paste of complex, while with other salts, droplets were observed only after several minutes or hours.

A similarly unique role of I^- is seen in the reaction of I_2 with starch where it cannot be substituted by other ions when the blue color is to be formed. French and co-workers recently demonstrated that a complex of I^- with the carbohydrate is essential for the development of the visible color.[38] The same authors showed that with α-cyclodextrin a complex α-CDX·I_3^- is formed in solution[39] and quote the preparation of a crystalline complex α-CDX·KI.[40] Prominent interaction of I^- with α-cyclodextrin is also revealed here by the optical rotation where its effect outranks that of Br^- or Cl^- (Table VI). I^- may serve not only to form with I_2 the necessary complex I_3^-, but also to bring about a conformation of starch or α-cyclodextrin which is suitable for association with this species.[39]

V. Different optical rotations with different solvents have been reported by Freudenberg for cyclodextrins,[11] and Cramer mentions that their concentrations cannot be determined exactly by polarimetry when other organic compounds are present in the aqueous solutions.[28b] Our analyses of cyclodextrins and fatty acids in water enabled us to measure the optical rotations under defined conditions (Table VI). The specific rotation of α-cyclodextrin is markedly lowered with increasing chain length of acids and the same holds, though to a lesser degree, for the β-compound. However, when the guest molecule has conjugated unsaturation, the optical rotation of α-cyclodextrin is increased. The specificity is suggested by the values found in the presence of 2,3-hexenoic and 3,4-hexenoic acids. Sorbic acid, or its ester, having the highest conjugation, affect the rotation the most.

Several speculations can be derived from this finding. The shift of optical rotation of an active substrate caused by association with an inactive cosolute may allow the derivation of rules concerning the structure of the latter. The use of optically active solvents is not practical for such a purpose, but cyclodextrin can serve as an associating "solvent" in many cases without introducing an excessive amount of optically active molecules which are not involved in the difference to be measured. The values of Table VI are not the optical rotations of associated cyclodextrins, although in some instances the amount of free host is very small. The rotation changes have opposite signs and this rules out that they result merely from differences in equilibria.

The ratios of optical rotations, α-CDX·heptanoic acid/α-CDX, are 0.93 between 578 and 248 mμ. A slight increase is found for the rotation ratio α-CDX·benzoic acid/α-CDX, from 1.12 to 1.28 over the range 578 to 297 mμ. The region 270 to 275 mμ, where λ_{max} is found for free and associated benzoic acid, could not be covered in the measurements at concentrations that would allow reference to the solubility experiments. The interesting correlation of ultraviolet absorption band of guest and rotatory dispersion of host will be easier with compounds having absorption better suitable than heptanoic or benzoic acids.[41]

Quantitation of the rotation shift may afford a method for assaying the portion of free cyclodextrin in association equilibria. Because absorption in the accessible ultraviolet range is not conditional, guest molecules of simple saturated structures can be screened. A further advantage is the fact that the presence of components extraneous to the equilibria is not required in such measurements.

(38) J. A. Thoma and D. French, *J. Am. Chem. Soc.*, **82**, 4144 (1960).
(39) J. H. Thoma and D. French, *ibid.*, **80**, 6142 (1958).
(40) H. A. Dube, Ph.D. Thesis, 1947, Iowa State College.
(41) C. Djerassi and K. Undheim, *J. Am. Chem. Soc.*, **82**, 5755 (1960).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA]

Podocarpic Acid Derivatives. Synthesis of Nimbiol

BY ERNEST WENKERT, VIRGIL I. STENBERG[1] AND PETER BEAK[2]

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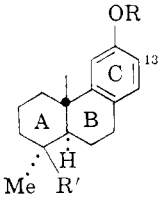
The conversion of podocarpic acid into O-methylpodocarpane and the latter's transformation into several hydrophenanthrones and a bicyclic ketoacid are described. Attempts to convert the acid and its derivatives to natural diterpenic substances are discussed. The synthesis of nimbiol, *via* 13-methylpodocarpic acid and O,13-dimethylpodocarpane, is portrayed.

As our studies on the total synthesis of the resin acids approached completion, we became interested in their conversion into other diterpenes. *d*-Podocarpic acid (Ia), whose synthesis we recently reported,[3] appeared to be a suitable starting material for the synthesis of ring C substituted aromatic, hydroaromatic and *seco* compounds. The present communication concerns itself with an attempted construction of the phyllocladene (II) nucleus and the synthesis of nimbiol (III).

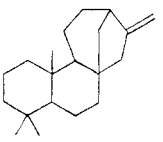
Phyllocladene.—Two routes were used for the conversion of *d*-podocarpic acid (Ia)[4] into O-methylpodocarpane (Ib). Tosylation of O-methylpodo-

(1) Public Health Service Predoctoral Research Fellow, 1959–1960.
(2) National Science Foundation Coöperative Graduate Fellow, 1959–1960.
(3) E. Wenkert and A. Tahara, *J. Am. Chem. Soc.*, **82**, 3229 (1960).
(4) The natural acid could be isolated readily from rimu oleoresin, kindly supplied by S. B. Penick and Co. In order to obtain other terpenic plant constituents, the isolation procedure of I. R. Sherwood and W. F. Short [*J. Chem. Soc.*, 1006 (1938)] was followed by chromatography of the residues of the ethanol extract from which podocarpic acid had been crystallized. However, no other natural substances were discovered.

