[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS, LAWRENCE, KANSAS]

The Synthesis of Abietadienoic Acids from Dehydroabietic Acid[1]

BY ALBERT W. BURGSTAHLER[2] AND LEONARD R. WORDEN[3]

RECEIVED JUNE 27, 1963

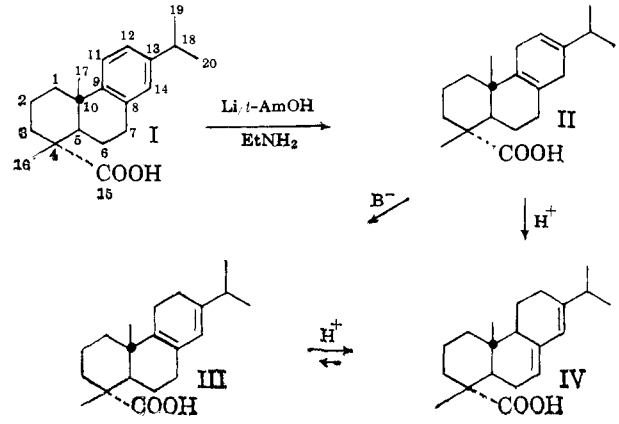
Two routes have been developed for the synthesis of abietic acid (IV) from dehydroabietic acid (I). In the first, dehydroabietic acid was reduced with lithium and *t*-amyl alcohol in ethylamine under carefully defined conditions to give $\Delta^{8,12}$-abietadienoic acid (II) in 90% yield. Isomerization of this product with acid then afforded abietic acid, while appropriate treatment with base furnished palustric acid ($\Delta^{8,13}$-abietadienoic acid, III). By contrast, prolonged reduction of dehydroabietic acid with lithium in ethylamine in the absence of an added proton source gave almost exclusively an aldehydic product having the Δ^{8}-abietenal structure Va. A second route to abietic acid was achieved by transformation of dehydroabietic acid into 13-methoxydeisopropyldehydroabietic acid (IXc), followed by reduction of the aromatic ring, treatment with acid, and reinsertion of the isopropyl group. In addition, the first preparation of (±)-abietic acid has been accomplished by reduction, with subsequent acid isomerization, of (±)-dehydroabietic acid.

Although only a minor constituent of fresh oleoresin, abietic acid (IV, Chart I) represents the major component of heat-treated or acid-isomerized rosin. For over a century, along with other resin acids, abietic acid has been the subject of numerous and extensive chemical investigations, but only in comparatively recent years, after "a prolonged and difficult series of experiments,"[4] have the structure and complete stereochemistry of this important diterpene become firmly established.[5] Its synthesis also has been the object of a number of research programs,[6] including one of our own, of which a preliminary report has been published.[7] In this paper we present details of that work along with an account of some additional experiments.

Since (±)-dehydroabietic acid, which in its (+)-form (I) constitutes about 4% of the acids in pine gum oleoresin,[8] already had been synthesized[9] when we began our studies, we centered our attention primarily on the transformation of the naturally occurring antipode of this aromatic resin acid into the more abundant abietic-type dienoid resin acids. In the present investigation two pathways were explored for this purpose. The first (Chart I) involves the direct reduction of dehydroabietic acid to a dihydro product (II) capable of being isomerized into abietic acid (IV) or into palustric acid (III). The second (Chart III) consists of the transformation of dehydroabietic acid by a stepwise sequence into the 13-methoxy derivative (IXc) of deisopropyldehydroabietic acid and conversion of the latter into abietic acid by reduction of the aromatic ring, treatment with acid, and reintroduction of the isopropyl group. Both routes were successful, although as would be expected, the first, more direct route proved to be far more satisfactory.

Earlier experiments showed that dehydroabietic acid (I) is not reduced to any appreciable extent by sodium

CHART I



or lithium and ethanol in liquid ammonia under the usual Birch-type conditions even in the presence of ether as a cosolvent.[10] Consequently, we turned to the more powerful lithium–ethylamine reducing system developed by Benkeser and co-workers,[11] and in our initial experiments with this reagent we noted that over a period of several hours it reduced not only the aromatic ring of dehydroabietic acid but, in the absence of an added proton source, the carboxyl group as well (see Chart II). However, in the presence of a very weakly acidic proton source such as *t*-amyl or *t*-butyl alcohol,[12] selective reduction of dehydroabietic acid to the desired $\Delta^{8,12}$-abietadienoic acid (II) could be achieved in yields up to 90%. Interestingly, alcohols more acidic than *t*-amyl or *t*-butyl alcohol (*e.g.*, ethanol or isopropyl alcohol) almost completely inhibited the reduction.[12b] Likewise, use of nonredistilled tank ethylamine also inhibited reduction, presumably for the same reason that tank liquid ammonia frequently has an adverse effect on Birch reductions—namely because traces of iron compounds from the tank catalyze amide formation at the expense of reduction.[12b] Optimum conditions for the reduction were found when lithium, *t*-amyl alcohol, and dehydroabietic acid were employed in the approximate molar ratio 40:40:1. When this ratio was changed to 20:20:1, or when less lithium than *t*-amyl alcohol was used, underreduction occurred leading to recovery of considerable amounts of difficultly separated dehydroabietic acid. When more

(1) Taken in part from the Ph.D. Thesis of Leonard R. Worden, The University of Kansas, 1963. We gratefully acknowledge support for portions of this work by a grant (G-19936) from the National Science Foundation.

(2) Alfred P. Sloan Research Fellow, 1961–1964.

(3) National Institutes of Health Predoctoral Fellow, 1961–1963.

(4) J. L. Simonsen and D. H. R. Barton, "The Terpenes," 2nd Ed., Vol. III, Cambridge University Press, New York, N. Y., 1952, p. 383.

(5) For discussion and leading references, see W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.*, **83**, 2563 (1961).

(6) For recent summaries, see (a) N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.* (London), **16**, 117 (1962); (b) M. Tsutsui and E. A. Tsutsui, *Chem. Rev.*, **59**, 1059 (1959); (c) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

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

(8) G. C. Harris, *ibid.*, **70**, 3671 (1948). In the formula I we have employed steroid numbering for the ring carbon atoms while the substituent carbons are designated according to the scheme of W. Klyne, *J. Chem. Soc.*, 3072 (1953).

(9) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); **84**, 284 (1962). Other syntheses have since been recorded by R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962), and by S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963).

(10) More recent experiments in which the modified procedure of Dryden and co-workers (ref. 12b) was used have indicated that dehydroabietic acid is reduced slowly with lithium and *t*-butyl alcohol in tetrahydrofuran and liquid ammonia, but the yield of the dihydro acid II after 3 hr. is only about 35%.

(11) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955), and later papers.

(12) *Cf.* (a) G. Stork and W. N. White, *ibid.*, **78**, 4604 (1956); (b) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961); see also (c) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *ibid.*, **28**, 1094 (1963).

lithium than *t*-amyl alcohol was used, overreduction took place with formation of a Δ^8-abietenoic acid (*cf.* Vc, Chart II).

