[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA, AND INDIANA UNIVERSITY, BLOOMINGTON, IND.]

Synthesis of Some Resin Acids[1]

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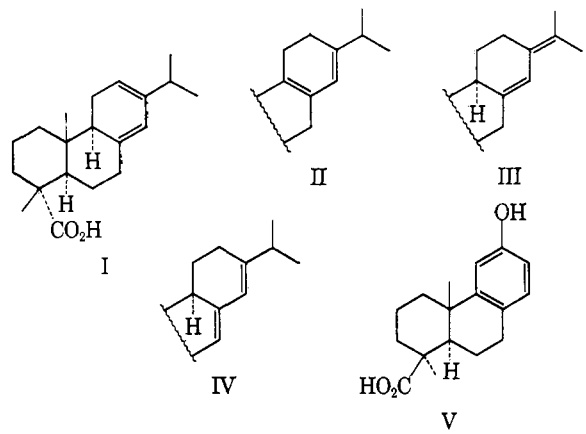
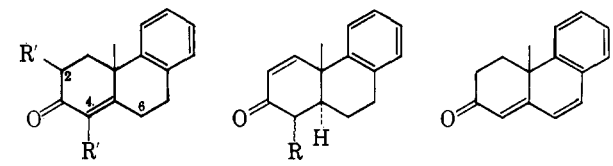
Two methods of synthesis of hydrophenanthrene ketones are described. The stereochemistry of alkylation of hydrophenanthrene β-keto ester salts is discussed. The synthesis and resolution of *rac*-deisopropyldehydroabietic and desoxypodocarpic acids are portrayed. The preparation of their dextrorotatory antipodes constitutes the completion of the total synthesis of four resin acids.

The acidic constituents of the oleoresins of various *Pinus* conifers have been the subject of numerous chemical investigations for nearly a century and a half. Only relatively recent times have seen the successful separation of the discrete diterpenic $C_{20}H_{30}O_2$ acid components and the determination of their gross structures and of their relative and absolute configurations.[2] As a consequence of these studies formulas I–IV have become the accepted structures of the abietadienic acid constituents of pine gum: levopimaric, palustric, neoabietic, and abietic acids, respectively. The chemically related aromatic resin acid, podocarpic acid, which was isolated originally 90 years ago and is the major acid constituent of the oleoresins of various *Podocarpus* and *Dacrydium* conifers, has been shown to possess structure V.[3]



As a follow-up of our previous chemical studies in this field[4] the total synthesis of four of the above acids (all but I) has been completed. The present communication describes the last phase of the synthesis.

Hydrophenanthrones.—Our early efforts were directed toward the construction of the hydrophenanthrene nucleus and resulted in the development of two novel methods of synthesis of the ketone VIa[4a,f,5] and a new scheme of synthesis of VIIa.[4b] A fourth and potentially most direct route to a hydrophenanthrone, involving the acid-catalyzed reaction between 1-methyl-2-naphthol and methyl vinyl ketone, had yielded the dienone VIII. This procedure now has been given general applicability by the conversion of the latter into VIa by reduction with lithium in liquid ammonia,[6] followed by sodium methoxide-induced double bond isomerization.

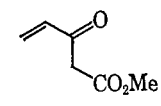


VIa, R = R′ = H
b, R = H, R′ = CO_2Me
c, R = CO_2Me, R′ = H

VIIa, R = H
b, R = CO_2Me

VIII

The unsaturated ketone VIa has been converted previously to the crucial ketoester VIb (along with VIc).[4d] The central position of VIb in the total synthesis of the resin acids and the consequent need of large quantities of the ester suggested a search for more than one method of its synthesis. A Robinson annellation on 1-methyl-2-tetralone with vinyl carbomethoxymethyl ketone (IX) appeared to be a promising, direct path to VIb in view of the reported successful use of the ethyl ester analog of IX in other Michael reactions.[7] The methyl ester IX was synthesized by the Nazarov procedure[7] and permitted to condense with the tetralone under the influence of sodium methoxide catalyst. The sole, isolable product, in 87% yield, was the desired ketoester VIb.



IX

The extraordinary usefulness and versatility of the yet rarely employed Nazarov reagent was noted once more in connection with a problem of synthesis in the gibberellic acid field. Attempts to synthesized Xa by various base-induced acylations of Xb and its α,β-un-

(1) For a preliminary report on part of this work *cf.* E. Wenkert and A. Tahara, *J. Am. Chem. Soc.*, **82**, 3229 (1960). The full study was presented for the first time in a lecture by E. W. at a Stereochemistry Symposium on May 14, 1963, at the École Polytechnique, Paris, France.

(2) *Inter alia cf.* (a) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, 2nd Ed., University Press., Cambridge, Eng., 1952, p. 374; (b) D. H. R. Barton and G. A. Schmeidler, *J. Chem. Soc.*, 1197 (1948); S 232 (1949); (c) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 339 (1948); (d) W. Schuller and R. V. Lawrence, *ibid.*, **83**, 2563 (1961), and references contained therein.

(3) (a) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938); (b) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **64**, 928 (1942).

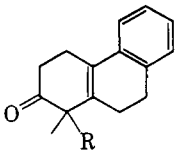
(4) (a) E. Wenkert and T. E. Stevens, *ibid.*, **78**, 2318 (1956); (b) *ibid.*, **78**, 5627 (1956); (c) E. Wenkert and B. G. Jackson, *ibid.*, **80**, 217 (1958); (d) *ibid.*, **81**, 5601 (1959); (e) E. Wenkert and J. W. Chamberlin, *J. Org. Chem.*, **25**, 2027 (1960); (f) E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, *J. Am. Chem. Soc.*, **82**, 4675 (1960); (g) E. Wenkert, R. W. J. Carney, and C. Kaneko, *ibid.*, **83**, 4440 (1961); (h) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(5) Neither of these methods fits their description in a recent, uncritical review by N. A. J. Rogers and J. A. Barltrop [*Quart. Rev.* (London), **16**, 117 (1962)]: "The unsaturated ketone, prepared by a Robinson ring-extension reaction from the corresponding 2-tetralone, ...".