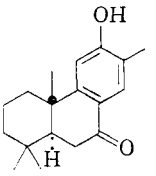


I

a, R = H, R′ = CO_2H
b, R = R′ = Me
c, R = Me, R′ = CH_2OH
d, R = Me, R′ = CHO
e, R = Me, R′ = CO_2Me
f, R = *i*-Pr, R′ = CO_2Me
g, R = H, R′ = CO_2Me
h, R = Me, R′ = CO_2H



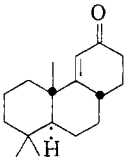
II



III

carpol (Ic), obtained by standard methods,[5] and lithium aluminum hydride reduction of the tosylation mixture[6] gave O-methylpodocarpane (Ib) in one operation. Alternately, the alcohol Ic was oxidized to O-methylpodocarpal (Id) by the Sarett method, used successfully previously on the alcohols derived from dehydroabietic, pimaric and isopimaric acids (see Experimental),[7] and the aldehyde reduced to Ib by a modified Wolff–Kishner reaction.[8]

Reduction of O-methypodocarpane (Ib) with excess lithium and alcohol in liquid ammonia[9] and treatment of the reaction mixture with acid led to a mixture of ketones. The major product was an unsaturated ketone whose spectral properties and non-isomerizability on sodium methoxide treatment showed it to have structure IV. The only characterizable minor product was the saturated ketone V. Its *trans-anti-trans* stereochemistry could be deduced from its identity with the ketone derived from IV by reduction with lithium in liquid ammonia. Hydrogenation of the unsaturated ketone IV in alcohol over palladium–charcoal led to a mixture of hydrophenanthrones containing *at least* 44% of the *trans*-ketone V. Such nonspecificity was reminiscent of a similar result in the hydrogenation of the tricyclic ketone VI.[10] Whereas the second hydrogenation product, necessarily VII, was not characterized fully, it was gratifying to know that both B/C *cis* and *trans* stereochemical systems were readily available. Their use in the synthesis of natural substances such as rimuene (VIII) was clear, but was not attempted in view of the uncertainty of the stereochemistry of rimuene at C-9 and 13 at the time these investigations were in progress.[7]



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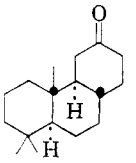
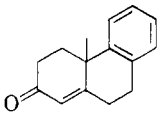


V



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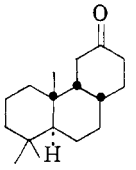
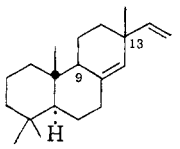
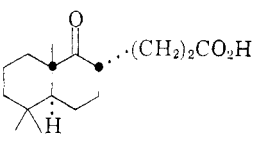


VII

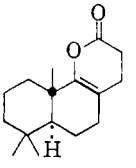


VIII

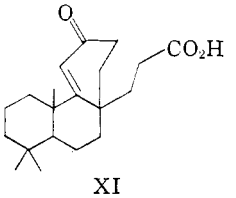
Ozonolysis of IV and hydrogen peroxide treatment of the ozonide[11] produced the ketoacid IX, whose exposure to acetyl chloride gave the enol lactone X. It had been hoped that condensation of the ketoacid IX with methyl vinyl ketone would lead to the tricyclic ketoacid XI, a potential progenitor of the phyllocladene skeleton (II). However, despite the expenditure of much effort no combination of IX or its derivatives, various bases and methyl vinyl, β-chloroethyl, β-chlorovinyl or ethynyl ketones led to useful products. Thus quaternization of sterically highly protected C-8 by external reagents, especially under equilibrium conditions, was blocked. Other routes of synthesis are being explored.[12]



IX



X



XI

Nimbiol.[13]—When during our preliminary investigations on the chemistry of podocarpic acid the full structure of nimbiol (III), a phenolic plant constituent of *Melia azadirachta* Linn., was announced,[14] it was decided to synthesize this bio-

(5) H. H. Zeiss, C. E. Slimowicz and V. Z. Pasternak, *J. Am. Chem. Soc.*, **70**, 1981 (1948).

(6) *Cf.* A. S. Hussey, H. P. Liao and R. H. Baker, *ibid.*, **75**, 4727 (1953).

(7) These oxidations were performed by Mr. James W. Chamberlin, in 1958, and were followed by Wolff–Kishner reductions of the aldehydes to hydrocarbons. In this manner it could be shown that rimuene, a pimaradienic diterpene, possessed neither the pimaric nor isopimeric type of C-9,13 stereochemistry. These observations are in agreement with those made in the laboratories of Professors L. H. Briggs and R. E. Ireland (private communications).

(8) Our reduction was different from that described in the classic work by W. P. Campbell and D. Todd [*J. Am. Chem. Soc.*, **64**, 928 (1942)] as well as that published by R. Hodges and R. A. Raphael [*J. Chem. Soc.*, 50 (1960)] after completion of this phase of our work. Another synthesis of *d*-O-methylpodocarpane (Ib) was reported by M. Fétizon and J. Delobelle, *Compt. rend.*, **246**, 2774 (1958).

(9) Such reduction on another podocarpic acid derivative (Ic) has been discussed by R. H. Bible, Jr. (lecture, entitled "The Chemistry of Podocarpic Acid," at the Symposium on Diterpenic Acids and Related Compounds before the Division of Organic Chemistry of the American Chemical Society, New York, N. Y., September 14, 1960).

(10) E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 2318 (1956); *cf.* also E. Wenkert and B. G. Jackson, *ibid.*, **81**, 5601 (1959).

(11) *Cf.* R. B. Turner, *ibid.*, **72**, 582 (1950).

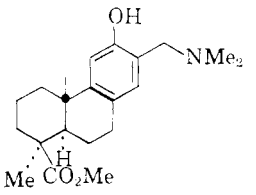
(12) For recent syntheses of degradation products of phyllocladene, whose stereochemistry is now fully understood [P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960)], see R. F. Church, R. E. Ireland and J. A. Marshall [*Tetrahedron Letters*, No. 17, 1 (1960)], and R. B. Turner and P. E. Shaw [*ibid.*, No. 18, 24 (1960)].

(13) Much of this work was presented before the Division of Organic Chemistry of the American Chemical Society, Cleveland, Ohio, April 6, 1960, *cf.* Abstracts of Papers, p. 36-O.