Isolation and purification of the acid II was conducted conveniently through the sparingly soluble (in acetone) di-*n*-butylamine salt. The structure of this acid, which follows from its mode of preparation, was confirmed by the presence of only end absorption in the ultraviolet spectrum (no conjugated double bond system) and only one olefinic proton signal (4.55 τ) in the nuclear magnetic resonance (n.m.r.) spectrum.[13]

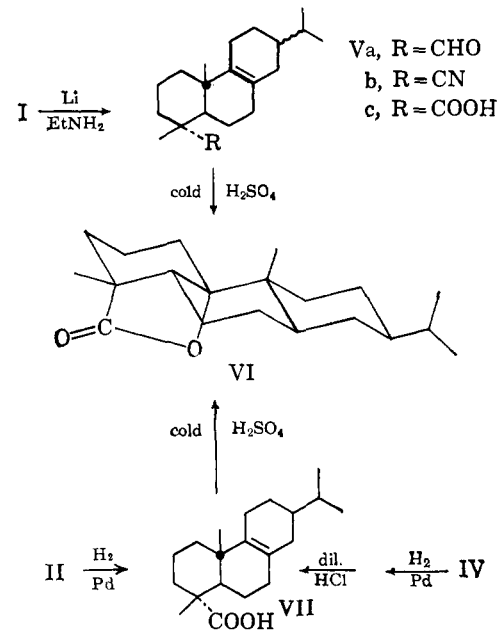
As would be expected, acid isomerization of the acid II proceeded readily to give a mixture of conjugated dienoid resin acids[14] containing, after 2 hr., about 85% of abietic acid (IV) along with lesser amounts of palustric acid (III) and neoabietic acid (Xa, Chart III). Isolation and purification of the abietic acid so formed was achieved without difficulty through the diisoamylamine salt.[15] All spectral and other properties of the regenerated acid were identical with those of an authentic sample of abietic acid isolated directly from rosin[15] or prepared by acid isomerization of neoabietic acid (Xa).[16]

As an extension to complete the total synthesis of (±)-abietic acid, application of the foregoing reduction–isomerization sequence to a sample of synthetic (±)-dehydroabietic acid[9] kindly supplied by Professor Robert E. Ireland of the University of Michigan, to whom we express our warmest thanks, furnished racemic abietic acid, m.p. 148–150°. The spectral properties of this product in solution were identical with those of naturally occurring (−)-abietic acid.

In contrast to the results of isomerization with mineral acid, treatment of the $\Delta^{8,12}$-dienoic acid II with potassium hydroxide at high temperature or with lithium ethylamide in refluxing ethylamine[12c] brought the double bonds into homoannular conjugation and thereby gave palustric acid (III). This acid was identified by its optical rotation and characteristic ultraviolet spectrum (λ_{max} 265–266 mμ)[14] as well as by its infrared and n.m.r.[13] spectra and mixture melting point comparison with an authentic sample.[16] The further isomerization of palustric acid into abietic acid[14] and the conversion of abietic acid into neoabietic acid[17] have been reported previously. Unfortunately, the transformation of any of these acids into levopimaric acid ($\Delta^{8(14),12}$-abietadienoic acid, the remaining important abietic-type dienoid resin acid) has not been achieved. However, they can all be converted into common Diels–Alder adducts derived from the levopimaric acid structure.[18]

As already noted, prolonged reduction of dehydroabietic acid with an excess of lithium in ethylamine in the absence of an added proton source proceeded beyond the dehydro stage of the acid II and afforded mainly the monounsaturated aldehyde Va (Chart II). The presence of a free aldehyde function in this product was demonstrated spectroscopically and chemically, while the position of the double bond was verified by the absence of a vinyl proton signal in the n.m.r. spectrum and by hydroxylation of the double bond with subsequent cleavage by lead tetraacetate according to the method of Castells and Meakins[19] to give a diketone, which could have arisen only from a tetrasubstituted double bond. Formation of a Δ^8-monoolefin also follows from the fact that an initially produced $\Delta^{8,12}$-diene would be expected to undergo isomerization by lithium ethylamide in the absence of an alcohol[11] to yield the $\Delta^{8,13}$-diene system of palustric acid (III), which other experiments in our laboratories[20] have demonstrated is reduced readily by lithium in ethylamine to a Δ^8-abietenoic acid (Vc).

CHART II



Isolation of an aldehyde from the reduction of a carboxylic acid under conditions in which a large excess of reducing agent is present throughout the reaction is at first sight surprising. Moreover, since aldehydes themselves are reduced readily by metal–amine systems, the aldehyde Va must have been produced as some type of base-stable intermediate or derivative. In support of this view other work in our laboratories has shown that this type of reduction is applicable to other acids and that it probably proceeds through the dilithium or diethylammonium salt of the aldehyde hydrate.[21] In any event the aldehyde Va readily afforded a semicarbazone and a yellow 2,4-dinitrophenylhydrazone, through which derivatives it could be partially purified and then regenerated. On the other hand, it could not be oxidized to the corresponding acid Vc by such reagents as silver oxide or chromic acid. To effect this transformation, the aldehyde was converted into its oxime, which then was dehydrated to the corresponding nitrile Vb, and the latter hydrolyzed to the Δ^8-acid Vc.

The properties of the acid Vc closely resemble those of the dihydroabietic acid VII derived from partial

(13) This spectrum was determined at Iowa State University through the courtesy of Professor Ernest Wenkert.

(14) *Cf.* V. M. Loeblich, D. E. Baldwin, and R. V. Lawrence, *J. Am. Chem. Soc.*, **77**, 2823 (1955); also D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *ibid.*, **78**, 2015 (1956). According to these authors, after 48 hr. the equilibrium concentration of abietic acid in ethanolic HCl is increased to 95%.

(15) *Cf.* G. C. Harris and T. F. Sanderson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 1.

(16) We thank Mr. Ray V. Lawrence, U. S. Department of Agriculture, Naval Stores Research Laboratory, Olustee, Fla., for providing comparison samples of abietic, neoabietic, and palustric acid and for sending us generous quantities of WW gum rosin from which both abietic and neoabietic acid were isolated.

(17) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 334 (1948); see also ref. 14.

(18) For discussion and leading references, see N. J. Halbrook, J. A. Wells, and R. V. Lawrence, *J. Org. Chem.*, **26**, 2641 (1961).

(19) J. Castells and G. D. Meakins, *Chem. Ind.* (London), 248 (1956); J. Castells, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2917 (1962).

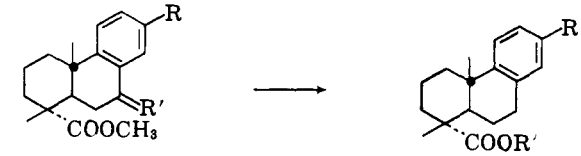
(20) A. W. Burgstahler and J. S. Swenton, unpublished work.

