $CHCl_3$) (Found: C, 66·6; H, 6·25. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%).

Diacetyl α-Apopodophyllol.—Anhydropodophyllol (500 mg.) was treated as above, although solution in the isopropenyl acetate was initially incomplete, and on evaporation of the solvent a green oil was obtained; this *diacetate* (500 mg., 83%) was solidified by trituration with light petroleum (b. p. 60—80°) and had m. p. 97—99° (from ethanol–water) (Found: C, 64·8; H, 5·7. $C_{26}H_{28}O_9$ requires C, 64·5; H, 5·8%).

The same product was obtained in similar yield from podophyllol, having an identical infrared spectrum $\nu_{max.}$ 1735 $cm.^{-1}$ (ester C=O) (OH absent), $\lambda_{max.}$ 310 mμ, $[\alpha]_D^{22}$ +73° (*c* 1·0 in $CHCl_3$).

Diacetyl α-Apopicropodophyllol.—This was obtained on treatment of picropodophyllol and anhydropicropodophyllol with isopropenyl acetate, when chromatography on alumina and elution with chloroform–benzene (1 : 1) afforded a semi-solid product in 80% yield from both starting materials (500 mg.), $[\alpha]_D^{22}$ −41° (*c* 1·0 in $CHCl_3$). Infrared and ultraviolet spectra were consistent with the formation of the α-apo-diacetate but it could not be crystallised and analytical figures were unsatisfactory (Found: C, 65·7; H, 6·0. $C_{26}H_{28}O_9$ requires C, 64·5; H, 5·8%). Characterisation was effected by hydrolysis and by reduction to α-apopicropodophyllol, as follows.

(*a*) Diacetyl α-apopicropodophyllol (250 mg.) was refluxed in ethanol (10 ml.) with potassium hydroxide (500 mg.) for 1 hr. Dilution with water (10 ml.) and acidification with hydrochloric acid afforded the diol as a yellow solid (180 mg., 86%), which was further purified as in the preparation from α-apopicropodophyllin or by solution in the minimum quantity of ethyl acetate, filtration, and precipitation with light petroleum (b. p. 60—80°), m. p. 92—93°.

(*b*) The diacetate (1·00 g.) in tetrahydrofuran (10 ml.) was reduced with lithium aluminium hydride (0·75 g.) in tetrahydrofuran (10 ml.) as above. Isolation with hydrochloric acid, followed by chloroform extraction, gave a yellow solid (800 mg., 96%) purified as in (*a*) above and identical with that product and α-apopicropodophyllol from reduction of α-apopicropodophyllin.

[9] Borsche and Niemann, *Annalen*, 1932, **499**, 59.
[10] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1952, **74**, 5676.

α-*Apopodophyllol* (with S. E. MHASALKAR).—The diacetate (400 mg.) was hydrolysed as in (*a*) and afforded a crude yellow solid (280 mg., 84%), which was also obtained in superior yield (90%) by lithium aluminium hydride reduction. Several crystallisations from ethyl acetate–light petroleum (b. p. 60—80°) afforded the *diol*, m. p. 144—146°, $[\alpha]_D^{19}$ +90° (*c* 1·0 in $CHCl_3$) (Found: C, 66·7; H, 5·9. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%).

Reaction of Podophyllol with Iodine.—Podophyllol (102 mg.) was dissolved in dimethylformamide (1 ml.) and heated with iodine (20 mg.) on a steam-bath. After 1 hr. the solution was poured into water (20 ml.) containing sodium thiosulphate (0·25 g.), when a white oil separated and solidified on standing. The solid (82 mg., 81%) was crystallised from ethanol and characterised as anhydropodophyllol by its m. p. (253—255°) and infrared spectrum.

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