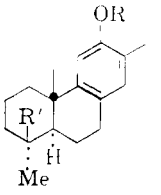
(14) S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chemistry & Industry*, 1284 (1959). For a complete description of this work see P. Sengupta, S. N. Choudhuri and H. N. Khastgir, *Tetrahedron*, **10**, 45 (1960).

synthetically unusual diterpenic product from *d*-podocarpic acid.[15] Besides the necessary introduction of the 7-keto and 13-methyl substituents, the projected synthesis appeared to be another exercise in the conversion of a carboxyl group into a methyl function. Rather than take the by now plebeian approach,[8] analogous to the above reduction–oxidation–reduction scheme of the synthesis of O-methyl-podocarpane (Ib), it was decided to take advantage of the uncommon properties of the sterically hindered podocarpic carboxyl group[16] in its reduction.

Alkylation of the dry sodio salt of methyl podocarpate[17] with unactivated alkyl halides did not yield any 13-alkyl derivatives. Treatments of the salt with methyl iodide or isopropyl iodide led only to the O-alkyl derivatives Ie and If, respectively. However, the Mannich reaction of methyl podocarpate, formaldehyde and dimethylamine afforded high yields of the dimethylaminomethyl compound XII. Reduction of the latter's methiodide with lithium in liquid ammonia achieved two desired ends in one operation: creation of a 13-methyl substituent and reductive hydrolysis[16a] of the ester function. 13-Methylpodocarpic acid (XIIIa) and 13-methylpodocarpol (XIIIb) were the major and minor products, respectively. Diazomethane treatment of the acid converted it into the methyl ester XIIIc.



XII



XIII

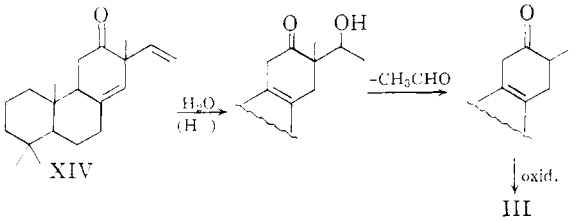
a, R = H, R′ = CO_2H
b, R = H, R′ = CH_2OH
c, R = H, R′ = CO_2Me
d, R = Ts, R′ = CH_2OTs
e, R = H, R′ = Me
f, R = H, R′ = $CONH_2$
g, R = H, R′ = CN
h, R = H, R′ = CHO

The use of both the acid XIIIa and the alcohol XIIIb in further work led to two parallel syntheses of nimbiol (III). Tosylation of the alcohol gave a ditosylate (XIIId) whose reduction with lithium aluminum hydride produced desoxynimbiol (XIIIe). Acetylation, chromic acid oxidation[18] and hydrolysis completed a nine-step conversion of *d*-podocarpic acid (Ia) into nimbiol (III).

Acetic anhydride and thionyl chloride treatments of 13-methylpodocarpic acid (XIIIa) yielded a derivative which, without isolation, was exposed to lithium amide in liquid ammonia. In accord with previous experience,[16a] both an amide (XIIIf) and a nitrile (XIIIg) were the products. It was noteworthy that a longer reaction time than in former runs[16a] led to a higher yield of nitrile. Further conversion of amide into nitrile was accomplished by thionyl chloride treatment and basic hydrolysis. Reduction of the nitrile XIIIg with lithium aluminum hydride under controlled conditions[16b] and mild acid hydrolysis gave 13-methylpodocarpal (XIIIh). While early attempts to reduce the latter by the Wolff–Kishner method seemed to yield small amounts of desoxynimbiol (XIIIe), these experiments were not duplicable on a large scale. It has not been possible to explain the unusual difference in reduction behavior of the aldehydes Id and XIIIh. However, since the phenolic hydroxyl group must have prevented successful reduction, it had to be masked. When, indeed, the two successive reductions were carried out on the O-methoxymethyl derivative of the nitrile, prepared by the reaction of chloromethyl ether and the potassium salt of the nitrile XIIIg in *t*-butyl alcohol, no intermediates were isolated and the final crude product was treated with dilute acid, desoxynimbiol (XIIIe) was obtained. Its conversion into nimbiol (III) has been described already (*vide supra*).

In view of our recent total synthesis of *d*-podocarpic acid (Ia),[16b] the present work constitutes a total synthesis of nimbiol (III) also.

Biosynthetic Considerations.—Both podocarpic acid and nimbiol are phenolic plant constituents whose less than the requisite C_{20}-carbon content might prevent them from being considered true diterpenes. However, both have been suggested to be derived from C_{20}-systems, the former from an aromatic precursor,[18] while the latter from a 12-ketorimuene (XIV),[14] an intermediate from an earlier stage of biosynthetic development. The following hydration–retroaldolization scheme represents a slightly modified version of the transformation of XIV into nimbiol.



XIV III

Retroaldolization is one of the most important biochemical fragmentation processes. While it is well recognized in the carbohydrate area, it may be of phytochemical significance in the terpene field also.[19] The aconite alkaloids, whose skeletal arrangements have been considered to be derived from the rimuene (VIII) structure through the atisine (XV) skeleton,[20] are highly oxygenated and substituted C_{19}-systems. Their single-carbon loss undoubtedly is due to a retroaldolization.

(15) Three other syntheses have appeared recently. R. H. Bible, Jr., made *d*-nimbiol from podocarpic acid [*Tetrahedron Letters*, No. 9, 20 (1960); *Tetrahedron*, **11**, 22 (1960)], while M. Fétizon and J. Delobelle [*Tetrahedron Letters*, No. 9, 16 (1960)], and P. C. Dutta and P. K. Ramachandran [*Chemistry & Industry*, 997 (1960)] prepared *d,l*-nimbiol by total synthesis. Drs. Bible and Fétizon kindly furnished the authors the manuscripts prior to publication.

