[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Hydroxyl and Amino Derivatives of Dehydroabietic Acid and Dehydroabietinol

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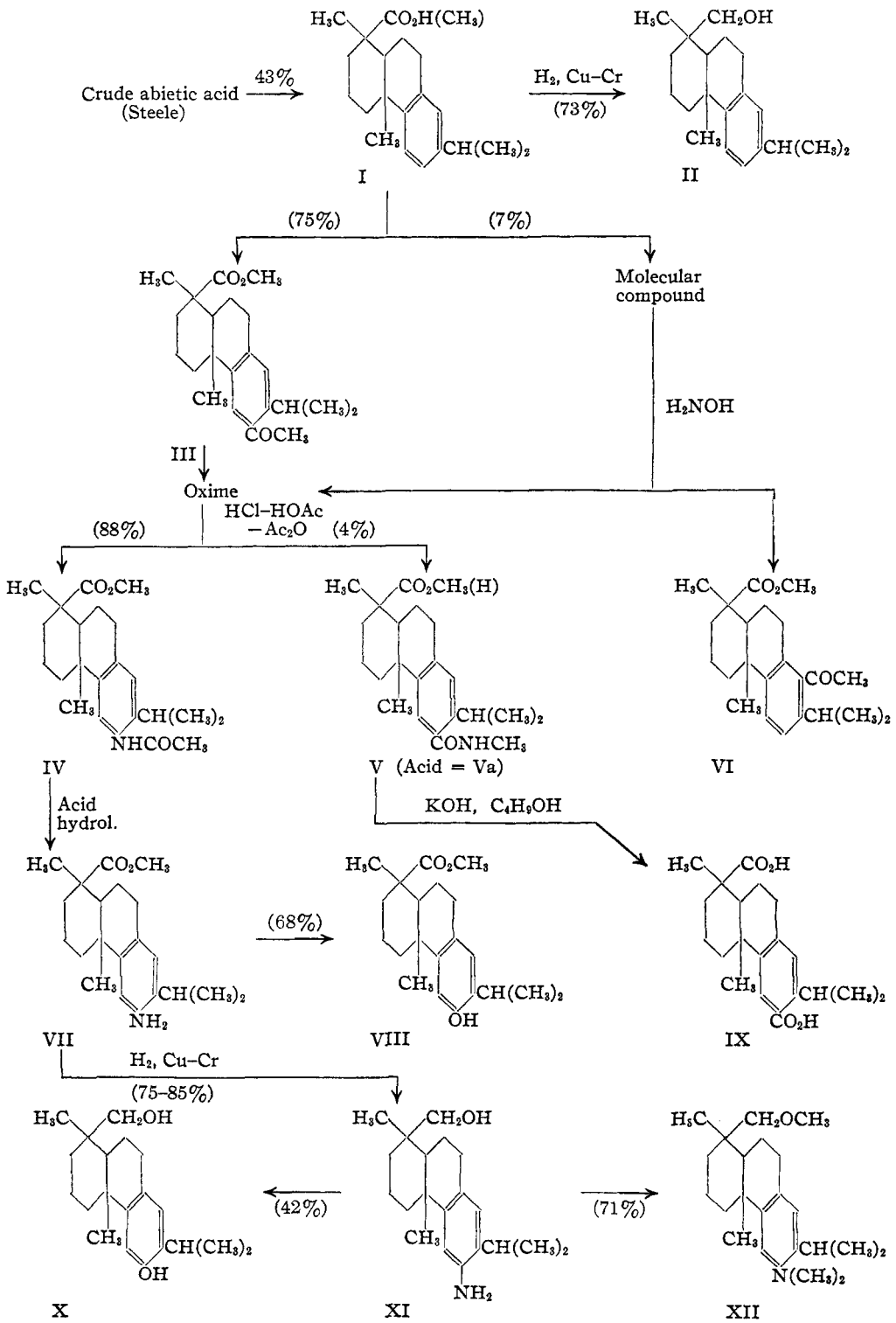
The objective of our work in the resin acid field has been to utilize abietic acid as a starting material for the synthesis of hydrophenanthrene derivatives having a sufficient structural similarity to certain other important natural products of this group to offer promise of exhibiting some of their physiological actions. A foundation for this project was laid in the first investigation[2] by the isolation and characterization of the partially aromatized dehydroabietic acid, and later a practical method was found for the preparation of the pure acid in quantity.[3] On investigating methods for the introduction of the hydroxyl and amino groups into the aromatic ring, it was found that nitration proceeds too readily to the stage of disubstitution and that the readily prepared sulfodehydroabietic acid on alkali fusion gives an intractable mixture containing products of degradation and dehydrogenation. An analogous dehydrogenation has been observed by Mosettig and Stuart[4] who found that 9,10-dihydrophenanthrene-2-sulfonic acid gives 2-phenanthrol on fusion with alkali.