(21) A. W. Burgstahler, L. R. Worden, and T. B. Lewis, *J. Org. Chem.*, **28**, 2918 (1963). An apparently related finding has been observed in the formation of crotonaldehyde in unspecified yield in the reduction of certain 12-acetoxy-11-keto steroids with calcium in liquid ammonia [J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956); *cf.* A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958)].

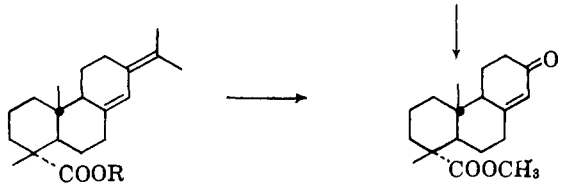
hydrogenation either of $\Delta^{8,12}$-abietadienoic acid (II) or of abietic acid (IV) with subsequent mild acid isomerization[22] of the resulting $\Delta^{8(14)}$-double bond into the $\Delta^{8(9)}$-position. However, since the acid Vc gave the dihydroabietic γ-lactone VI of known stereochemistry (13β-isopropyl group)[23] in much poorer yield than did the acid-isomerized dihydroabietic acid VII derived from the catalytic reductions, it appears that the configuration at C-13 in these acids differs at least partially in the two series. Moreover, since chemical reduction would be expected to give predominantly the more stable (equatorial) 13α-isopropyl configuration in the acid Vc,[24] whereas catalytic hydrogenation would be expected to favor formation of the less stable (axial) 13β-isopropyl isomer in the acid VII (α-side approach to the catalyst promoted by the angular methyl group),[6c] these differences in the yield of the lactone VI appear to be in the direction one would expect. On the other hand, this interpretation of the stereochemistry at C-13 in these acids is not supported by results of the Rosenmund reduction of the acid chloride derived from the acid VII. This reaction furnished an unsaturated aldehyde which at least in part appeared to be identical with the aldehyde Va produced in the lithium–ethylamine reduction of dehydroabietic acid. Consequently, assignment of a predominantly 13α-configuration to the isopropyl group in the aldehyde Va and its derivatives, although reasonable, is not free from ambiguity and must be considered tentative.

As already mentioned, we also have developed an alternative route to abietic acid from dehydroabietic acid involving an oxidation–reduction sequence (Chart III) leading to the unsaturated keto ester XI, which in turn has been obtained previously by partial ozonolysis of methyl neoabietate (Xb).[25] In part, this route parallels related work of Wenkert and co-workers[26] which appeared shortly after our original report[7] was published.

CHART III



VIIIa, R = CH(CH$_3$)$_2$, R' = H₂ IXa, R = C(CH$_3$)$_2$OH, R' = H
b, R = C(CH$_3$)$_2$OAc, R' = O b, R = OH, R' = CH$_3$
c, R = COCH$_3$, R' = O c, R = OCH$_3$, R' = H



Xa, R = H
b, R = CH$_3$

XI

Oxidation of methyl dehydroabietate (VIIIa) with chromic acid in acetic acid–acetic anhydride by the procedure of Sanderson[27] afforded the acetoxy keto ester VIIIb in 35% yield and the diketo ester VIIIc in 17% yield. Wolff–Kishner reduction of the acetoxy keto ester VIIIb with accompanying hydrolysis then gave the hydroxy acid IXa in 95% yield. After esterification with diazomethane this product was converted *via* the corresponding C-18 hydroperoxide[28] (not isolated) into the phenolic ester IXb, m.p. 149.5–150°, which also has been prepared recently by the Wenkert group[26] from deisopropyldehydroabietic acid and by a related route from dehydroabietic acid.

After methylation of the phenolic function in the ester IXb, alkaline hydrolysis furnished the corresponding methoxy acid IXc. Reduction of the latter with lithium and *t*-amyl alcohol in ethylamine, followed by acid treatment of the resulting dihydro product and subsequent re-esterification, then gave the previously mentioned unsaturated keto ester XI,[25,26] m.p. 126–127°, in approximately 30% over-all yield from the phenolic ester IXb. A similar route to XI involving reduction of the methylated derivative of the phenolic ester IXb, with subsequent oxidation of the resulting carbinol, has been described by the Wenkert group.[26] For preparative purposes, however, this keto ester is more easily obtained directly from methyl neoabietate (Xb) by partial ozonolysis.[25,26]

Finally, in order to complete the sequence, selective reaction of the ketone function in the keto ester XI with isopropylmagnesium bromide in benzene–ether, followed by acid dehydration and alkaline hydrolysis according to procedures already developed with methylmagnesium iodide,[25] then furnished abietic acid (IV) but in rather poor over-all yield.

Incidental to the reduction of the methoxy acid IXc in the preceding scheme, we also examined the reduction of O-methylpodocarpic acid (XIIa) with lithium and *t*-amyl alcohol in ethylamine. After treatment of the product with acid and esterification with diazomethane, the unsaturated keto ester XIIIa was obtained as its 2,4-dinitrophenylhydrazone in 25% over-all yield. The similar reductions of O-methylpodocarpinol (XIIb) with lithium and *t*-butyl alcohol in tetrahydrofuran and liquid ammonia,[29] and of O-methylpodocarpane (XIIc) with lithium and ethanol in tetrahydrofuran and liquid ammonia,[30] have been reported to give the unsaturated ketones XIIIb and XIIIc in about 40 and 45% yield,

XIIa, R = COOH
b, R = CH$_2$OH
c, R = CH$_3$

XIIIa, R = COOCH$_3$
b, R = CH$_2$OH
c, R = CH$_3$

respectively. Apparently, hydrogenolysis of the methoxyl group[29] as well as overreduction of the aromatic ring[30] are responsible for the comparatively low yields obtained in these reductions.

(22) *Cf.* L. Velluz, G. Miller, A. Petit, and J. Mathieu, *Bull. soc. chim. France*, 401 (1954), and references cited therein.

(23) L. J. Gough, T. F. Sanderson, V. I. Stenberg, and E. Wenkert, *J. Org. Chem.*, **25**, 1269 (1960).

(24) *Cf.* D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956). For recent discussion see M. Alauddin and M. Martin Smith, *J. Org. Chem.*, **28**, 886 (1963).

(25) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 339 (1948).

(26) E. Wenkert, R. W. J. Carney, and C. Kaneko, *ibid.*, **83**, 4440 (1961).

(27) T. F. Sanderson (to Hercules Powder Co.), U. S. Patent 2,750,368, June 12, 1956 [*Chem. Abstr.*, **51**, 1278*f* (1957)]. We thank Mr. Sanderson for a generous gift of dehydroabietonitrile as well as directions for the preparation of pure dehydroabietic acid and methyl dehydroabietate from it.

(28) *Cf.* P. F. Ritchie, T. F. Sanderson, and L. F. McBurney, *J. Am. Chem. Soc.*, **76**, 723 (1954); see also T. F. Sanderson (to Hercules Powder Co.), U. S. Patent 2,750,367, June 12, 1956 [*Chem. Abstr.*, **51**, 1278*c* (1957)], and ref. 26.

