with petroleum ether and subsequent crystallization from methanol–water gave 41 mg. of desoxypodocarponitrile (XXV), m.p. 83–87°, identical in all respects with the nitrile obtained directly by the sodamide treatment of the acid chloride (mixed m.p. 83–87°).

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

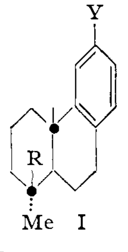
Partial Degradation and Reconstitution of Podocarpic Acid. A Novel Method of Hydrolysis of Highly Sterically Hindered Esters[1]

BY ERNEST WENKERT AND B. G. JACKSON

RECEIVED AUGUST 19, 1957

The degradation of podocarpic acid to its desoxy derivative and the latter's conversion to the resin acid is portrayed. Lithium–liquid ammonia treatment of highly sterically hindered methyl esters has been shown to yield preponderantly acids. The utility of this method for easy hydrolysis of hindered esters as well as for diagnosis of the steric disposition of ester functions on rigid ring systems is described.

As part of a chemical investigation in the diterpene field it became of interest to remove the phenolic hydroxyl group of podocarpic acid (Ia) as well as to convert the resulting desoxy compound back to the natural product.



I

a, R = CO_2H, Y = OH
b, R = CO_2Me, Y = OH
c, R = CO_2H, Y = H
d, R = CO_2Me, Y = H
e, R = CH_2OH, Y = H
f, R = CO_2Me, Y = Ac
g, R = CO_2Me, Y = OAc
h, R = CO_2Me, Y = $OPO(OEt)_2$
i, R = $CONH_2$, Y = H

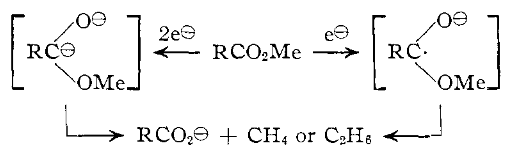
On exposure of methyl podocarpate (Ib) to a Kenner desoxygenation,[2] *i.e.*, phosphorylation followed by reduction with lithium in liquid ammonia, desoxypodocarpic acid (Ic), its methyl ester (Id) or desoxypodocarpinol (Ie) were formed. Methyl desoxypodocarpate (Id), prepared in this manner or obtained by diazomethane treatment of desoxypodocarpic acid (Ic), could be acetylated with acetyl chloride and aluminum chloride in carbon disulfide solution yielding a ketoester If. Emmons oxidation[3] of the latter led to methyl podocarpate acetate (Ig), identical in all respects with the product obtained from a reaction between methyl podocarpate (Ib) and acetic anhydride. Treatment of the acetate with aqueous sodium hydroxide gave a quantitative yield of methyl podocarpate (Ib).

One of the less readily explicable results of the above reaction cycle was associated with the metal reduction of methyl podocarpate phosphate (Ih). When the reaction was quenched rapidly by early addition of ammonium chloride, the major product was the expected desoxy ester Id, accompanied by small amounts of its acid Ic and alcohol Ie. However, a procedure of adding ethanol to the reaction mixture upon the complete dissolution of the lithium in the medium followed by slow evaporation of the ammonia led preponderantly to the acid Ic and some alcohol Ie.

The formation of desoxypodocarpinol (Ie) was not at all astonishing, since esters are well known to be susceptible to reduction under the above reaction conditions, but the production of desoxypodocarpic acid required explanation. Two ready interpretations, based on the possibility of water, undoubtedly present in the liquid ammonia, having been the important reagent, readily could be dismissed. Base-catalyzed hydrolysis of the methyl ester was inconceivable due to the known stability of the axial carbomethoxy group to even more stringent hydrolytic conditions,[4] and Cannizzaro disproportionation of an intermediate aldehyde was highly improbable because of the production of grossly unequal amounts of acid and alcohol and because of the non-isolation of aldehyde in rapidly quenched reactions.