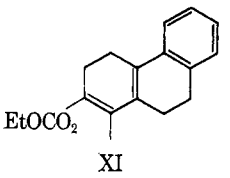
(6) *Cf.* R. E. Schaub and M. J. Weiss, *Chem. Ind.* (London), 2003 (1961).

(7) (a) I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); English translation, *ibid.*, **23**, 1793 (1953); (b) K. Hohenlohe-Oehringen, *Monatsh.*, **93**, 576 (1962).

saturated isomer, prepared by a condensation of β-tetralone and ethyl vinyl ketone, were not successful, despite the ease of the methylation of the ketone mixture (Xb and its double bond isomer) to the *gem*-dimethyl compound Xc. At best, the acylations, *e.g.*, a reaction with ethyl chlorocarbonate and potassium *t*-butoxide, afforded O-acyl products (*e.g.*, XI). However, a condensation of β-tetralone with the Nazarov reagent, followed by alkylation with methyl iodide and potassium *t*-butoxide, readily gave the desired product Xa.

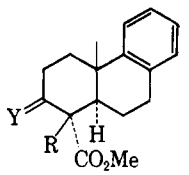


Xa, R = CO_2Me
b, R = H
c, R = Me

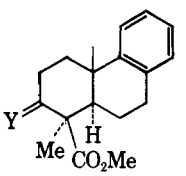


XI

Deisopropyldehydroabietic and Desoxypodocarpic Acids.—Ketoester XIIa, the previously prepared dihydro derivative of VIb,[4d] seemed to be the logical candidate for the introduction of the C_4-methyl group common to all abietadienic diterpenes. Methylation of XIIa was expected to lead to XIIIa, and hence selectively to the stereochemistry characteristic of podocarpic acid (V), on the assumption of the angular methyl group's offering serious 1,3-diaxial steric interference to the incoming methylating agent on the β-side of the molecular face of the intermediate ketoester (XIIa) anion. This view was strengthened by the reported stereochemical course of the alkylation of the chemically related ketone XIV with ethyl bromoacetate (α attack leading to XV).[8] However, methylation of XIIa with methyl iodide and potassium *t*-butoxide led to a 2.4:1 mixture[9] of the ketoesters XIIb and XIIIa whose stereochemistry could be assigned rigorously after their Clemmensen reduction to methyl *d,l*-deisopropyldehydroabietate (XIIc) and methyl *d,l*-desoxypodocarpate (XIIIb). The identity of the last two substances was established by comparison of their infrared spectra with those of their authentic *d*-antipodes.[4c,g] Thus, contrary to expectation, the methylation had proceeded in an unselective manner and, in fact, had yielded more product of abietic-type stereochemistry than of the podocarpic acid type.

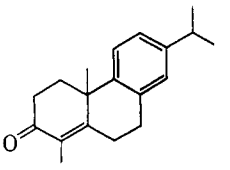


XIIa, R = H, Y = O
b, R = Me, Y = O
c, R = Me, Y = H_2

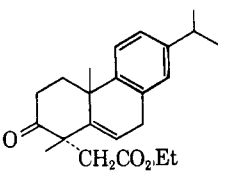


XIIIa, Y = O
b, Y = H_2

Hydrolysis of XIIIb and XIIc gave acids XVIa and XVIb whose resolution through the cinchonine and N-methylcinchonine salts, respectively, led to *d*-desoxypodocarpic acid (XVIa) and *d*-deisopropyldehydroabietic acid (XVIb). In view of our previous conversions of

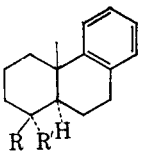


XIV

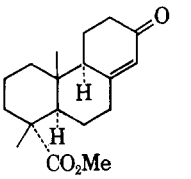


XV

XVIa into podocarpic acid (V)[4c] and of XVIb into the ketoester XVII and in view of the latter's past transformation into abietic acid (IV)[10] and the resin acid's isomerization to its double bond isomers,[11] *this completes the total synthesis of d-palustric (II), d-neoabietic (III), l-abietic (IV), and d-podocarpic (V) acids.*



XVIa, R = CO_2H, R′ = Me
b, R = Me, R′ = CO_2H



XVII

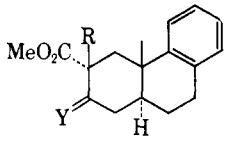
Stereochemistry of Alkylation.—The apparent anomaly in the steric course of the methylation of ketoester XIIa suggested a general study of the alkylation of hydrophenanthrone ketoesters be undertaken. In this connection it was noteworthy that ketoester VIc had been methylated already and that this reaction had led selectively to one C_2-methyl compound of as yet unassigned configuration.[4d] Since C_2-alkylation could be expected to have the same steric requirements as C_4-alkylation, the methylation of ketoester XVIIIa, the C_2-analog of XIIa, was investigated. It led to a single product whose C_2-stereochemistry was identical with that of the VIc methylation product, since hydrogenation of the latter compound yielded the same product. The stereochemistry was determined by subjection of the saturated, methylated ketoester to Clemmensen reduction and comparison of the behavior of the product with that of two models, XIIc and XIIIb, in two diagnostic tests of conformation, rate of alkaline hydrolysis, and product analysis of a reductive hydrolysis.[4c] A 4-hr. (200°) basic hydrolysis of the reduced ester and of methyl deisopropyldehydroabietate (XIIc), the equatorial ester model, yielded preponderantly acid products, while the hydrolysis of methyl desoxypodocarpate (XIIIb), the axial ester model, led mostly to recovered starting material. All three esters gave acid and alcohol products on reaction with lithium in liquid ammonia, but the ester of unknown constitution as well as methyl deisopropyldehydroabietate (XIIc) yielded largely neutral products, while methyl desoxypodocarpate (XIIIb) gave mostly an acid product. Hence the C_2-ester must be equatorial and its α-methyl group axial. On the assumption that ring A is in a chair conformation—a reasonable supposition for a compound without trigonal ring carbons in ring A—the ester can be assigned structure XVIIIc, while its keto precursor and the VIc methylation product must be XVIIIb and XIX, respectively.