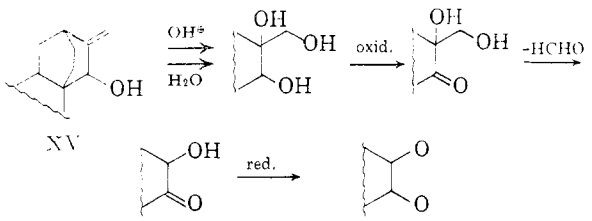
(16) (a) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 217 (1958); (b) E. Wenkert and A. Tahara, *ibid.*, **82**, 3229 (1960).

(17) *Cf.* E. Wenkert, R. D. Youssefyeh and R. G. Lewis, *ibid.*, **82**, 4675 (1960).

(18) *Cf.* E. Wenkert and B. G. Jackson, *ibid.*, **80**, 211 (1958).

(19) *Cf.* A. J. Birch and H. Smith, *Chem. Soc. Special Publication No. 12*, 4 (1958).

(20) E. Wenkert, *Chemistry & Industry*, 282 (1955); K. Wiesner and Z. Valenta, *Forts. Chem. Org. Natur.*, **16**, 26 (1958).



Experimental

O-Methylpodocarpane (Ib). (a).—A solution of 525 mg. of O-methylpodocarpol (Ic)[5] and 290 mg. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was allowed to stand at 0° for 50 hr. Then the mixture was poured into ice-water and extracted with chloroform. The extract was washed with 5% hydrochloric acid and 2*N* sodium hydroxide, dried over anhydrous sodium sulfate and evaporated. A solution of the resulting gum and 1.6 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran was refluxed for 68 hr. The suspension was diluted with 150 ml. of ether and the excess hydride decomposed with a sodium sulfate slurry saturated with water. After filtration, the solution was dried over anhydrous sodium sulfate and evaporated. The resulting gum was chromatographed on 20 g. of alumina. Elution with petroleum ether gave 59 mg. of oily O-methylpodocarpane (Ib), while chloroform elution led to 458 mg. of crude starting alcohol Ic, m.p. 65–85°. Both substances were identified by comparisons of their infrared spectra with those of authentic samples.

(b).—A solution of 8.3 g. of O-methylpodocarpol (Ic) in 40 ml. of anhydrous pyridine was added to a mixture of 11.9 g. of chromic acid in 120 ml. of anhydrous pyridine. After standing at room temperature for 1 hr. the mixture was poured into ice-water and extracted with ether. The extract was washed with 5% hydrochloric acid and 2 *N* sodium hydroxide, dried over sodium sulfate and evaporated. Crystallization of the crude neutral product, 6.25 g., from aqueous ethanol gave air-sensitive O-methylpodocarpal (Id), m.p. 130–133° (lit.[8] m.p. 133–135°). The alkaline extracts were acidified and extracted with ether. The organic extract was dried over sodium sulfate and evaporated, yielding 0.97 g. of crude acid, m.p. 135–150°. Crystallization of the latter from aqueous methanol gave O-methylpodocarpic acid (Ih), m.p. 158–160° (lit.[4] m.p. 158°).

A solution of 7.67 g. of O-methylpodocarpal (Id) and 85 ml. of 95% hydrazine in 350 ml. of anhydrous diethylene glycol was heated at 110–120° for 90 min. After cooling for 15 min., 40.6 g. of potassium hydroxide pellets was added and the mixture refluxed (155–165°) for 7 hr.[21] The solution was poured into 2 l. of ice-water made strongly acid with HCl and extracted with ether. The extract was dried over sodium sulfate, evaporated and chromatographed on 100 g. of alumina. Elution with petroleum ether gave 5.68 g. of an oil which crystallized on standing. Crystallization from aqueous ethanol yielded needles of O-methylpodocarpane (Ib), m.p. 31–32° (lit.[8] m.p. 30.5–31.5°), $[\alpha]_D$ 71.7° ($CHCl_3$); spectra: ultraviolet (95% ethanol), λ_{max} 279 mμ (ε 1500) and $\lambda_{shoulder}$ 284 mμ (ε 1390), 313 mμ (ε 155); infrared ($CHCl_3$), C=C 6.22(m), 6.36(w) μ.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 84.0; H, 10.4.

The best conversion of alcohol Ic into Ib in a continuous run was 71%.

The transformation of the alcohols of dehydroabietic, pimaric and isopimaric acids involved the same conditions as the one for the above synthesis of O-methylpodocarpal (Id), except for the reaction time. Oxidation of 790 mg. of dehydroabietol for 105 min. gave 650 mg. of oily aldehyde which yielded 700 mg. of a semicarbazone. Crystallization from aqueous methanol produced dehydroabietal semicarbazone, m.p. 221–224° (lit.[8] m.p. 217–219°). Oxidation of 217 mg. of pimarol for 90 min. gave 35 mg. of starting alcohol and 98 mg. of oily aldehyde which could be converted into 97 mg. of crude pimaral semicarbazone, m.p. 205–210° (lit.[22] m.p. 223–225°). Oxidation of 840 mg. of isopimaral for 105 min. gave 10 mg. of starting alcohol and 690 mg. of oily aldehyde which afforded 530 mg. of semicarbazone, m.p. 225–228°. Crystallization from methanol–chloroform yielded isopimaral semicarbazone, m.p. 228–230°.

Anal. Calcd. for $C_{21}H_{33}ON_3$: C, 73.42; H, 9.68; N, 12.23. Found: C, 73.51; H, 9.75; N, 12.15.