(29) R. H. Bible, Jr., and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

(30) E. Wenkert, V. I. Stenberg, and P. Beak, *J. Am. Chem. Soc.*, **83**, 2320 (1961).

Experimental[31]

(+)-$\Delta^{8,12}$-**Abietadienoic Acid (II).**—Purified (+)-dehydroabietic acid (I), m.p. 171–172°, $[\alpha]_D$ +64°,[32] was prepared by alkaline hydrolysis (sodium hydroxide in diethylene glycol at 180° for 3 hr.) of recrystallized (methanol) methyl (+)-dehydroabietate (VIIIa), m.p. 63.5–64°, $[\alpha]_D$ +62°. The latter was obtained by the action of diazomethane on (+)-dehydroabietic acid of 95% purity resulting from the prolonged (6–8 hr.) hydrolysis of (+)-dehydroabietonitrile[27] with 6% sodium hydroxide in diethylene glycol at 190–200°.

In a typical reduction 300 mg. (1 mmole) of (+)-dehydroabietic acid (I) in 4.3 ml. (40 mmoles) of *t*-amyl alcohol was placed in a flask equipped with a Dry-Ice condenser and a high-speed stirrer (sodium dispersion motor),[33] Redistilled, anhydrous ethylamine (30 ml., Matheson Co., Joliet, Ill.) and then 240 mg. (35 mg.-atoms) of finely divided lithium shot[34] were added. After a 15-min. period, during which all the lithium dissolved and a pale blue cast pervaded the solution, an additional 240 mg. (35 mg.-atoms) of lithium shot was introduced. When the characteristic deep blue color first persisted, *t*-amyl alcohol (*ca.* 5 ml.) was added until the mixture remained colorless. After distillation of the ethylamine the mixture was treated with ice, acidified slowly with dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried, and evaporated under reduced pressure. Residual *t*-amyl alcohol was removed by vacuum codistillation with absolute ethanol. The gummy product was dissolved in *ca.* 2–3 ml. of acetone, 0.2 ml. of di-*n*-butylamine (Sharples Chemical, Inc., Philadelphia, Pa.) was added, and the resulting salt was crystallized from hot acetone to give glistening white needles (385 mg., 89% yield), m.p. 140–143°. By spectrophotometric assay, approximately 90% of this product was shown to be the di-*n*-butylamine salt of the (+)-$\Delta^{8,12}$-dienoic acid II, the remaining 10% consisting of the corresponding salts of (+)-dehydroabietic acid (1%) and (+)-Δ^{8}-abietenoic acid (Vc, 9%).[35] One recrystallization of this salt from acetone gave material of 96% purity,[35] m.p. 141.5–144.5°, $[\alpha]_D$ +31°, which could not be purified further by additional recrystallization.

Anal. Calcd. for $C_{28}H_{49}NO_2$ (431.68): C, 77.90; H, 11.44; N, 3.24. Found: C, 77.96; H, 11.34; N, 3.26.

The acid II also could be isolated as the more soluble diisobutylamine salt, m.p. 117.5–120.5° (needles from acetone). Successful repetition of the reduction was limited by the small capacity of our sodium dispersion motor to approximately 10 times the above scale.

For liberation of the acid II from the di-*n*-butylamine salt a slurry of 1.0 g. of the salt in 10 ml. of ethanol was treated with a slight excess of acetic acid. The resulting solution was warmed and diluted with hot water to the point of incipient cloudiness, whereupon (+)-$\Delta^{8,12}$-abietadienoic acid (II) crystallized as colorless plates (0.62 g., 89% recovery), m.p. 155–157°. One recrystallization from ethanol–water raised the m.p. to 160.5–162°, $[\alpha]_D$ +55°.

Anal. Calcd. for $C_{20}H_{30}O_2$ (302.44): C, 79.42; H, 10.00. Found: C, 79.19; H, 9.79.

The sensitivity of this acid to disproportionation was demonstrated by the change in composition when a sample containing 1% of (+)-dehydroabietic acid (I) and 3% of (+)-Δ^{8}-abietenoic acid (Vc) was heated in an open container at 40° for 1 week. Assay[35] of the product showed that it then contained 9% of (+)-dehydroabietic acid and 11% of (+)-Δ^{8}-abietenoic acid.

Di-*n*-butylamine Salt of (±)-$\Delta^{8,12}$-Abietadienoic Acid (II).—Reduction of 400 mg. of chromatographically pure, sublimed (±)-dehydroabietic acid[9,36] by the procedure described above for the reduction of (+)-dehydroabietic acid furnished 482 mg. (84%) yield) of di-*n*-butylammonium (±)-$\Delta^{8,12}$-abietadienoate. After one recrystallization from acetone this salt formed a powdery white solid, m.p. 126–127°, which was 90% pure by ultraviolet assay.[35]

Anal. Calcd. for $C_{28}H_{49}NO_2$ (431.68): C, 77.90; H, 11.44; N, 3.24. Found: C, 78.07; H, 11.35; N, 3.83.

(+)-**Palustric Acid (III).**—A solution of 302 mg. (1 mmole) of (+)-$\Delta^{8,12}$-abietadienoic acid (II) of *ca.* 90% purity[35] in 10 ml. of ethylene glycol containing 2 g. of potassium hydroxide was heated under nitrogen at 210° for 4 hr. When cool, the solution was diluted with ice water and acidified with dilute acetic acid. Extraction with ether furnished 270 mg. of solid acid, which after three recrystallizations from methanol–water, gave 120 mg. of nearly pure (+)-palustric acid (III), m.p. 159–165°, $[\alpha]_D$ +68°, λ_{max} 265–266 mμ (ε 8,900), n.m.r.[13] 4.54 τ (one olefinic proton). A mixture m.p. determination with an authentic sample[16] of (+)-palustric acid (m.p. 161–166°)[14] was undepressed, and the respective infrared and n.m.r.[13] spectra were identical. The acid II also could be isomerized with lithium ethylamide in ethylamine,[12c] but the result was less satisfactory. Attempted isomerization with potassium *t*-butoxide in dimethyl sulfoxide[37] at room temperature or at 100° was unsuccessful.

(−)-**Abietic Acid (IV). A. From (+)-$\Delta^{8,12}$-Abietadienoic Acid (II).**—A solution of 1.0 g. (3.3 mmoles) of (+)-$\Delta^{8,12}$-abietadienoic acid (II) of *ca.* 90% purity[35] in 16 ml. of absolute ethanol containing 4 ml. of concentrated hydrochloric acid was heated under reflux for 2.5 hr. After dilution with water the mixture was extracted with ether, and the product was recovered as the diisoamylamine salt, which crystallized from acetone in long white needles (1.37 g., 90% yield), m.p. 133–136°, $[\alpha]_D$ −47°. Three recrystallizations from acetone changed the specific rotation to −61° (lit.[15] −60°) and the m.p. to 136–139°. (−)-Abietic acid also could be isolated but not purified as the di-*n*-butylamine salt, which crystallized as long, interlaced needles from acetone; m.p. 152.5–155°, $[\alpha]_D$ −33°. Even though a satisfactory elemental analysis was obtained, recrystallization of this salt did not improve its specific rotation.