(8) (a) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956). For the full description of this work *cf.* (b) *ibid.*, **84**, 284 (1962).

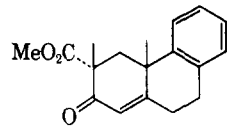
(9) (a) The major product of this mixture was misquoted in ref. 8b. (b) The earliest methylation experiments were carried out by B. G. Jackson.

(10) A. W. Burgstahler and L. R. Worden, *J. Am. Chem. Soc.*, **83**, 2587 (1961), footnote 10.

(11) N. M. Joyce, Jr., and R. V. Lawrence, *J. Org. Chem.*, **26**, 1024 (1961), and preceding papers.

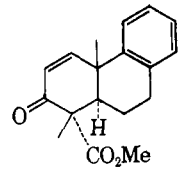


XVIIIa, R = H, Y = O
b, R = Me, Y = O
c, R = Me, Y = H_2



XIX

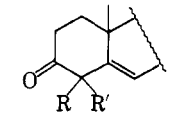
The exclusive formation of 2β-methyl compounds in the alkylation of ketoesters VIc and XVIIIa is in conformity with the results of the methylation of XIIa, although not in quantitative agreement. The lack of selectivity in the latter case, as compared with that of XVIIIa, may be, *inter alia*, the consequence of more 1,3-diaxial interference with the reaction site in XIIa (by the angular methyl and 2β- and 6β-hydrogens) than in XVIIIa (by the angular methyl and 4β-hydrogen). This interpretation suggested that methylation of a dehydro derivative of XIIa, a $\Delta^{1,2}$- or $\Delta^{6,7}$-system, might show greater stereoselectivity than XIIa itself and thus lead to the abietic-type C_4-stereochemistry. A test of this point seemed close at hand in the methylation of ketoester VIIb, especially in view of our previous five-step stereoselective synthesis of its logical precursor VIIa from 4-methyl-1-naphthol.[4d] Base-catalyzed condensation of VIIa with dimethyl oxalate and pyrolytic decarbonylation of the resultant diketoester yielded VIIb. Treatment of this ketoester with methyl iodide and potassium *t*-butoxide resulted in a single product whose structure could be shown to be XX by its hydrogenation to XIIb.[12] Hence, *the total synthesis of the hydroaromatic resin acids II–IV is now stereoselective in all steps.* Furthermore, the stereochemically consistent methylation results indicate that the angular methyl group exerts much less potent 1,3-diaxial interference in the carbon–carbon bond-forming reaction than initially anticipated and that the alkylations proceed by axial attack of the alkylating agent on the enolate salt substrate.



XX

While self-consistent, the steric course of our methylations was still in apparent disagreement with that of the reported alkylation of ketone XIV (→XV).[8] Since the alkylating agent (ethyl bromoacetate) in this reaction had been considerably larger than that (methyl iodide) in our methylations and since the size of the alkyl halide had been considered one of two important factors determining the stereochemical path of the reaction,[8] it was decided to test the effect of the size of the electrophilic reagent in the alkylations under consideration. Whereas bromoacetic ester was the logical choice as alkylating agent, it was not used since its interaction with any of our available β-ketoesters would have generated products whose stereochemical analysis might have been difficult. As a consequence, the bulky "methylating agent," chloromethyl sulfide, was chosen since Raney nickel-induced desulfurization of its alkylation products was expected to yield recognizable methylation products. Furthermore, XIIa was the ketoester of choice for this experiment because of its being the only one whose methylation had not been stereospecific and consequently the one the ratio of whose alkylation products was most sensitive to change. Its treatment with chloromethyl sulfide and potassium *t*-butoxide yielded a mixture. Raney nickel treatment of the unseparated mixture, followed by chromic acid oxidation of the partly C_3-overreduced product mixture, led to ketoesters XIIb and XIIIa in 1:3.5 ratio. Whereas the more than eightfold enrichment of podocarpic-type stereochemistry (alkylation from the α-side) in the alkylation of XIIa with chloromethyl sulfide, as compared with the methylation of XIIa, represents a change in the anticipated direction, it still is far less dramatic than the exclusive α-side alkylation in the conversion of XIV into XV. Thus a more subtle factor than the size of the alkylating agent appeared to be responsible for the continuing inconsistency of the stereochemical results of the alkylation of XIV[8] and of our ketoesters.