The possibility existed that the strongly nucleophilic amide ion, a product of the phosphate reduction,[2] could have hydrolyzed the ester by a displacement on the methoxy carbon atom in analogy with hydrolyses of other sterically hindered esters, albeit under more energetic conditions.[5] However this suggestion was abandoned when it was shown that methyl desoxypodocarpate (Id) yielded only starting material and 15% amide Ii on exposure to lithium amide in liquid ammonia. Finally, any possible participation of the phosphate group in acid production was dismissed on discovery that lithium–liquid ammonia reduction of methyl podocarpate (Ib) led mainly to podocarpic acid (Ia).

This novel hydrolysis of a methyl ester thus appeared to be a reductive process of the following *formal* representation



Its successful competition with normal ester reduction must be due to the great resistance of the

---

[1] This work was presented in part to the Symposium of the Chemical Society on "Recent Advances in the Chemistry of Terpenoid Compounds," Glasgow, Scotland, July 11–12, 1957, and in part to the 16th International Congress of Pure and Applied Chemistry, Paris, France, July 18–25, 1957.

[2] G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

[3] W. B. Emmonds and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955).

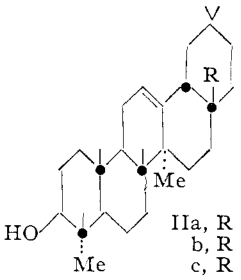
[4] W. P. Campbell and D. Todd, *ibid.*, **64**, 928 (1942).

[5] *Cf.* H. L. Goering, T. Rubin and M. S. Newman, *ibid.*, **76**, 787 (1954).

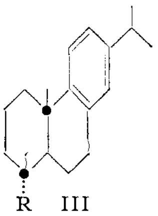
axially oriented trigonal carbonyl carbon atom to expand to the more sterically demanding tetrahedral state.[6,7] While the fate of the methyl function has not been ascertained, most probably the group is reduced to methane or ethane. The closest analogy to this *reductive hydrolysis* is the reported cleavage of alkyl aryl ethers to phenols.[8]

While this new reaction appeared to be useful as an easy hydrolysis of highly sterically hindered esters, it also suggested itself as a diagnostic tool for differentiating axial from equatorial carboxyl groups in rigidly held ring systems. Esters of the latter, possessing less steric hindrance, could be expected to reduce to the alcohol, while those of the former should undergo *reductive hydrolysis*. This hypothesis proved correct at least in the several more cases studied.

Methyl desoxypodocarpate (Id), an axial ester, on metal–ammonia treatment gave a 77% yield of the acid Ic and a 23% yield of alcohol Ie. Methyl oleanolate (IIa), a less sterically hindered axial ester, yielded 68% oleanolic acid (IIb) and 28% erythrodiol (IIc). However, methyl dehydroabietate (IIIa), an equatorial ester, afforded 3% dehydroabietic acid (IIIb) and 62% dehydroabietinol (IIIc).

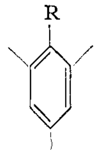


IIa, R = CO_2Me
b, R = CO_2H
c, R = CH_2OH



III

The sterically hindered aromatic ester methyl mesitoate (IVa) was reduced exclusively to alcohol IVb.



IVa, R = CO_2Me
b, R = CH_2OH

Acknowledgments.—The authors are most grateful to Drs. Bible, Djerassi, Gilman, Hoehn, Ivett and Zeiss for supplying compounds used in this study, and to the Institute for Atomic Research, Ames, Iowa, for the use of a Baird infrared spectrophotometer.