Ketones IV and V.—A mixture of 2.00 g. of O-methylpodocarpane (Ib), 170 ml. of anhydrous ethanol, 30 ml. of tetrahydrofuran and 350 ml. of ammonia was cooled in a Dry Ice–acetone-bath and stirred vigorously while 20 g. of lithium was added over an 80-min. period. Toward the end of this period a henna color appeared at the top of the otherwise deep blue mixture.[23] Stirring was continued until the blue color had faded, whereupon the ammonia was allowed to evaporate. The residue was taken up in 2 l. of ice-water and extracted with ether. The extract was washed with 5% hydrochloric acid and evaporated *in vacuo*. The remaining oil was dissolved in 320 ml. of 95% ethanol, mixed with 3.4 ml. of concd. hydrochloric acid and heated at 70° for 1 hr. The solution was poured onto ice–water and extracted with ether. The extract was dried over sodium sulfate and evaporated.

The residue was chromatographed on 100 g. of alumina. Elution with petroleum ether gave 78 mg. of starting material Ib; 49:1 petroleum ether–benzene, saturated ketone; 24:1 petroleum ether–benzene, a mixture of unsaturated and saturated ketones; 7:3 petroleum ether–benzene, unsaturated ketone; and chloroform, 40 mg. of unidentified oil. The eluates containing mixtures of ketones were combined and rechromatographed. Similar fractions from the two chromatograms were combined.

Repetition of the ethanolic hydrochloric acid treatment on the saturated ketone fraction, whose yield was 80 mg., and infrared analysis of the products revealed it to contain only up to 5–10% of material equilibratable with the conjugated unsaturated ketone. After microdistillation (oil-bath at 196° (5 mm.)) the ketone solidified. Four crystallizations from aqueous ethanol gave crystalline ketone V, m.p. 48–49°, $[\alpha]_D$ 33.8° ($CHCl_3$); infrared spectrum (CCl_4), C=O 5.84(s) μ.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.17; H, 11.40.

Its 2,4-dinitrophenylhydrazone, m.p. 158–160°, was identical with the derivatives of the saturated ketone obtained by two different reductions of ketone IV (*vide infra*).

The unsaturated ketone, whose yield was 905 mg., solidified on rechromatography. Five crystallizations from aqueous dimethylformamide gave crystalline ketone IV, m.p. 56–57.5°, $[\alpha]_D$ −14.3° ($CHCl_3$); spectra: ultraviolet (95% ethanol), λ_{max} 240 mμ (ε 19,400); infrared (CCl_4), C=O 5.99(s) μ, C=C 6.24 (m) μ.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.07; H, 10.61.

Reduction of Ketone IV. (a) Hydrogenation.—A mixture of 200 mg. of the enone IV and 30 mg. of 10% palladium–charcoal in 5 ml. of ethyl acetate was hydrogenated at atmospheric pressure. When after 2 hr. one equivalent of hydrogen had been taken up, the catalyst was filtered and the solvent evaporated. The oily product was dissolved in 100 ml. of benzene and passed through a column of 2 g. of alumina. Evaporation of the filtrates yielded 163 mg. of an oil, whose infrared spectrum exhibited only a 5.84 μ carbonyl peak. When 30 mg. of the oil was seeded with a crystal of ketone V, obtained from the Birch reduction of Ib (*vide supra*), slow crystallization occurred. The resulting oily solid was dried on a porous plate for several hours, leading to 13 mg. of needles, m.p. 35–46°, whose infrared spectrum in Nujol was the same as that of V (*vide supra*). Four crystallizations of its 2,4-dinitrophenylhydrazone from aqueous ethanolic ethyl acetate yielded yellow needles, m.p. 160–162°.

Anal. Calcd. for $C_{23}H_{32}O_4N_2$: C, 64.46; H, 7.53; N, 13.08. Found: C, 64.49; H, 7.58; N, 13.21.

(b) Chemical Reduction.—A solution of 77 mg. of enone IV in 10 ml. of anhydrous tetrahydrofuran was added to a stirred solution of 80 ml. of ammonia, containing 80 mg. of dissolved lithium and being cooled by a Dry Ice–acetone-

(21) *Cf.* A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 3517 (1959).

(22) N. A. Sörensen and T. Bruun, *Acta Chem. Scand.*, **1**, 112 (1947); G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 3870 (1948); D. H. R. Barton, T. Bruun and N. A. Sörensen, *Acta Chem. Scand.*, **5**, 1356 (1951).

(23) *Cf.* J. A. Barltrop and A. C. Day, *J. Chem. Soc.*, 671 (1959).

bath, and the stirring continued for 10 min. Solid ammonium chloride was added and the mixture allowed to evaporate. The residue was taken up in water and extracted with ether. The extract was washed with 5% hydrochloric acid, dried over sodium sulfate and evaporated. The residue was chromatographed on 5 g. of alumina. Elution with 49:1 petroleum ether–benzene gave 42 mg. of desired saturated ketone, while elution with 24:1 petroleum ether–benzene yielded 5 mg. of starting ketone. Three crystallizations of the product from aqueous ethanol afforded needles of ketone V, m.p. 46–49°, identical in all respects with the saturated ketone from the Birch reduction of Ib (*vide supra*). Its 2,4-dinitrophenylhydrazone, m.p. 158–159°, corresponded to that of the latter.

trans-**2-(β-Carboxyethyl)-5,5,9-trimethyl-1-decalone (IX).**—Two equivalents of ozone was passed through a solution of 122 mg. of the enone IV in 6 ml. of 1:1 ethyl acetate–glacial acetic acid. The solution was treated with 1 ml. of water and 0.1 ml. of 30% hydrogen peroxide and left standing for 23 hr. After the addition of 45 ml. of 2*N* sodium hydroxide to the solution, cooled in an ice-bath, it was extracted with ether and the extracts discarded. The aqueous solution was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated. Four crystallizations of the crude acid, 119 mg., gave the ketoacid IX, m.p. 88.5–90°; $[\alpha]_D$ − 10.4° ($CHCl_3$); infrared spectrum ($CHCl_3$): OH 2.8–3.4(w), C=O 5.89(s) μ.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 77.14; H, 9.84. Found: C, 77.04; H, 9.65.