The remaining gross difference in the alkylations of XIV and the above ketoesters was the nature of the ketonic substrates—XIV being an α,β-unsaturated ketone while our compounds were saturated β-ketoesters. As a consequence, the methylation of VIb, an excellent analog of XIV, assumed importance. While this reaction had been attempted previously,[4d] albeit in a superficial fashion, it had failed because of the instability of its Δ^5-unsaturated products.[13] Repetition of the reaction now, followed by catalytic hydrogenation of the resultant Δ^5-system, yielded XIIIa as the sole product. This extraordinary finding illustrates most lucidly the importance of the nature of the enolate salt (rather than the size of the alkylating agent) in determining the stereochemical course of alkylation. If, as indicated above, it be accepted that, in the absence of overpowering steric hindrance, stereoelectrical control (axial attack by the alkylating agent) governs the stereochemistry of alkylation, the anion of ketoester VIb must assume a ring A boat conformation in the transition state of its methylation. Thus it may be more than coincidence that the first few examples of 3-keto-Δ^5-4,4-disubstituted, angular methyl compounds (XXI), substances with ring A substitution patterns identical with those of the methylation product of VIb, are found to possess ring A in boat form.[14]



XXI

The conversion of VIb into XIIIa by direct methylation and hydrogenation has made *the total synthesis of podocarpic acid (V) stereoselective in all steps.* Our resolution of *d,l*-deisopropyldehydroabietic acid (XVIb)

(12) For similar observations in the chemistry of a structurally related ketonitrile *cf.* M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).

(13) In our hands ring C aromatic Δ^5-hydrophenanthrenes have been greatly susceptible to decomposition by air oxidation (*cf.* ref. 4h).

(14) (a) B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *Chem. Ind.* (London), 1667 (1961); (b) private communication from Y. Mazur; (c) X-ray analysis of the structure of cedrelone, unfortunately containing the added complicating feature of a Δ^1 linkage, has shown this triterpenic substance to possess a half-boat ring A [I. G. Grant, J. A. Hamilton, T. A. Hamor, R. Hodges, S. G. McGeachin, R. A. Raphael, J. M. Robertson, and G. A. Sim, *Proc. Chem. Soc.*, 444 (1961)].

and *d,l*-desoxypodocarpic acid (XVIa) has converted previous syntheses of these racemates[15] into formal total syntheses of the four resin acids II–V.[16] *In view of previous transformations of d-podocarpic acid (V) into ferruginol,*[17] *sugiol,*[18] *dehydroferruginol,*[19] *and nimbiol,*[20] *the present work constitutes a total synthesis of these diterpenic plant constituents also.*

Experimental

Hydrophenanthrones. (a) **VIa.**—A solution of 100 mg. of the dienone VIII and 100 mg. of lithium in 5 ml. of tetrahydrofuran and 80 ml. of liquid ammonia was stirred for 3 min. Thereupon excess ammonium chloride was added and the mixture allowed to evaporate under nitrogen. The residue was taken up in 5% hydrochloric acid and extracted with chloroform. The extract was evaporated and the residue extracted with two 10-ml. portions of boiling hexane. Evaporation of the solvent left 90 mg. of an oil whose solution in 20 ml. of 10% methanolic sodium hydroxide was refluxed for 30 min. The solution was acidified with 5% hydrochloric acid and extracted with chloroform. The extract was dried (sodium sulfate) and evaporated. Crystallization of the residual solid from hexane yielded 71 mg. of ketone VIa, m.p., m.m.p. 87–88°; infrared spectrum identical with that of an authentic sample.[4a]

(b) **Xb.**—A solution of 18.2 g. of methyl iodide in 30 ml. of dry benzene was added to a solution of 20.1 g. of 1-diethylamino-3-pentanone in 75 ml. of benzene and the mixture kept at 0° for 14 hr. The benzene layer was decanted and the residual oil washed with benzene and dissolved in 35 ml. of methanol. This solution was added dropwise to an ice-cold solution of 19.6 g. of β-tetralone and 6.0 g. of sodium in 100 ml. of methanol and 75 ml. of benzene. The mixture was left standing at room temperature for 15 hr., then refluxed for 1 hr., cooled, diluted with water, and extracted with chloroform. The extract was dried and evaporated. Distillation of the remaining oil yielded 9.0 g. of unreacted β-tetralone, b.p. 70° (0.2 mm.), and 13.0 g. of a mixture of Xb and its α,β-double bond isomer, b.p. 130–135° (0.05 mm.); spectra: infrared (film), C=O 5.82 (s), 6.00 (s), C=C 6.20 (m) μ; ultraviolet (EtOH), λ_{max} 257mμ (log ε 4.00).

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.71; H, 7.68.

(c) **Xc.**—A solution of 214 mg. of methyl iodide in 3 ml. of benzene was added dropwise to a solution of 210 mg. of the ketone mixture Xb in 2 ml. of benzene and 47 mg. of potassium in 5 ml. of *t*-butyl alcohol under nitrogen and the mixture stirred for 3 hr. It was washed with 5% hydrochloric acid, dried, and evaporated. Crystallization of the residue from hexane yielded 200 mg. of ketone Xc, m.p. 75–76°; spectra: ultraviolet (EtOH), λ_{max} 260 mμ (log ε 4.11), $\lambda_{shoulder}$ 292 mμ (log ε 3.40); proton magnetic resonance ($CDCl_3$ solution with internal TMS standard), 3-proton singlets 1.21, 1.22 p.p.m. (C—Me); 4-proton multiplet 6.90–7.15 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.15; H, 8.14.

Enol Carbonate XI.—A solution of 1.3 g. of ethyl chloroformate in 10 ml. of benzene was added to a solution of 2.1 g. of the ketone mixture Xb in 5 ml. of benzene and 0.47 g. of potassium in 20 ml of *t*-butyl alcohol under nitrogen and the mixture stirred for 2 hr. It was washed with water, dried, and evaporated. Crystallization of the residue from hexane yielded 2.4 g. of colorless flakes of ester XI, m.p. 79–80°; spectra: infrared ($CHCl_3$), C=O 5.74 (s), C=C 6.00 (w) μ; ultraviolet (EtOH) λ_{max} 310 mμ (log ε 4.15), 323 (4.21), 335 (4.00).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 76.03; H, 7.09. Found: C, 76.40; H, 7.27.

Other combinations of base and solvent led to the same product.