Experimental

Desoxypodocarpic Acid (Ic), Its Methyl Ester (Id) and Alcohol (Ie).—A mixture of 700 mg. of methyl podocarpate, m.p. 212.5–213°, [α]D +104.6° (EtOH), 5 ml. of anhydrous tetrahydrofuran, 25 ml. of carbon tetrachloride, 1.3 ml. of diethyl phosphite and 1.5 ml. of anhydrous triethylamine was refluxed for six hours. After cooling the mixture was washed with 5% hydrochloric acid, with 5% aqueous sodium hydroxide, and finally with water. After drying the solution over magnesium sulfate and evaporation of the solvent, there was obtained 1.21 g. of a dark brown gum, which was used directly in the next reaction without further purification.

A solution of 5.68 g. of methyl podocarpate diethyl phosphate (Ih) in 50 ml. of anhydrous tetrahydrofuran was added to 500 ml. of liquid ammonia. This was followed by the addition of 0.35 g. of lithium metal wire. As soon as the lithium had dissolved, 5 g. of ammonium chloride was added, and the mixture was allowed to stand until the ammonia had evaporated. The residue was dissolved in a mixture of chloroform and 5% hydrochloric acid, the chloroform layer separated and the aqueous layer washed three times with chloroform. The combined chloroform extracts were washed with 5% aqueous sodium hydroxide solution, dried over magnesium sulfate and evaporated. Crystallization of the resulting colorless solid from methanol–water gave 1.59 g. (54% based on methyl podocarpate) of methyl desoxypodocarpate (Id), m.p. 140–141°. Four recrystallizations from aqueous methanol gave colorless needles, m.p. 141–142°, [α]D +138.2° (EtOH); ultraviolet spectrum (95% ethanol): λ_{max} 265 mμ (ε 460) and 272 mμ (ε 436).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.55; H, 8.99.

The mother liquors of the crystallizations of the ester were combined and extracted with chloroform. The residue obtained after drying over magnesium sulfate and evaporation of the solvent was chromatographed on 5 g. of alumina. Elution with petroleum ether gave an additional 20 mg. of the ester Id, while 20:1 petroleum ether–ether elution gave 63 mg. (2.5% based on methyl podocarpate) of desoxypodocarpinol (Ie), m.p. 88–91°. Three recrystallizations in aqueous methanol yielded colorless needles, m.p. 93.5–94°, [α]D +29.3° (EtOH).

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.26; H, 9.66.

When the sodium hydroxide washings of the initial ester isolation were acidified, extracted with chloroform, the latter dried over magnesium sulfate and the solvent evaporated, there was obtained a colorless solid, which on crystallization from methanol–water gave 0.295 g. (10% based on methyl podocarpate) of desoxypodocarpic acid (Ic), m.p. 195–197°. Four recrystallizations in aqueous methanol led to colorless needles, m.p. 197–198°, [α]D +40.8° (EtOH); ultraviolet spectrum (95% ethanol): λ_{max} 265 mμ (ε 670) and 272 mμ (ε 640).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.16; H, 8.67.

When the phosphate ester Ih was treated with lithium–ammonia in a manner exactly as above with the exception that alcohol was used instead of ammonium chloride, the products consisted only of acid and alcohol. The phosphate from 700 mg. of methyl podocarpate gave 338 mg. of Ic and 118 mg. of Ie.

Methyl 12-Acetyldesoxypodocarpate (If).—A solution of 1.00 g. of methyl desoxypodocarpate (Id) and 0.30 ml. of acetyl chloride in 15 ml. carbon disulfide was added to a stirred suspension of 0.65 g. of anhydrous aluminum chloride in 25 ml. of carbon disulfide. The mixture was refluxed and stirred for one hour, the solvent evaporated and the residue taken up in 5% hydrochloric acid and chloroform. After separation of the chloroform layer and three chloroform extractions of the aqueous layer, the combined organic extracts were dried over magnesium sulfate and evaporated to dryness. Chromatography of the crystalline crude product on 30 g. of alumina and elution with petroleum ether gave 565 mg. of starting material, while elution with 9:1 petroleum ether–ether yielded 219 mg. (43% based on recovered starting ester) of methyl 12-acetyldesoxypodocarpate (If), m.p. 147–157°. Five crystallizations in aqueous methanol gave colorless needles, m.p. 160.5–161.5°, [α]D +157° (EtOH); ultraviolet spectrum (95% ethanol): λ_{max} 258 mμ (ε 19,200).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.61; H, 7.94.