Lactone X.—A solution of 50 mg. of the ketoacid IX in 2 ml. of freshly distilled acetyl chloride was refluxed for 40 hr. The excess acetyl chloride was removed *in vacuo* and the residue taken up in ether. The organic solution was washed with 5% sodium bicarbonate solution, dried over sodium sulfate and evaporated. Two sublimations of the crude product, 31 mg., gave pure enol lactone X, m.p. 93–94° after sintering at 91°; infrared spectrum ($CHCl_3$): C=O 5.73(s) μ.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.71; H, 10.02.

Alkylations of Methyl Podocarpate (Ig).—Dry benzene was distilled twice from 100 mg. of methyl podocarpate (Ig) in a predried flask and 10 ml. of dry methanol added. After the reaction of the solution with 8 mg. of added sodium was complete, all methanol was distilled off in vacuum. A solution of 0.6 ml. of methyl iodide in 15 ml. of toluene was added to the dry sodio salt and the mixture refluxed for 25 hr. The mixture was filtered, the residue washed with ether and the combined organic solutions evaporated. Fractional crystallization of the semi-solid residue from aqueous methanol gave 35 mg. of a solid, m.p. 104–107°. Recrystallization from the same solvent pair afforded methyl O-methylpodocarpate (Ie), m.p. and m.m.p. 127–129° (lit.[4] m.p. 128°). Alumina chromatography of the mother liquors and petroleum ether elution yielded 42 mg. (74% total) more of the product and 14 mg. (14%) of crude starting material, m.p. 196–204°.

A mixture of the above sodio salt of Ig and 10 ml. of isopropyl iodide was refluxed for 48 hr. Thereafter the solvent was removed under reduced pressure and the residue taken up in water and extracted with ether. The extract was dried over sodium sulfate and evaporated. Dissolution of the residue in petroleum ether left 41 mg. of crude insoluble starting material, m.p. 200–207°. Recrystallization of the solid, m.p. 114–119°, which had crystallized from the petroleum ether solution on standing, from aqueous methanol gave methyl O-isopropylpodocarpate (If), m.p. 131.5–133°; infrared spectrum ($CHCl_3$), C=O 5.81(s); C=C, 6.24 (m), 6.38(w) μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.30; H, 9.13.

Alumina chromatography of the mother liquors and petroleum ether elution yielded 40 mg. (40% total) more of If and 15 mg. (56% total) more of starting material.

Methyl 13-Dimethylaminomethylpodocarpate (XII).—A solution of 200 mg. of methyl podocarpate (Ig) and a threefold excess of 35% dimethylamine in 2 ml. of dioxane and 2 ml. of 95% ethanol, to which a threefold excess of 37% formaldehyde solution was added dropwise, was allowed to stand at room temperature for 3.5 hr. and then was refluxed for 5.5 hr. The solvents and excess reagents were removed under reduced pressure and the residue taken up in 10% hydrochloric acid and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated. Trituration of the remaining solid, 25 mg. (12%), with methanol gave crystals which on sublimation and crystallization from methanol yielded colorless needles of an unknown compound (probably dimethyl O-methylene-bis-podocarpate), m.p. 129.5–130.5°; $[\alpha]_D$ 116°($CHCl_3$), crude mol. wt. (Rast) *ca.* 500; infrared spectrum ($CHCl_3$), no OH, C=O 5.83(s); C=C 6.23(m), 6.38(w) μ.

Anal. Calcd. for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.13; H, 8.53.

The acid solution was neutralized and extracted with ether. The extract was washed with water, filtered through anhydrous sodium sulfate and evaporated. The remaining crystals, 203 mg. (85%), m.p. 148–152°, were recrystallized from aqueous methanol, yielding methyl 13-dimethylaminomethylpodocarpate (XII), m.p. 152–153°, $[\alpha]_D$ 116° ($CHCl_3$); infrared spectrum ($CHCl_3$), OH,NH 2.88(w), 3.03–3.30(m), 3.70–4.30(m); C=O 5.83(s); C=C 6.16(m), 6.34(m) μ.

Anal. Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.10; H, 8.87; N, 4.20.

13-Methylpodocarpic Acid (XIIIa).—A solution of 4.54 g. of the amine XII and 18.3 ml. of methyl iodide in 175 ml. of dry ether was stirred for 17 hr. A precipitate had begun forming immediately upon the first addition of methyl iodide. The liquids were removed under reduced pressure leaving a quantitative yield of pale yellow solid, m.p. 209–211°. Three crystallizations from absolute ethanol–petroleum ether gave colorless rectangular plates of the methiodide of XII, m.p. 210–211°.

Anal. Calcd. for $C_{22}H_{34}O_3NI$: N, 2.86. Found: N, 2.63.

The salt was relatively unstable in either the solid state or in solution and decomposed slowly to a compound of unidentified constitution, m.p. 168–169°.

A slurry of 5.00 g. of the methiodide in 300 ml. of tetrahydrofuran was added to a 1 l. of liquid ammonia solution of 1.0 g. of lithium. Another 1.2 g. of lithium was added in small portions to the colorless stirred solution, cooled in a Dry Ice–acetone-bath. While the blue color recurring after each addition always faded, it persisted at end of the addition of lithium. After 30 min., water was added dropwise until the blue color had disappeared. Thereupon the ammonia was allowed to evaporate and the residue taken up in 10% hydrochloric acid. The mixture was extracted with ether and the extract itself extracted with 10% sodium hydroxide, washed with water and filtered through anhydrous sodium sulfate. Evaporation of the ether left 915 mg. (33%) of gum. In runs wherein insufficient lithium had been used, methyl 13-methylpodocarpate (XIIIc) could be shown by infrared analysis to be a contaminant of the gum. Fractional distillation of the gum yielded 13-methylpodocarpol (XIIIb), m.p. 87–88.5°, $[\alpha]_D$ 52.7° ($CHCl_3$); infrared spectrum ($CHCl_3$), OH 2.80(m), 3.00 (w) μ.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.13; H, 9.70.