Methyl Acrylylacetate (IX).—A solution of 219.0 g. of β-ethoxypropionyl chloride[7] in 200 ml. of ether was added slowly to a cooled slurry of methyl sodioacetoacetate, prepared from 175.0 g. of methyl acetoacetate and 37.0 g. of sodium, in 1 l. of ether, and the suspension stirred for 18 hr., and then filtered. Gaseous ammonia was bubbled through the cooled filtrate for 1 hr. and the solution washed with water, 5% hydrochloric acid, sodium bicarbonate, water again, and dried. Evaporation of the solvent and fractional distillation of the residue yielded 75.0 g. of methyl β-ethoxypropionylacetate, b.p. 90–94° (3 mm.); infrared spectrum (film), C=O 5.70–5.82 (s), C=C 6.02–6.15 (m) μ.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.42; H, 8.28.

A mixture of 6.0 g. of methyl β-ethoxypropionylacetate and 80 mg. of *p*-toluenesulfonic acid was heated in a distillation apparatus under vacuum at 120–130°. Redistillation of the distillate yielded 3.5 g. of methyl acrylylacetate (IX), b.p. 65° (19 mm.); infrared spectrum (film), C=O 5.74 (s), 5.95 (m), C=C 6.04 (s), 6.32 (s) μ.

Anal. Calcd. for $C_8H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.16; H, 6.09.

Ketoesters. (a) **Xa.**—A solution of 3.00 g. of methyl acrylylacetate in 5 ml. of benzene was added slowly to an ice-cold mixture of 3.36 g. of β-tetralone and sodium methoxide (530 mg. of sodium in 15 ml. of absolute methanol) in 5 ml. of benzene under nitrogen. The mixture was left standing at room temperature for 18 hr. and then refluxed for 30 min. The cooled mixture was acidified with 5% hydrochloric acid and extracted with chloroform. Distillation of the extract at low pressure removed the solvent and led to recovery of 1.10 g. of starting ketone. An ether solution of the distillation residue was extracted rapidly with ice-cold 5% aqueous sodium hydroxide, the aqueous solution acidified with 5% hydrochloric acid, and extracted with ether. The extract was dried and evaporated. Chromatography of the residue, 2.8 g., on 40 g. of silica gel and elution with benzene gave 1.80 g. of a liquid ketoester and its enol; spectra: ultraviolet (EtOH), λ_{max} 280 mμ (log ε 4.04), $\lambda_{shoulder}$ 305 (3.85), 330 (3.60); infrared ($CHCl_3$), C=O 5.82 (s), C=C 6.10 (m), 6.32 (m) μ.

A mixture of 750 mg. of the ketoester in 5 ml. of benzene and 126 mg. of potassium in 10 ml. of *t*-butyl alcohol was heated briefly under nitrogen and evaporated under reduced pressure. Benzene was added and the mixture re-evaporated. A solution of 1.50 mg. of methyl iodide in 10 ml. of benzene was added to a cooled solution of the residue in 10 ml. of benzene and the mixture stirred at room temperature for 16 hr. It then was washed with 5% sodium hydroxide and with water and dried. Evaporation of the solvent and crystallization of the residue, 500 mg., from methanol yielded colorless plates of ketoester Xa, m.p. 90–92°; spectra: ultraviolet (EtOH), λ_{max} 262 mμ (log ε 4.08), $\lambda_{shoulder}$ 292 (3.43); infrared (CCl_4), C=O 5.75 (s), 5.82 (s) μ; p.m.r., 3-proton singlets 1.53 p.p.m. (C—Me); 3.72 p.p.m. (O—Me); 4-proton multiplet 7.15–7.35 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.55; H, 6.70.

(b) **VIb.**—A solution of 4.40 g. of methyl acrylylacetate in 10 ml. of benzene was added slowly to an ice-cold solution of 4.02 g. of 1-methyl-2-tetralone and sodium methoxide (0.60 g. of sodium in 20 ml. of methanol) in 10 ml. of benzene under nitrogen. The mixture was stirred at room temperature for 18 hr. and refluxed for 30 min. The usual work-up and low-pressure distillation of the products led to 2.70 g. of unreacted ketone. Chromatography of the distillation residue, 4.5 g., on 100 g. of silica gel and elution with 5% ethyl acetate in chloroform afforded 1.1 g. of unidentified material, which gave a positive ferric chloride test. Further elution with the same solvent pair and crystallization of the eluted solid, 2.40 g., from hexane yielded plates of ketoester VIb, m.p., m.m.p. 117–118°; infrared spectrum identical with that of an authentic specimen[4d]; p.m.r., 3-proton singlets 1.61 p.p.m. (C—Me), 3.82 p.p.m. (O—Me); 4-proton multiplet 7.05–7.25 p.p.m. (aromatic hydrogens).

(c) **VIIb.**—A suspension of 82 mg. of sodium methoxide and 133 mg. of ketone VIIa in 10 ml. of benzene was stirred under nitrogen at room temperature for 30 min. A solution of 500 mg. of dimethyl oxalate in 5 ml. of benzene was added to the suspension, cooled in an ice bath, and the mixture stirred at room temperature for 38 hr. and at 60° for 30 min. The suspension was evaporated to dryness, treated with ether, and extracted with ice-cold 3% sodium hydroxide. The extract was acidified with

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(16) For previous total syntheses of *d,l*-podocarpic acid (V) *cf.* (a) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945); (b) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946); (c) F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind.* (London), 113 (1956).