Methyl Podocarpate Acetate (Ig).—A mixture of 288 mg. of methyl podocarpate (Ib), 70 mg. of anhydrous sodium

---

(6) For other anomalous reactions of the carboxyl group of podocarpic acid based on the same principle *cf.* E. Wenkert and B. G. Jackson, *ibid.*, **80**, 211 (1958).

(7) The irreducibility of the axial carbomethoxy group in methyl agathate by the Bouveault–Blanc procedure [L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, **14**, 203 (1931)] is in close agreement with the present observation. It would be of interest to know whether the high yield of acidic products in this reaction is not also due at least in part to a *reductive hydrolysis*.

(8) A. J. Birch, *J. Chem. Soc.*, 430 (1944); 102 (1947).

acetate and 20 ml. of acetic anhydride was refluxed for three hours. After removal of the excess acetic anhydride under reduced pressure the residue was taken up in ether, the latter washed with 5% sodium hydroxide solution, dried over magnesium sulfate and evaporated to dryness. Aqueous methanol crystallization of the resulting crystalline mass gave 300 mg. (91%) of methyl podocarpate acetate (Ig), m.p. 124–125°. Three recrystallizations from methanol–water yielded fluffy white needles, m.p. 125–125.5°, $[\alpha]_D$ +113° (EtOH); ultraviolet spectrum (95% ethanol); λ_{max} 268.5 mμ (ε 680) and 275 mμ (ε 740).

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 73.10; H, 8.09.

A solution of trifluoroperacetic acid, prepared by the addition of 0.085 ml. of trifluoroacetic anhydride to an ice-cold, stirred suspension of 0.014 ml. of 90% hydrogen peroxide in 10 ml. of methylene chloride, was added to a stirred mixture of 0.35 g. of anhydrous disodium hydrogen phosphate, 100 mg. of methyl 12-acetylpodocarpate and 20 ml. of methylene chloride. After a three-hour reflux the mixture was cooled and filtered. The filtrate was washed with 10% sodium carbonate solution, dried over sodium sulfate and evaporated to dryness. Crystallization of the crude crystalline product in methanol–water gave 86 mg. (74%) of methyl podocarpate acetate (Ig), m.p. 117–121°. Two recrystallizations from aqueous methanol raised the melting point to 125–125.5°, and was undepressed on admixture with an authentic sample of the ester. The infrared spectra of the two samples of ester were identical.

A mixture of 100 mg. of methyl podocarpate acetate (Ig), 150 mg. of potassium hydroxide, 15 ml. of ethanol and 10 ml. of water was refluxed for four hours. After cooling, the solution was poured into 50 ml. of 10% hydrochloric acid, extracted three times with chloroform, the combined extracts dried over magnesium sulfate and concentrated. Crystallization of the residue in methanol–water gave 86 mg. (99%) of fluffy, colorless needles, m.p. 210–213°. Recrystallization from the same medium produced methyl podocarpate, m.p. 212–213°, undepressed by admixture with an authentic sample. The infrared spectra of the two ester samples were identical.