Anal. Calcd. for $C_{28}H_{49}NO_2$ (431.68): C, 77.90; H, 11.44; N, 3.24. Found: C, 77.92; H, 11.30; N, 3.41.

(−)-Abietic acid (IV) of $[\alpha]_D$ −103° was secured from the diisoamylamine salt of $[\alpha]_D$ −61° in 90% yield by the procedure described above for the recovery of (+)-$\Delta^{8,12}$-abietadienoic acid from its di-*n*-butylamine salt. One recrystallization of this material from ethanol–water gave abietic acid, m.p. 164–169°, $[\alpha]_D$ −106°.[38] The infrared spectrum (CS_2 and KBr disk), ultraviolet absorption [λ_{max} 235 (ε 21,500), 241.5 (23,000), and 250 mμ (15,500)], and n.m.r. spectrum[13] (two olefinic protons, 4.26 and 4.66 τ) were identical with those of an authentic specimen.[16]

B. **From the (+)-Keto Ester XI.**—A solution of 290 mg. (1 mmole) of the (+)-keto ester XI, m.p. 125–127°, in 30 ml. of dry benzene was added to a stirred solution of 5 mmoles of isopropylmagnesium bromide in 30 ml. of ether. The mixture was stirred for an additional 3 hr. and after treatment with ice water and ammonium chloride was extracted with ether. The infrared spectrum of the neutral product thus isolated showed hydroxyl absorption at 2.7–2.9 μ, a strong ester carbonyl peak at 5.8 μ, and only a trace of conjugated starting ketone at 6.0 μ. Treatment of the crude product with 3 ml. of concentrated hydrochloric acid in 20 ml. of ethanol on the steam bath for 2 hr. produced the typical abietic acid absorption peaks at 235, 241, and 250 mμ. Alkaline hydrolysis (10% sodium hydroxide in ethylene glycol at 180° for 2 hr.) of the product recovered by extraction with ether furnished *ca.* 200 mg. of a pale yellow semisolid acid, which on treatment with diisoamylamine in acetone gave a poor yield (60 mg.) of the diisoamylamine salt of (−)-abietic acid (IV) as colorless needles, m.p. 133–136°. These on recrystallization from acetone had m.p. and mixture m.p. 136–139°, $[\alpha]_D$ −58°, and an ultraviolet spectrum identical with that of an authentic sample. The regenerated acid had m.p. and mixture m.p. 164–168°, $[\alpha]_D$ −103°.

(±)-**Abietic Acid (IV).**—Acid isomerization of 430 mg. of the crude di-*n*-butylamine salt of (±)-$\Delta^{8,12}$-abietadienoic acid (II),

(31) Melting points are corrected and were determined in open capillaries. Boiling points are uncorrected. Analytical samples were dried under vacuum either at the boiling point of the recrystallization solvent or at 40° below the melting point, whichever was lower. Ether solutions were dried over anhydrous magnesium sulfate. Unless stated otherwise, infrared spectra were determined in chloroform, ultraviolet spectra in absolute ethanol, and n.m.r. spectra (60 Mc.) in carbon tetrachloride or deuteriochloroform[14] with tetramethylsilane as an internal reference. "Petroleum ether" refers to the fraction with b.p. 35–60°.

(32) L. F. Fieser and W. P. Campbell, *J. Am. Chem. Soc.*, **60**, 159 (1938).

(33) Slow speed stirring resulted in incomplete reduction.

(34) P. D. Bartlett and E. B. Lefferts, *J. Am. Chem. Soc.*, **77**, 2804 (1955).

(35) The amount of di-*n*-butylammonium (+)-dehydroabietate present was measured by the extinction coefficient of the aromatic absorption in the 275-mμ region. The di-*n*-butylammonium (+)-$\Delta^{8,12}$-abietadienoate content was determined by isomerization of a weighed sample of the salt to abietic acid with hot ethanolic hydrochloric acid[14,15] and estimation of the amount of (−)-abietic acid formed after 2–3 hr. by examination of the extinction coefficient at 241.5 mμ. The corrected figure for the extinction coefficient of a similarly treated sample of pure di-*n*-butylammonium (−)-abietate or of pure (−)-abietic acid was found to be 85% of the original value. The remainder of the reduction product was assumed to be (+)-Δ^{8}-abietenoic acid (Vc), which would have arisen from overreduction of the aromatic ring (see text).

(36) We are deeply indebted to Professor Ireland for a generous supply of the (±)-dehydroabietic acid used in this step.

(37) *Cf.* D. J. Cram, B. Rickborn, and G. R. Knox, *J. Am. Chem. Soc.*, **82**, 6412 (1960), and later papers; see also C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961), and D. Devaprabhakara, C. G. Cardenas, and P. D. Gardner, *ibid.*, **85**, 1553 (1963), and references cited there.

(38) Although very highly purified (−)-abietic acid with m.p. 174–175° and $[\alpha]_D$ −115.6° (ethanol) has been reported [V. N. Krestinskiĭ and I. I. Bardyshev, *J. Gen. Chem. USSR*, **10**, 1894 (1940)], (−)-abietic acid with $[\alpha]_D$ more negative than −106° cannot be prepared through the diisoamylamine salt (*cf.* ref. 15).

under the conditions described for isomerization of the (+)-enantiomer, resulted in the formation of 280 mg. [52% over-all yield from (±)-dehydroabietic acid] of white, powdery diisoamylammonium (±)-abietate, m.p. 136–139°, λ_{max} 241.5 mμ (ε 17,000). One recrystallization from acetone–ethanol raised the m.p. to 138–141° and the $\epsilon_{241\ m\mu}$ to 18,900.

Anal. Calcd. for $C_{30}H_{53}NO_2$ (449.73): C, 78.37; H, 11.62; N, 3.05. Found: C, 78.05; H, 11.69; N, 3.25.

The free (±)-acid (150 mg., m.p. 145–148°), liberated by acidification of a solution of the salt in ethanol with acetic acid, showed $\epsilon_{241\ m\mu}$ 19,000 and therefore was not yet pure. Chromatography of this material on 80 g. of acid-washed silica gel (Grace Chemical Co., Baltimore, Md., 100-mesh, dried at 160° for 6 hr. after being washed with 1 *N* hydrochloric acid and then with water) gave the desired product in the fractions 21–24 (10-ml. cuts) eluted with benzene containing 3% of ether. This yielded 140 mg. of diisoamylamine salt, m.p. 137–140°, λ_{max} 241.5 mμ (ε 21,000). The regenerated (±)-abietic acid (60 mg.) after two recrystallizations from ethanol–water had m.p. 148–150°; λ_{max} 235 (ε 19,500), 241.5 (22,000), and 250 mμ (14,300). Its infrared (in carbon disulfide) and n.m.r. spectra were identical with those of the naturally occurring acid.