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cold 5% hydrochloric acid and extracted with ether. The extract was acidified with cold 5% hydrochloric acid and extracted with ether. The extract was washed with water, dried, and evaporated. A mixture of the residual glyoxalate, 113 mg., and 100 mg. of powdered soft glass was heated at 130° for 30 min. and an ether suspension of the pyrolysate filtered. Evaporation of the filtrate, chromatography of the residue on 5 g. of silica gel, and elution with 1:1 hexane–benzene afforded 20 mg. of starting ketone VIIa and 20 mg. of glyoxalate. Further elution with the same solvent pair gave 51 mg. of a solid whose crystallization from hexane yielded 42 mg. of colorless needles of ketoester VIIb, m.p. 103–104°; infrared spectrum ($CHCl_3$), C=O 5.75 (s), 5.95 (s) μ.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.47; H, 6.86.

Methylation of β-Ketoesters.—All methylations were carried out in the following manner. A solution of the ketoester in *t*-butyl alcohol was added dropwise to a solution of potassium in *t*-butyl alcohol under nitrogen and the mixture refluxed for 20 min. The solvent was evaporated, benzene added several times, and also removed. A benzene solution of methyl iodide was added to the dry salt and the mixture refluxed under nitrogen for 18 hr. It then was washed with water, dried, evaporated, and the residue separated by chromatography.

A reaction between the salt from 140 mg. of the ketoester XIIa and 20 mg. of potassium and 3 ml. of methyl iodide in 10 ml. of benzene led to 150 mg. of oily product whose chromatography on 16 g. of 1:1 silicic acid–Celite and elution with 33:1 hexane–ether afforded 34 mg. of a solid. Its crystallization from aqueous methanol gave 15.3 mg. of colorless needles of methyl *d,l*-3-ketodesoxypodocarpate (XIIIa), m.p. 111–113°; spectra: infrared (CCl_4), C=O 5.77 (s) μ; p.m.r., 3-proton singlets 1.32, 1.47 p.p.m. (C—Me), 3.71 p.p.m. (O—Me); 4-proton multiplet 7.0–7.3 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.72; H, 7.93.

Further elution with the same solvent pair yielded 55 mg. of solid whose crystallization from aqueous methanol gave 36.1 mg. of colorless flakes of methyl *d,l*-3-ketodeisopropyldehydroabietate (XIIb), m.p. 103–104.5°; spectra: infrared (CCl_4), C=O 5.77 (s) μ; p.m.r., 3-proton singlets 1.30, 1.43 p.p.m. (C—Me), 3.66 p.p.m. (O—Me); 4-proton multiplet 6.9–7.3 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.44; H, 7.93.

A reaction[9b] between the salt prepared from 50 mg. of ketoester XVIIIa and 7.2 mg. of potassium and 1 ml. of methyl iodide in 10 ml. of benzene led to 59 mg. of a semisolid substance whose chromatography on 6 g. of 1:1 silicic acid–Celite and elution with 33:1 hexane–ether afforded 38 mg. of a solid. Crystallization from aqueous methanol yielded 25 mg. of ketoester XVIIIb, m.p. 124–126°; infrared spectrum (CCl_4), C=O 5.74 (s), 5.80 (s) μ.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.75; H, 7.69.

A reaction of the salt prepared from 40 mg. of ketoester VIIb and 7 mg. of potassium and 0.6 ml. of methyl iodide in 5 ml. of benzene and crystallization of the product from methanol gave 32 mg. of colorless needles of ketoester XX, m.p. 129–130°; spectra: infrared ($CHCl_3$), C=O 5.75 (s), 5.95 (s) μ; p.m.r., 3-proton singlets 1.28, 1.53 p.p.m. (C—Me), 3.64 p.p.m. (O—Me); 1-proton doublets 6.00, 6.17 p.p.m. (J 10 c.p.s.) (C_2—H), 7.44, 7.61 p.p.m. (J 10 c.p.s.) (C_1—H); 4-proton multiplet 7.0–7.4 p.p.m. (aromatic hydrogens) (the crystallization mother liquor contained nothing other than XX, as revealed by t.l.c.).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.99; H, 6.97.

A reaction of the salt from 400 mg. of ketoester VIb and 64 mg. of potassium and 6 ml. of methyl iodide in 20 ml. of benzene led to a crude product which was exposed to hydrogenation without purification because of its slow decomposition in air.

Hydrogenation of Unsaturated Ketoesters.—Hydrogenation of the above product of methylation of VIb and 200 mg. of 5% palladium–charcoal in 20 ml. of glacial acetic acid at atmospheric pressure, filtration of the catalyst after cessation of hydrogen absorption, and evaporation of the filtrate under vacuum yielded 400 mg. of semicrystalline solid. Inspection by t.l.c. showed it to consist mostly of XIIIa and to contain none of XIIb. Chromatography on 12 g. of silica gel and elution with 100:1 benzene–ether afforded 300 mg. of a solid whose crystallization from aqueous methanol gave methyl *d,l*-3-ketodesoxypodocarpate (XIIIa), m.p., m.m.p. 110–112°; infrared spectrum identical in all respects with that of the above sample of XIIIa.

Hydrogenation of 10 mg. of ketoester XX and 10 mg. of 5% palladium–charcoal in 10 ml. of glacial acetic acid at atmospheric pressure, work-up as usual, and crystallization of the product from aqueous methanol yielded 8 mg. of methyl *d,l*-3-ketodeisopropyldehydroabietate (XIIb), m.p., m.m.p. 102–103°; infrared spectrum identical with that of an above sample of XIIb.

A mixture of 20 mg. of ketoester XIX, 5 mg. of 5% palladium–charcoal, and a drop of sulfuric acid in 10 ml. of methanol was hydrogenated at atmospheric pressure and room temperature. At the end of hydrogen uptake the catalyst was filtered and the filtrate evaporated under vacuum. An ether solution of the residue was washed with 10% sodium carbonate and with water, dried over magnesium sulfate, and evaporated. Crystallization of the residue, 19 mg., from aqueous methanol gave 10 mg. of ketoester XVIIIb, m.p., m.m.p. 122–124°; infrared spectrum identical with that of an above sample of XVIIIb.