Neutralization of the alkaline extract and extraction with ether led to a solution which was washed with water, dried over anhydrous sulfate and evaporated *in vacuo*. Since the acidic gum, 1.89 g. (64%), crystallized only with great difficulty, it was sublimed fractionally yielding 13-methylpodocarpic acid (XIIIa), m.p. 109–110°, $[\alpha]_D$ 84° ($CHCl_3$); infrared spectrum ($CHCl_3$), OH 2.8(m), 2.90–3.30(m); C=O 5.80(m) (shoulder), 5.93(s); C=C 6.20(m), 6.39(m) μ.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.74; H, 8.39.

An ether solution of diazomethane was added to a solution of 1.00 g. of 13-methylpodocarpic acid (XIIIa) in 15 ml. of methanol. After 5 min. the solution was evaporated under reduced pressure at 40–50° leaving 1.04 g. (99%) of solid residue. Crystallization from aqueous methanol afforded crystalline methyl 13-methylpodocarpate (XIIIc), m.p. 173° and 179–181°, $[\alpha]_D$ 128° ($CHCl_3$); spectra: ultraviolet (95%) ethanol, λ_{max} 285 mμ (log ε 3.59), λ_{min} 251 mμ (log ε 3.06); infrared ($CHCl_3$), OH 2.70(m), 3.05 (w); C=O 5.80(s); C=C 6.18(w), 6.35(w) μ.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.42; H, 8.71.

Desoxynimbiol (XIII). (a) *Via* **13-Methylpodocarpol (XIIIb).**—A 36-hr. reaction between 274 mg. of 13-methylpodocarpol (XIIIb) and 762 mg. of *p*-toluenesulfonyl chloride in 2 ml. of pyridine was executed and worked up in the same manner as the tosylation of O-methylpodocarpol (Ic) (*vide supra*). Trituration of the gummy product gave crystals which on crystallization from benzene–petroleum ether yielded 323 mg. (56%) of solid, m.p. 113–116°. Four recrystallizations gave the ditosylate XIIId, m.p. 117–118.5°, $[\alpha]_D$ 35° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{38}O_6S_2$: C, 65.95; H, 6.57. Found: C, 65.95; H, 6.57.

A 46-hr. reaction between 200 mg. of the ditosylate XIIId and 268 mg. of lithium aluminum hydride in 4 ml. of tetrahydrofuran was carried out in a manner similar to the reduction of O-methylpodocarpol (Ic) tosylate (*vide supra*). The pale yellow oily product, 118 mg., was chromatographed on 12 g. of alumina. Elution with benzene gave 67 mg. (76%) of desoxynimbiol (XIIIe) as an oil; infrared spectrum ($CHCl_3$), OH 2.80(m), 3.00(w); C=C 6.23(w), 6.38(w) μ. Elution with 9:1 benzene–ether yielded 30.9 mg. (33%) of starting diol XIIIb. The desoxynimbiol fraction was purified no further, but used directly in the next reaction.

(b) *Via* **13-Methylpodocarponitrile (XIIIg).**—A mixture of 4.00 g. of 13-methylpodocarpic acid (XIIIa) and 100 mg. of anhydrous sodium acetate in 10 ml. of acetic anhydride was refluxed for 2 hr. After vacuum removal of the solvent the residue was taken up in water and extracted with ether. The crude gum, resulting from the concentration of the extract, was refluxed in 15 ml. of thionyl chloride for 2 hr. After vacuum removal of the excess reagent the residue was added to a lithium amide suspension, prepared by the addition of 6.6 g. of lithium and a few ferric nitrate crystals to 500 ml. of liquid ammonia. The latter was allowed to evaporate slowly over a 46-hr. period, whereupon the white residue was decomposed with 10% hydrochloric acid. The acidic mixture was filtered, the brown residue washed with ether and the aqueous filtrate extracted with ether. The combined ether solutions were evaporated and the residual oil chromatographed on alumina. Elution with benzene–ether gave first 488 mg. (13%) of nitrile and then 926 mg. of amide. Treatment of the aqueous filtrate with excess of tartaric acid and subsequent neutralization and usual work-up yielded 721 mg. of more oily product consisting mostly of amide. Crystallization of the amide fraction first from aqueous methanol and then from aqueous acetone produced colorless needles of 13-methylpodocarpamide (XIIIf) acetonide, m.p. 109–110°; infrared spectrum ($CHCl_3$), OH, NH 2.70(m), 2.75(m), 2.84(m); C=O 5.82(s), 6.10(s) μ.

Anal. Calcd. for $C_{18}H_{25}O_2N \cdot C_3H_6O$: C, 73.00; H, 9.05; N, 4.05. Found: C, 72.89; H, 9.04; N, 4.49.

On heating the amide to its melting point it lost its acetone of solvation; $[\alpha]_D$ 142° ($CHCl_3$); infrared spectrum ($CHCl_3$), OH, NH 2.70(m), 2.79(m), 3.00(m), 3.05–3.30(w) (shoulder); C=O 5.97(s) (shoulder), 6.03(s), 6.62(s); C=C 6.20(w) μ.

Anal. Calcd. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77. Found: C, 74.97; H, 8.85.

Crystallization of the nitrile fraction from aqueous acetone and aqueous methanol yielded 13-methylpodocarponitrile (XIIIg), m.p. 183–184°, $[\alpha]_D$ 49.6° ($CHCl_3$); infrared spectrum ($CHCl_3$), OH 2.70(m), 3.05(m); C≡N 4.49(m); C=C 6.19(m), 6.68(m) μ.