The Friedel and Crafts reaction of methyl dehydroabietate was observed to proceed smoothly in nitrobenzene solution to give as the chief product a substance characterized as the 6-acetyl derivative[3] (III), and this has now proved a suitable intermediate for the preparation of the compounds desired. In the preparation of large quantities of the substance there accumulated an adequate amount of the previously observed by-product for further characterization. This sharply melting substance formerly was thought to be a different crystalline modification of the 6-acetyl derivative, for it has the same composition and gives an identical oxime, but it is now recognized as a molecular compound of the 6- and 8-isomers. No separation could be accomplished by crystallization, but it was found that the more hindered 8-acetyl compound (VI) is unattacked by hydroxylamine even under rather drastic conditions and may be separated from the oxime of the 6-derivative by mechanical segregation of the crystals. The structure VI was established by oxidation with nitric acid and identification of the product as prehnitic acid (1,2,3,4-acid).

On treatment with hydrogen chloride in acetic acid–anhydride in the cold the oxime of methyl 6-acetyldehydroabietate rearranges very smoothly to give a mixture consisting largely of the desired acetyl amine ester IV but containing an appreciable quantity of the methyl amide ester V. A separation is not practical at this stage but can be accomplished after partial hydrolysis. Short boiling with hydrochloric–acetic acid results in complete hydrolysis of the ester group of V without attacking the methyl amide substituent, giving the alkali-soluble methyl amide acid Va. The acetyl amine ester IV under these conditions is converted largely into the corresponding amine ester VII, which is found in the neutral fraction along with a small amount of the unchanged acetyl compound. With this isomer (IV) there is but little hydrolysis of the ester group, and as this apparently occurs after elimination of the acetyl group the material carried into the alkaline extract can be separated from Va by precipitation of the hydrochloride from ether. To obtain pure methyl 6-aminodehydroabietate the partially hydrolyzed neutral fraction is submitted to further treatment with hydrochloric–acetic acid to destroy the remaining acetyl compound. After separation of a quantity of the free amino acid with alkali, the amino ester is obtained easily in a pure, crystalline condition.

The separations indicated were all sharp, and the total yields of pure end-products based upon the oxime used were as follows: methyl 6-aminodehydroabietate (VII), 62%; 6-aminodehydroabietic acid, 26%; 6-methylamidodehydroabietic acid (Va), 4%. The last-named substance was characterized by saponification to 6-carboxydehydroabietic acid, the 1-methyl ester of which was described previously.[3] Various derivatives of the amino acid and ester of the other series were prepared, and the amine VII was converted by diazotization with nitrosylsulfuric acid in pyridine[5] and by hydrolysis into methyl 6-hydroxydehydroabietate. There is a possibility that this phenolic

(1) Squibb Research Fellow.
(2) Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938).
(3) Fieser and Campbell, *ibid.*, **60**, 2631 (1938).
(4) Mosettig and Stuart, *ibid.*, **61**, 1 (1939).
(5) De Milt and Van Zandt, *ibid.*, **58**, 2044 (1936).



substance is structurally related to podocarpic acid, for on the basis of the evidence adduced by Sherwood and Short[6] it is conceivable that the phenolic acid isolated from resins of Java and New Zealand differs from the acid corresponding to VIII only in the absence of the isopropyl group in the 7-position.