Methiomethylation of XIIa.—A reaction between the salt of 300 mg. of ketoester XIIa and 86 mg. of potassium and 3 ml. of chloromethyl sulfide and work-up by the procedure described above for the methylation of ketoesters led to a product whose solution in 20 ml. of methanol was mixed with 7 ml. of W-6 Raney nickel suspension and refluxed for 1 hr. Acetic acid, 1 ml., was added to the cooled suspension and the mixture filtered. The catalyst was washed with acetone and the combined filtrate and washings evaporated. The residue gave a negative sulfur test but revealed hydroxyl (nonwater) infrared absorption. As a consequence, it was dissolved and left standing at room temperature for 4 hr. in 8 ml. of a 1% chromic anhydride–1% water solution of acetic acid. The solution was extracted with ether and the extract dried and evaporated. Chromatography of the oily residue, 308 mg., on 30 g. of silica gel and elution with benzene produced 54 mg. of an unknown material with no infrared carbonyl absorption. Further elution with benzene as well as 200:1 benzene–ether yielded two products whose crystallization from aqueous methanol led to 80 mg. of methyl *d,l*-3-ketodesoxypodocarpate (XIIIa), m.p., m.m.p. 110–112°, and 23 mg. of methyl *d,l*-3-ketodeisopropyldehydroabietate (XIIb), m.p., m.m.p. 102–103°; infrared spectra identical with those of authentic samples (*vide supra*).

Clemmensen Reductions.—A suspension of amalgamated zinc (prepared by shaking 6 g. of zinc moss in a solution of 0.6 g. of mercuric chloride and 0.4 ml. of concentrated hydrochloric acid in 6 ml. of water for 15 min. and thereafter washing the undissolved zinc with water) and 300 mg. of methyl *d,l*-3-keto-deisopropyldehydroabieatate (XIIb) in 6 ml. of 15% hydrochloric acid was refluxed for 45 hr. During the reaction period 0.5-ml. portions of concentrated hydrochloric acid were added to the mixture at 6-hr. intervals. The mixture was extracted with ether and the extract washed with water, dried, and evaporated. Crystallization of the residue, 280 mg., from aqueous methanol yielded colorless needles of methyl *d,l*-deisopropyldehydroabietate (XIIc) m.p. 110–112° (lit.[15c] m.p. 114–115°); infrared spectrum [$CHCl_3$, C=O 5.77 (s) μ] identical with that of the *d*-antipode.[4g]

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.51; H, 8.87.

A suspension of amalgamated zinc, prepared from 1 g. of zinc moss as above, and 8 mg. of methyl *d,l*-3-ketodesoxypodocarpate (XIIIa) in 1.5 ml. of 15% hydrochloric acid was refluxed for 45 hr., while 0.2-ml. portions of concentrated hydrochloric acid were added at 6-hr. intervals. Normal work-up of the reaction mixture, chromatography of the crude product on 3 g. of alumina, and hexane elution yielded 6 mg. of a solid whose crystallization from aqueous methanol gave methyl *d,l*-desoxypodocarpate (XIIIb), m.p., m.m.p. 130–131° (lit.[15a,b] m.p. 128–129°, 131–132°); infrared spectrum [$CHCl_3$, C=O 5.77 (s) μ] identical with that of an authentic sample, prepared by the crystallization of a mixture of 17 mg. of the *d*-antipode[4c] and 17 mg. of the *l*-antipode[4h] from aqueous methanol; m.p. of solvate (28 mg.) 112–114°, m.p. 131–132° after drying under vacuum at 75° for 12 hr.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.62; H, 9.13.

A suspension of zinc amalgam, prepared from 4 g. of zinc moss as above, and 44 mg. of ketoester XVIIIb in 8 ml. of 15% hydrochloric acid was refluxed for 45 hr., while 1.6-ml. portions of concentrated hydrochloric acid were added at 6-hr. intervals. Normal work-up of the reaction mixture, diazomethane treatment of the crude product, and crystallization of solid product,

42 mg., from aqueous methanol gave the ester XVIIIc, m.p. 98–100°; infrared spectrum (CCl_4), C=O 5.77 (s) μ.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.11; H, 9.12.

Hydrolyses.—A solution of 280 mg. of methyl *d,l*-deisopropyldehydroabietate (XIIc) and 0.8 g. of dry lithium iodide in 20 ml. of dry collidine was refluxed under nitrogen for 10 hr.[4h] The solution was acidified with 10% hydrochloric acid and extracted with ether. The organic solution was extracted with 10% sodium hydroxide. The alkaline solution was reacidified and extracted with ether. The extract was washed with water, dried, and evaporated. Crystallization of the residue from aqueous methanol yielded 185 mg. of colorless crystals of *d,l*-deisopropyldehydroabietic acid (XVIb), m.p. 171–173° (lit.[15b,d,e] m.p. 174–175°, 177–179°, 174°); infrared spectrum identical with that of the *d*-antipode.[4g,21]

A solution of 14 mg. of methyl *d,l*-desoxypodocarpate (XIIIb), 10 mg. of potassium hydroxide, and 0.2 ml. of water in 1 ml. of ethylene glycol was refluxed (*ca.* 190°) for 72 hr. The mixture was diluted with 10 ml. of water and extracted with ether. The aqueous solution was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried (sodium sulfate), and evaporated. Crystallization of the residue, 9 mg., from aqueous methanol yielded 5 mg. of *d,l*-desoxypodocarpic acid (XVIa), m.p., m.m.p. 232–234° (lit.[15a,b,d] m.p. 232–233°, 232–233°, 240–241°); infrared spectrum identical with that of an authentic sample prepared by the crystallization of a mixture of 13 mg. of the *d*-antipode[4c,22] and 13 mg. of the *l*-antipode[4h] from aqueous methanol; m.p. 232–233°.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.06; H, 8.53.