Lithium Amide Treatment of Methyl Desoxypodocarpate (Id).—A solution of 100 mg. of methyl desoxypodocarpate (Id) in 25 ml. of anhydrous tetrahydrofuran was added to a suspension of 490 mg. of lithium amide in *ca.* 75 ml. of liquid ammonia. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The residue was partitioned between chloroform and 10% hydrochloric acid and the aqueous phase further extracted with chloroform. The combined organic extracts were washed with 10% sodium hydroxide, dried over magnesium sulfate and evaporated. The residue was chromatographed on 10 g. of alumina yielding 58 mg. of starting ester in the petroleum ether eluates and 15 mg. of desoxypodocarpamide (Ii) m.p. 191–195°, on methanol elution. The latter proved identical in m.p., mixed m.p. and infrared spectrum with an authentic sample.[6]

General Procedure for ***Reductive Hydrolysis.***—A solution of the methyl ester in 25 ml. of tetrahydrofuran was added to approximately 75 ml. of liquid ammonia. Sufficient lithium metal to cause a persistent blue color was then added to the ester solution. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid. After separation of the organic layer, the aqueous phase was extracted three times with chloroform. The combined chloroform extracts were washed with four 25-ml. portions of 5% sodium hydroxide solution, dried over magnesium sulfate and evaporated, giving the crude neutral fraction. The sodium hydroxide washings were collected, acidified with concentrated hydrochloric acid and extracted thrice with chloroform. Drying over magnesium sulfate and evaporation of the combined extracts yielded the crude acidic products.

A 200-mg. run of methyl podocarpate (Ib) led to neutral material which on methanol–water crystallization gave 9 mg. of starting ester, m.p. 205–210°, and to acidic products which gave 111 mg. of podocarpic acid (Ia), m.p. 179–192°, on crystallization in aqueous methanol, m.p. 192–194° on recrystallization from same solvent. Infrared spectra of both compounds were identical with those of authentic samples.

A 100-mg. run of methyl desoxypodocarpate (Id) led to 21 mg. of desoxypodocarpinol (Ie), m.p. 90–93°, on ether elution of an alumina chromatography of the neutral products, and to 75 mg. of desoxypodocarpic acid (Ic), m.p. 195–199°, from the acid fraction.

The neutral fraction from a 55-mg. run of methyl oleanolate (IIa) was crystallized in methanol–water giving 15 mg. of erythrodiol (IIc), m.p. 215–230°. Recrystallization from the same solvent pair raised the melting point to 233–237°. The crude acid yielded 37 mg. of oleanolic acid (IIb), m.p. 308–310°, on crystallization from aqueous methanol. The infrared spectra of both compounds were identical with those of authentic material.

A 200-mg. run of methyl dehydroabietate (IIIa) led to 177 mg. of crude neutral material whose chromatography on alumina gave 118 mg. of dehydroabietinol (IIIc). Its 3,5-dinitrobenzoate melted at 123–124° (reported[9] m.p. 123–124°). Crystallization of the 17 mg. of acidic products in aqueous methanol led to 6 mg. of dehydroabietic acid (IIIb), m.p. 165–168°.

A 450-mg. run of methyl mesitoate (IVa) yielded 422 mg. of semi-crystalline neutral product which on trituration with petroleum ether and filtration afforded 182 mg. of 2,4,6-trimethylbenzyl alcohol (IVb), m.p. 85–88°. The remaining neutral fraction showed an infrared spectrum practically identical with pure benzyl alcohol (IVb). The crude acid products amounted to only 12 mg. and were not investigated.

(9) L. F. Fieser and W. P. Campbell, This Journal, **61**, 2528 (1939)

AMES, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

The Synthesis of 2,3,4,5,6-Pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone and Some of its Reactions[1]

BY RUSSELL REED, JR.

RECEIVED JULY 29, 1957

Treatment of pentachlorophenol with a mixture of nitric acid, trifluoroacetic acid and trifluoroacetic anhydride resulted in the formation of 2,3,4,5,6-pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone (I); some of the chemistry of I, which in several reactions appears to envolve pentachlorophenoxy radicals, is described.

Since a mixture of nitric acid and trifluoroacetic anhydride has been found to be an excellent reagent for the conversion of alcohols to nitrate esters,[2] the synthesis of pentachlorophenyl nitrate was attempted by the treatment of pentachlorophenol

---

(1) Presented in part before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Fla., April 12, 1957.

(2) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 1695 (1952).