Anal. Calcd. for $C_{20}H_{30}O_2$ (302.44): C, 79.42; H, 10.00. Found: C, 79.28; H, 10.15.

(+)-Δ⁸-Abietenal (Va). A. From (+)-Dehydroabietic Acid (I).—Redistilled, anhydrous ethylamine (250 ml.) was added to an intimate mixture of powdered (+)-dehydroabietic acid (12.0 g., 0.04 mole) and fine lithium shot[34] (2.8 g., 0.4 g.-atom) in a nitrogen atmosphere. The deep blue mixture was stirred magnetically under reflux (Dry-Ice condenser), and at 2-hr. intervals (at which times the color discharged) additional 1-g. portions of lithium shot were added. This addition was repeated five times. The final addition of lithium was followed by a series of brilliant color changes terminating in the previously mentioned characteristic deep blue color, which was allowed to persist for 2 hr. The reaction then was quenched by the slow addition of ammonium chloride (exothermic reaction), and the solvent was allowed to evaporate overnight at room temperature. Ice water was added, and the mixture was acidified to pH 1 with concentrated hydrochloric acid (ice bath). Isolation of the product by extraction with ether furnished 11.5 g. of a pale yellow, viscous oil showing characteristic aldehyde absorption in the infrared spectrum at 3.7 (w) and 5.8 (s) μ but no absorption attributable to carboxyl or aromatic functions. The crude product distilled over a 100° range at reduced pressure, but redistillation through an 18-in. Nester and Faust semimicro spinning-band column afforded 6.74 g. (59% yield) of colorless (+)-Δ⁸-abietenal (Va), b.p. 102–106° (0.03 mm.), $[\alpha]_D$ +37°. In addition to the absence of absorption in the vinyl proton region of the n.m.r. spectrum, chemical assay of this product by the method of Castells and Meakins[19] showed the double bond to be in the 8,9-position (single carbonyl peak at 5.85 μ and no aldehyde absorption at 3.7 μ after glycol cleavage of the osmate ester reduction product). Titration with monoperphthalic acid of the carbinol formed by reduction of the aldehyde with lithium aluminum hydride showed that exactly one double bond was present. Gas chromatography of the aldehyde on Chromosorb-P in a column programmed to an upper temperature limit of 275° indicated the presence of essentially one component, along with two minor impurities. For characterization of the aldehyde, the **semicarbazone**, m.p. 223° dec. (needles from ethanol), was prepared.

Anal. Calcd. for $C_{21}H_{35}N_3O$ (345.51): C, 73.00; H, 10.21; N, 12.16. Found: C, 72.83; H, 10.13; N, 12.71.

The bright yellow **2,4-dinitrophenylhydrazone** formed readily by reaction with 2,4-DNPH–sulfuric acid, but not with 2,4-DNPH–hydrochloric acid. On chromatography on alumina (elution with benzene–chloroform) and slow crystallization (3 days) from methanol–ethyl acetate (9:1) this derivative melted at 157.5–159° (m.p. unchanged by further crystallization).

Anal. Calcd. for $C_{26}H_{36}N_4O_4$ (468.58): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.69; H, 7.88; N, 11.96.

Another preparation of this same derivative gave a similar solid, m.p. 171–175° (mixture m.p. 160–170°), whose n.m.r. and infrared spectra were identical with those of the lower-melting sample.

Anal. Calcd. for $C_{26}H_{36}N_4O_4$ (468.58): C, 66.64; H, 7.74. Found: C, 66.87; H, 7.66.

Still another preparation of this derivative from another sample of the aldehyde showed a m.p. range of 170–190°.

Attempted oxidation of the aldehyde with silver oxide in cold or hot ethanol, or with one equivalent of chromium trioxide in acetic acid at 25°, led only to recovery of starting material. Attempted oxidation with five equivalents of chromium trioxide[39] at 35° gave starting material and a mixture of acids from which no pure product could be isolated.

(39) *Cf.* G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 3870 (1948).

B. From the (+)-Δ⁸-Abietenoic Acid VII.—(+)-Δ⁸-Abietenoic acid prepared by partial hydrogenation of (+)-Δ⁸,¹²-abietadienoic acid (II) was converted into the corresponding acid chloride in quantitative yield by reaction with thionyl chloride and a trace of pyridine[40] in dry ether. The acid chloride (212 mg.) was dissolved in 50 ml. of sodium-dried xylene. After introduction of 300 mg. of 5% palladium on barium sulfate, the well-stirred mixture was heated to 135–140° while dry hydrogen was admitted through a gas delivery tube. Titration of the entrained hydrogen chloride with standard base indicated that 80% of the acid chloride had been reduced after 40 min. at this temperature. The reduction was stopped, and after filtration and removal of the solvent under reduced pressure, the aldehydic product was isolated as the crude semicarbazone in 45% over-all yield from (+)-Δ⁸-abietenoic acid. Two recrystallizations from ethanol gave needles whose m.p. and mixture m.p. (223° dec.) were identical with that of the semicarbazone obtained above from the chemical reduction product of (+)-dehydroabietic acid. The 2,4-dinitrophenylhydrazone, however, melted over a wider range than did preparations of this same derivative from the lithium–ethylamine reduction product of (+)-dehydroabietic acid.

(+)-Δ⁸-Abietenonitrile (Vb).—A mixture of 3.84 g. (0.013 mole) of (+)-Δ⁸-abietenal (Va) obtained from (+)-dehydroabietic acid by chemical reduction, 4.0 g. (0.06 mole) of hydroxylamine hydrochloride, and 40 ml. of pyridine was dissolved at room temperature in the minimum volume (150 ml.) of absolute ethanol. The resulting solution was refluxed for 6.5 hr. and then refrigerated overnight. Water was added, the ethanol was removed by distillation under reduced pressure, and the oxime was extracted with ether. The ether extracts were washed with dilute hydrochloric acid and saturated sodium chloride solution. They then were dried and evaporated to give 4.0 g. (quantitative yield) of (+)-Δ⁸-abietenal oxime as a colorless gum which was dehydrated without further purification.

A stirred solution of the oxime in 100 ml. of pyridine was cooled and treated with 8 ml. of phosphorus oxychloride, and the resulting mixture was stirred at 23–26° for 24 hr. It then was heated to 40–50° for 1 hr., poured into cold water, and extracted with ether. After extraction with dilute hydrochloric acid to remove pyridine and with 1% sodium hydroxide to remove any unchanged oxime, the ether solution was dried and evaporated. Distillation of the residual oil afforded 2.4 g. (64% yield) of the (+)-nitrile Vb as a viscous, pale yellow liquid, b.p. 133–135° (0.04 mm.), λ_{max} 4.5 (m) μ, $[\alpha]_D$ +24°.

Anal. Calcd. for $C_{20}H_{31}N$ (285.46): C, 84.14; H, 10.95; N, 4.91. Found: C, 84.09; H, 10.89; N, 4.89.

