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The Synthesis of Abietadienoic Acids from Dehydroabietic Acid[1]

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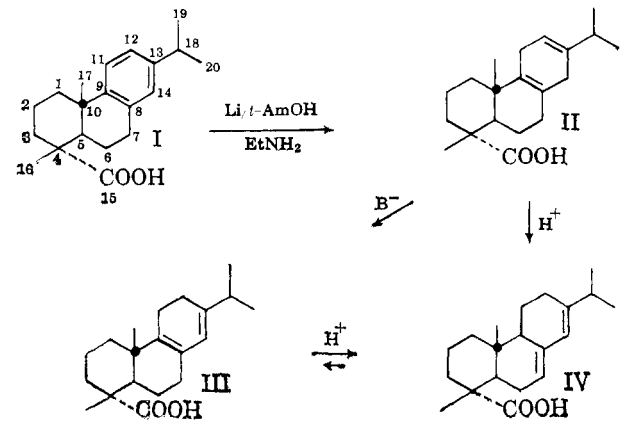
Two routes have been developed for the synthesis of abietic acid (IV) from dehydroabietic acid (I). In the first, dehydroabietic acid was reduced with lithium and *t*-amyl alcohol in ethylamine under carefully defined conditions to give $\Delta^{8,12}$-abietadienoic acid (II) in 90% yield. Isomerization 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

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(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).