Anal. Calcd. for $C_{18}H_{23}N$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.43; H, 8.71; N, 5.09.

More nitrile could be obtained by the following procedure. A solution of 400 mg. of 13-methylpodocarpamide (XIIIf) acetonide and 20 ml. of freshly distilled thionyl chloride was refluxed for 8 hr. After removal of the excess reagent under reduced pressure the residual oil was refluxed with 4 g. of potassium hydroxide in 18 ml. of ethylene glycol under nitrogen for 4 hr. The hydrolysate was diluted with 40 ml. of water and extracted with ether. When after evaporation of the solvent the remaining brown crystals, 372 mg., were chromatographed on alumina, 291 mg. (78%) of crystalline nitrile, m.p. 181–183°, was obtained.

A suspension of 38.7 mg. of lithium aluminum hydride in 35 ml. of tetrahydrofuran was added dropwise to a solution of 38.7 mg. of 13-methylpodocarponitrile (XIIIg) and the mixture refluxed for 2 hr. (A 1:1 hydride-to-nitrile weight ratio had been shown in preliminary experiments to be necessary to achieve the highest yields of desired product.) Thereafter the solvent was removed *in vacuo* and the residue heated for 10 min. on the steam-bath with 10 ml. of a 10% aqueous ethanolic hydrochloric acid solution. The mixture was extracted with chloroform and the extract washed with water and filtered through anhydrous sodium sulfate. Removal of the chloroform left 38.7 mg. (99%) of an oil which on standing crystallized; m.p. 149–150°; infrared spectrum ($CHCl_3$), no C≡N peak, C=O 5.81(s) μ. In view of its ready air oxidation no purification of 13-methylpodocarpal (XIIIh) was attempted. The aldehyde was exposed immediately to a Wolff–Kishner reduction. However, no useful data were obtained.

Sodium, 72 mg., was dissolved in 3 ml. of dry *t*-butyl alcohol, 71.3 mg. of 13-methylpodocarponitrile (XIIIg) was added and the solvent removed under reduced pressure. A mixture of the salt and 0.75 ml. of chloromethyl ether in 5 ml. of dry benzene was refluxed for 18 hr. The solvent was removed and the residue taken up in water and extracted with ether. The extract was washed with water, filtered through anhydrous sodium sulfate and evaporated. The remaining semi-solid mass, 93.5 mg., was chromatographed on 4 g. of alumina. Petroleum ether elution yielded 50.7 mg. (61%) of the methoxymethyl ether of XIIIg as an oil; infrared spectrum ($CHCl_3$), no OH; C≡N 4.49(m); C=C 6.22(m), 6.40(w) μ. Since all attempts at crystallization failed, the ether nitrile was used in the next reaction with further purification. Benzene–ether elution yielded 24 mg. (34%) of crude starting nitrile XIIIg, m.p. 160–170°.

Lithium aluminum hydride reduction of 13-methyl-O-methoxymethylpodocarponitrile was carried out in the same manner as the afore-mentioned reduction of 13-methylpodocarponitrile (XIIIg). The ether nitrile, 90.6 mg., gave 49 mg. of ether aldehyde as an oil. Wolff–Kishner reduction of the aldehyde followed the procedure for the reduction of O-methylpodocarpal (Id) (*vide supra*). But it was succeeded by the following hydrolysis. The oily reduction mixture from 44 mg. of 13-methyl-O-methoxymethylpodocarpal was refluxed with 5 ml. of a 5% aqueous dioxane–sulfuric acid solution for 2 hr. The solution was extracted with ether and the extract filtered through anhydrous sodium sulfate and evaporated. Chromatography of the residue on 1.5 g. of alumina and elution with benzene–ether gave 8.5 mg. (24%) of desoxynimbiol (XIIIe) (*vide supra*).

Nimbiol (III).—A mixture of 8.5 mg. of desoxynimbiol (XIIIe) and 20 mg. of sodium acetate in 1 ml. of acetic anhydride was refluxed for 8 hr. The solvent was removed under vacuum, water added, the solution extracted with ether and the extract washed with 10% sodium bicarbonate solution, with water and filtered through anhydrous sodium sulfate. Removal of the solvent left 8.9 mg. of gum, which on chromatography on 1 g. of alumina and elution with petroleum ether gave 7.2 mg. (73%) of an oil whose seeding with authentic material yielded crystals of desoxynimbiol acetate, crude m.p. 90–100°, $[\alpha]_D$ 69.7° ($CHCl_3$) [authentic material $[\alpha]_D$ 71.0° ($CHCl_3$)]; infrared spectrum same as that of an authentic sample.[24]

A mixture of 4 mg. of the acetate of XIIIe and 5 mg. of chromic oxide in 0.5 ml. of 80% acetic acid was allowed to stand at room temperature for 15 hr. The solution was diluted with 3 ml. of saturated brine solution and extracted with chloroform. The extract was washed with water, filtered through anhydrous sodium sulfate and taken to dryness. The residue, 2.6 mg. (62%), was crystallized from aqueous methanol yielding nimbiol acetate, m.p. 107–109° (authentic material, m.p. 108–111°); same infrared spectrum as that of an authentic specimen.[24]

The acetate of III, 4 mg., and 0.8 ml. of 2 *N* potassium hydroxide in 2.5 ml. of isopropyl alcohol were refluxed for 2 hr. The solution was acidified and extracted with ether. The extract was washed with water, dried and evaporated. Two crystallizations of the remaining solid, 2.8 mg. (71%), m.p. 220–235°, from methanol gave nimbiol, m.p. 244.5–246°, m.m.p. 245–248° with authentic material (m.p. 248–249°)[24]; identical infrared spectra.[25]

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