(+)-Δ⁸-Abietenoic Acid (Vc).—A solution of 1.45 g. of (+)-Δ⁸-abietenonitrile (Vb) and 6 g. of sodium hydroxide in 100 ml. of diethylene glycol was heated for 7 hr. at 215°. The resulting acid (Vc) was a glass whose di-*n*-butylamine salt crystallized from acetone in colorless needles (1.03 g., 47% yield), m.p. 144–148°, $[\alpha]_D$ +22°. Recrystallization altered these properties only slightly. The free acid crystallized from ethanol–water in irregular plates, m.p. 154–160°, $[\alpha]_D$ +33°. Although mixture m.p. determinations of either the acid or the salt with the corresponding compounds obtained in parts A and B below did not show depressions, the free acid of $[\alpha]_D$ +33° was converted into (−)-dihydroabietic γ-lactone (VI) of m.p. and mixture m.p. 129–131° in only 13% yield by the same procedure[41] used in part B below.

Di-*n*-butylamine Salt of the (+)-Δ⁸-Abietenoic Acid VII. A. From (+)-Δ⁸,¹²-Abietadienoic Acid (II).—Hydrogenation of 0.5 g. of (+)-Δ⁸,¹²-abietadienoic acid in ethanol with 80 mg. of 10% palladium on carbon at 60 p.s.i. was allowed to proceed for 70 min. Filtration of the catalyst, concentration of the solution, and crystallization of the product after dilution of the solution with hot water furnished colorless plates of (+)-Δ⁸-abietenoic acid (VII), m.p. 158–165°. The di-*n*-butylamine salt of this acid after three recrystallizations from acetone weighed 80 mg. and melted at 150–153°, $[\alpha]_D$ +58°.

Anal. Calcd. for $C_{28}H_{51}NO_2$ (433.70): C, 77.54; H, 11.85; N, 3.23. Found: C, 77.71; H, 11.72; N, 3.14.

B. From (−)-Abietic Acid (IV).—Hydrogenation of 816 mg. of (−)-abietic acid (IV) over 25 mg. of prereduced platinum oxide in ethanol required 24 min. for the absorption of 1.08 molar equivalents of hydrogen at a pressure of 1 atmosphere. The resulting dihydro acid was isomerized with concentrated hydrochloric acid–ethanol according to the procedure of Lombard.[42] Three recrystallization from acetone of the di-*n*-butylamine salt of the resulting (+)-Δ⁸-abietenoic acid (VII) gave 548 mg. (47% over-all yield) of colorless needles, m.p. 148–153°, $[\alpha]_D$ +50°. Regeneration afforded 330 mg. (40% over-all yield) of irregular plates of the free acid VII, m.p. 157–167°, which after further

(40) *Cf.* W. P. Campbell and D. Todd, *ibid.*, **64**, 928 (1942).

(41) E. E. Fleck and S. Palkin, *ibid.*, **61**, 3197 (1939); see also ref. 22.

(42) R. Lombard, *Bull. soc. chim. France*, [5] **11**, 526 (1944).

crystallization from dilute ethanol melted over the range 166–186°. Velluz, *et al.*,[22] record m.p. 185° and $[\alpha]_D$ +125° for pure preparations of this acid.

On treatment with concentrated sulfuric acid (*d* 1.84) at 0° according to the directions of Fleck and Palkin,[41] the acid VII of m.p. range 166–186° was converted in 42% yield into (−)-dihydroabietic γ-lactone (VI), m.p. 129–131°, λ_{max} 5.65 (s) μ (lit.[41] m.p. 131–132°).

(+)-**18-Hydroxydehydroabietic Acid (IXa).**—Oxidation of 62.9 g. (0.2 mole) of methyl (+)-dehydroabietate (VIIIa), m.p. 63–64°, with 90.0 g. (0.9 mole of chromium trioxide in 600 ml. of glacial acetic acid) and 450 ml. of acetic anhydride at 20–25° was carried out as described by Sanderson.[27] The crude product (63.4 g.) was chromatographed in four equal portions on 6.5-cm. diameter columns containing *ca.* 700 g. each of Alcoa F-20 alumina. The material eluted with benzene–ether (3:2) from one of the columns in fractions 3 and 4 (500-ml. cuts) was crystallized from methanol to give 6.66 g. (35% yield) of glistening plates of methyl (+)-18-acetoxy-7-oxodehydroabietate (VIIIb), m.p. 127.5–133° $[\alpha]_D$ +5° (lit.[27] m.p. 127–129°, 27% yield). Although the melting point could be raised to 131–133° by extensive recrystallization, the material of m.p. 127.5–133° gave a satisfactory combustion analysis and therefore was used without further purification.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.56; H, 8.01.

Fractions 7 through 13, which also were eluted with benzene–ether (3:2), yielded tacky solids which were combined and triturated with petroleum ether to give 2.81 g. (17% yield) of methyl (+)-13-acetyl-7-oxodeisopropyldehydroabietate (VIIIc) as a colorless crystalline powder, m.p. 144–145° (lit.[27] m.p. 143–144°, 9% yield). Comparable results were obtained by chromatography of the other three portions of the crude oxidation product.

For simultaneous reduction and hydrolysis, 3.86 g. (0.01 mole) of the (+)-keto diester VIIIb was subjected to the Huang-Minlon modification[43] of the Wolff–Kishner reduction with 4.5 ml. (0.13 mole) of 97% hydrazine and 6.6 g. (0.1 mole) of potassium hydroxide in 75 ml. of diethylene glycol. The solution was heated at 110° for 2 hr. and then at 210° for 2 hr. After careful addition of more potassium hydroxide (6.6 g.) the solution was heated for a final 2-hr. period to complete hydrolysis of the ester groups. The hot reaction mixture was poured onto cracked ice, and the cold mixture was acidified with dilute hydrochloric acid to pH 1. Recovery of the product by extraction with chloroform furnished 3.01 g. (95% yield) of crude (+)-18-hydroxydehydroabietic acid (IXa), which after one crystallization from 50% aqueous methanol was obtained as tiny felt-like needles, m.p. 185.5–186°, $[\alpha]_D$ +49°. The analytical sample required extensive drying under vacuum at 100° to remove the tightly held water of crystallization.

Anal. Calcd. for $C_{20}H_{28}O_3$ (316.42): C, 75.91; H, 8.92. Found: C, 76.01; H, 8.93.

The methyl ester, prepared by reaction of the acid with diazomethane in ether, crystallized from methanol–water in needles, m.p. 95–101.5°, which shriveled extensively when they were heated under vacuum at 78°. The water of crystallization persisted even when the hydroxy ester was eluted from basic alumina with benzene.

Anal. Calcd. for $C_{21}H_{30}O_3 \cdot 0.5H_2O$ (339.46): C, 74.30; H, 9.21. Found: C, 74.16; H, 8.66.