Comparison of the rates of alkaline hydrolysis of the esters XIIc, XIIIb, and XVIIIc was carried out in the following manner. A solution of 20 mg. of the ester, 10 mg. of potassium hydroxide, and 0.15 ml. of water in 1 ml. of ethylene glycol was refluxed (*ca.* 190°) for 4 hr. Water, 10 ml., and 2 ml. of concentrated hydrochloric acid were added and the mixture extracted with three 10-ml. portions of ether. The combined organic solutions were extracted with three 6-ml. aliquots of 10% sodium hydroxide. The remaining ether solution was washed twice with 3 ml. of water each, dried (magnesium sulfate), and evaporated. The residue—unreacted starting ester—was identified by its characteristic infrared spectrum.

The combined alkaline extracts were acidified with 5 ml. of concentrated hydrochloric acid and extracted three times with 10-ml. portions of ether. The combined organic solutions were washed twice with 3-ml. aliquots of water, dried (magnesium sulfate), and evaporated. The resulting acid was identified by its infrared spectrum.

Hydrolysis of ester XIIc led to recovery of 4 mg. of starting material and 16 mg. of deisopropyldehydroabietic acid (XVIb); XIIIb gave 18 mg. of recovered ester and 1 mg. of desoxypodocarpic acid (XVIa); XVIIIc yielded 5 mg. of ester and 15 mg. of acid.

Reductive Hydrolyses.—The following represented a second test of the stereochemistry of the ester XIIc, XIIIb, and XVIIIc. Sufficient lithium wire was added to a solution of 20 mg. of the ester in 5 ml. of tetrahydrofuran and 15 ml. of liquid ammonia to cause a blue color to persist in the solution for 30 min. Thereafter the mixture was left standing at room temperature until ammonia had evaporated. Chloroform, 10 ml., and 10 ml. of 10% hydrochloric acid was added to the residue and the aqueous phase extracted three times with 4-ml. aliquots of chloroform. The combined organic solutions were extracted four times with 4-ml. portions of 5% sodium hydroxide. The remaining chloroform solution was washed with 3 ml. of water, dried (magnesium sulfate), and evaporated. The neutral product was identified as alcohol by its infrared spectrum.

The combined alkaline extracts were acidified with 2 ml. of concentrated hydrochloric acid and extracted four times with 4-ml. portions of chloroform. The combined organic extracts were washed with 5 ml. of water, dried (magnesium sulfate), and evaporated. The acidic product was identified by its characteristic infrared absorption.

Reductive hydrolysis of ester XIIc led to 1 mg. of deisopropyldehydroabietic acid (XVIb) and 16 mg. of alcohol; XIIIb gave 13 mg. of desoxypodocarpic acid (XVIa) and 5 mg. of alcohol; XVIIIc yielded 4 mg. of acid and 14 mg. of alcohol.

Resolutions.—A mixture of 23.5 mg. of *d,l*-desoxypodocarpic acid (XVIa) and 26.8 mg. of cinchonine was crystallized three times from aqueous methanol. This led to 11.9 mg. of crystalline needles of *d*-desoxypodocarpic acid cinchonine salt, m.p., m.m.p. 198–200°, 210–215°; infrared spectrum identical with that of an authentic specimen, m.p. 199–201°, 210–215°, prepared by the mixing of the *d*-antipode[4c] of XVIa and cinchonine and crystallization from aqueous methanol.

Anal. Calcd. for $C_{30}H_{44}O_3N_2$: C, 78.22; H, 8.02; N, 5.07. Found: C, 78.49; H, 8.15; N, 5.10.

A methanol solution of 10.2 mg. of the salt was treated with 10% hydrochloric acid and the liberated organic acid crystallized from the solution. This resulted in the isolation of 4.6 mg. of colorless needles of *d*-desoxypodocarpic acid (XVIa), m.p., m.m.p. 195–197°, $[\alpha]^{25}D$ 138.4° (ethanol); infrared spectrum identical with that of an authentic sample,[4c] m.p. 197–198°.

An alcohol solution of 140 mg. of *d,l*-deisopropyldehydroabietic acid (XVIb) and 176 mg. of cinchonine methohydroxide was evaporated to dryness under reduced pressure. An ethyl acetate solution of the residual gum was refluxed for a few minutes and evaporated. The residue was triturated with chloroform, the resulting precipitate filtered, and the filtrate evaporated. The ethyl acetate and chloroform treatments were repeated several times until all salt insoluble in chloroform had been removed. Crystallization of the remainder from aqueous methanol yielded 100 mg. of colorless needles of *d*-deisopropyldehydroabietic acid N-methocinchonine salt, m.p., m.m.p. 194–196°, $[\alpha]^{23}D$ 140° (*c* 0.30, ethanol); infrared spectrum identical with that of an authentic specimen.

Anal. Calcd. for $C_{37}H_{46}O_3N_2 \cdot 2MeOH$: C, 74.25; H, 8.63. Found: C, 74.28; H, 8.39.

The salt was suspended in 5% hydrochloric acid and the mixture extracted with ether. The extract was washed, dried, and evaporated. Crystallization of the residue from aqueous methanol yielded colorless needles of *d*-deisopropyldehydroabietic acid (XVIb), m.p., m.m.p. 170–173°, $[\alpha]^{26}D$ 65° (*c* 1.58, ethanol); infrared spectrum identical with that of an authentic sample,[21] m.p. 172–173°.

Acknowledgment.—The authors are indebted to the National Science Foundation for support of this work.

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(22) $[\alpha]D$ +40.8° for this substance, as cited in ref. 4c, should be corrected to +140.8°.