Methyl (+)-13-Hydroxydeisopropyldehydroabietate (IXb).—A solution of 400 mg. (1.18 mmoles) of the above hydroxy ester hemihydrate in 10 ml. of acetic acid containing 0.3 ml. of *t*-butyl hydroperoxide and 3 drops of concentrated sulfuric acid was allowed to stand at 33° for 8 hr. and then at 22° for another 8 hr. (compare ref. 26 and 28). The product, recovered by dilution with water and extraction with ether, was heated under nitrogen for 30 min. on a steam bath with 5% alcoholic potassium hydroxide to hydrolyze phenolic acetate formed in the acetic acid solution. The mixture was diluted with water, extracted with ether to remove neutral material, and then acidified with cold 6 *N* hydrochloric acid and re-extracted with ether. Decolorization (Norit), drying, and concentration of the ether extracts gave 120 mg. (35% yield) of the crude (+)-phenolic ester IXb, which after one crystallization from benzene–petroleum ether melted at 145–148°. When recrystallized either from the same solvent pair or from methanol–water, this substance formed needles, m.p. 149.5–150°, $[\alpha]_D$ +57° (lit.[26] m.p. 147.5–148.5°, $[\alpha]_D$ +55°).

(+)-**13-Methoxydeisopropyldehydroabietic Acid (IXc).**—O-Methylation of 200 mg. (0.70 mmole) of the (+)-hydroxy ester IXb in the manner described by Wenkert and co-workers[26] furnished 190 mg. of methyl (+)-13-methoxydeisopropyldehydroabietate, which crystallized from methanol as fine prisms, m.p. 76–80° (lit.[26] m.p. 79.5–80.5°). Hydrolysis of the entire product with 1 g. of potassium hydroxide in 10 ml. of ethylene glycol at 160° for 2 hr. yielded 132 mg. of the free (+)-methoxy acid IXc, m.p. 106–110°. Recrystallization from methanol–water gave 105 mg. (52.5% over-all yield from the (+)-hydroxy ester IXb) of the pure acid as stout prisms, m.p. 111–111.5°, $[\alpha]_D$ +60° ($CHCl_3$).

Anal. Calcd. for $C_{18}H_{24}O_3$ (288.37): C, 74.97; H, 8.39. Found: C, 74.86; H, 8.32.

Methyl (+)-$\Delta^{8(14)}$-13-Oxodeisopropylabietenoate (XI). A. From the (+)-Methoxy Acid IXc.—A solution of 80 mg. (0.28 mmole) of the (+)-methoxy acid IXc in 20 ml. of anhydrous ethylamine and 1 ml. of *t*-amyl alcohol was treated with 250 mg. of lithium shot with rapid stirring until the deep blue color had persisted for 8 min., and then *t*-amyl alcohol was added dropwise until the color was discharged. Finally, more lithium was introduced to restore the blue color for an additional 5 min. Methanol was added to discharge the color, the ethylamine was allowed to distil, and the residue was dissolved in 35 ml. of 80% ethanol. The mixture then was acidified strongly with concentrated hydrochloric acid. After 2 hr. at 30° there was no increase in the intensity of the ultraviolet absorption at 240 mμ associated with the conjugated ketone chromophore. The infrared spectrum showed that aromatic starting material was present to the extent of about 15%. After esterification with diazomethane the crude product (*ca.* 80 mg.) was treated with semicarbazide acetate in ethanol to give, after recrystallization from dilute methanol, 78 mg. of the semicarbazone, m.p. 226–227°, of the unsaturated (+)-keto ester XI. For regeneration of the free keto ester this derivative was heated for 10 min. on the steam bath with 1 ml. of 20% sulfuric acid in 5 ml. of 1,2-dimethoxyethane. After dilution of the mixture with water, extraction with ether, and crystallization of the product from ether, 24 mg. [30% over-all yield from the (+)-methoxy acid IXc] of the unsaturated (+)-keto ester XI was obtained, m.p. and mixture m.p. with an authentic sample (see part B below) 125–127° (lit.[25,26] 127–128°). The infrared spectrum of this product was identical with that of a sample prepared as in part B below.

B. **From Methyl (+)-Neoabietate (Xb).**—Ozonization of methyl (+)-neoabietate was patterned after the procedure of Harris and Sanderson.[25,44] A slow stream of ozone in oxygen was passed into a solution of 1.05 g. (3.3 mmoles) of methyl (+)-neoabietate in 50 ml. of dry methylene chloride at −70° at such a rate that the absorption of 3.3 mmoles of ozone required *ca.* 20 min. The solution then was swept with nitrogen and stirred for 2 hr. at 20° with 10 g. of zinc dust and 5 ml. of glacial acetic acid. After filtration the solution was diluted with chloroform, extracted with water, and then with 1 *N* sodium hydroxide, dried, and evaporated under reduced pressure. The residue crystallized readily from ether–petroleum ether at −15° to yield 350 to 550 mg. (37 to 58% yield) of the unsaturated (+)-keto ester XI, m.p. 105–115°, which after two further crystallizations from the same solvent pair had m.p. 124–127°, $[\alpha]_D$ +35° [lit.[25,26] m.p. 127–128°, lit.[26] $[\alpha]_D$ +38° (CH_3OH)].

Lithium–Ethylamine Reduction of (+)-O-Methylpodocarpic Acid (XIIa).—To a solution of 100 mg. (0.35 mmole) of (+)-O-methylpodocarpic acid (XIIa)[45] in 3.0 ml. (28 mmoles) of *t*-amyl alcohol and 50 ml. of redistilled, anhydrous ethylamine, 100 mg. (14.5 mg.-atoms) of finely divided lithium[34] was added with rapid stirring and efficient cooling. After 15 min. the lithium had dissolved and a pale light blue cast appeared throughout the mixture. Then an additional 100 mg. of lithium was introduced, and when the first dark blue streaks began to appear, sufficient *t*-amyl alcohol (*ca.* 1 ml.) was added until the solution remained colorless. After evaporation of the ethylamine the residue was treated with ice, acidified with hydrochloric acid, and extracted with ether. The product remaining after evaporation of the ether was treated with methanolic hydrochloric acid at room temperature for 2 hr. and then at 50° for 5 min., and the resulting crude keto acid was esterified with diazomethane. The crude unsaturated keto ester XIIIa was isolated as its **2,4-dinitrophenylhydrazone**, which after chromatography on alumina and crystallization from ethanol was obtained as tiny red needles, m.p. 210–213°, yield 40 mg. (25%).

Anal. Calcd. for $C_{24}H_{30}N_4O_6$ (470.53): C, 61.26; H, 6.42; N, 11.91. Found: C, 61.21; H, 6.48; N, 11.81.

*Efforts to improve the yield of unsaturated ketone by conducting the reduction at −10° or with isopropyl alcohol present or under the conditions described by Bible and Burtner[29] (lithium and *t*-butyl alcohol in tetrahydrofuran and liquid ammonia) were not successful.*

(43) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(44) We thank John S. Swenton and Dennis L. Jackman for assistance in the isolation of neoabietic acid and for conducting repeated ozonizations of methyl neoabietate.

(45) We thank Dr. James A. Waters of the National Arthritis Institute, National Institutes of Health, Bethesda, Md., for a generous sample of this compound.