(6) Sherwood and Short, *J. Chem. Soc.*, 1006 (1938).

Having developed satisfactory methods for the introduction of the amino and hydroxyl group into the aromatic nucleus, we next sought to modify the functional group in the alicyclic part of the molecule, and the way was paved in model experiments using methyl dehydroabietate. Bouveault reduction of the ester with sodium and amyl alcohol was tried briefly but found to result chiefly in hydrolysis. Satisfactory results were obtained, however, by high pressure hydrogenation over copper chromite catalyst,[7] dehydroabietinol (II) being obtained in 73% yield. The carbinol is a liquid giving a crystalline dinitrobenzoate. The hydrogenation of methyl 6-aminodehydroabietate presented the further complication that ammonia was liberated if the temperature was raised too high, but under carefully controlled conditions the amino alcohol XI was obtained in excellent yield as a crystalline solid. The reduction of methyl 6-hydroxydehydroabietate gave unpromising results in the first trials, but the desired carbinol X was obtained easily from the amino alcohol XI by the diazo reaction.

6-Hydroxydehydroabietinol (X) is one end-product envisioned in the original plan of our research,[2] for it is a hydrophenanthrene derivative with one aromatic ring having a phenolic hydroxyl group at one end of the molecule and an alcoholic hydroxyl group at the other. The substance therefore possesses some of the structural features of oestradiol and it is being tested for oestrogenic activity.[7a]

It also seems possible that in the resin acid series suitable amino derivatives may be found to have a morphine-like action. As a start in this direction one such compound has been prepared in consultation with Dr. L. F. Small, who has kindly agreed to submit the substance for pharmacological tests. Like morphine, 6-aminodehydroabietinol (XI) is an amino alcohol derivative of a hydrophenanthrene having one benzenoid nucleus, and in analogy with the extensive observations of Small, Eddy, and associates[8] it was thought that the substance might have some activity but that the quality would be improved by methylation, preferably of both the amino and the hydroxyl groups. Methylation was accomplished moderately well in some experiments with dimethyl sulfate and ammonium hydroxide, but the results were erratic. A better method was found in exhaustive treatment with methyl iodide and silver oxide in ether, which gives a water soluble product apparently consisting of the methohydroxide of XII. The aqueous extract on treatment with ammonium iodide gave a precipitate of the methiodide and this decomposed smoothly on heating in vacuum, giving the amine XII as a viscous oil. The substance was isolated as the crystalline hydrochloride and the presence of the ether group established by a methoxyl determination. Both functional groups are thus covered by methylation and the substance is of the type sought.

(7) Compare the hydrogenation of abietic acid esters, Hercules Powder Co., U. S. Patent 1,901,630 (1933).

(7a) Assays of X kindly conducted at the Squibb Institute for Medical Research are reported as follows by Dr. G. A. Harrop. When given at a dose level of 20 γ to 45 castrated rats, 23% of the animals showed a completely cornified smear, while at a level of 5 γ 60% of 40 rats gave a full oestrous response. The difference suggests that the substance may be rather toxic at the higher dosage. In another series a 2.5-γ dose produced full oestrus in 24% of 100 rats and and at a level of 5 γ the response in 40 rats was 55%. Under the conditions of these experiments oestrone produces a high oestrous response at a level of 7.5 γ. The resin acid derivative thus appears to possess marked oestrogenic activity.

(8) Small, Eddy, Mosettig and Himmelsbach, Studies on Drug Addiction, Supplement No. 138 to the Public Health Reports, 1938.

Experimental Part[9]

Preparation of Dehydroabietic Acid.—In preparing further quantities of this substance by the previously described procedure[3] it was found that purification of the starting material by the Palkin process can be dispensed with an entirely satisfactory material obtained from crude Steele's abietic acid, once crystallized as the acid sodium salt. The hydrolysis of sulfodehydroabietic acid is conveniently modified by using 60% sulfuric acid (480 cc. of concentrated acid and 500 cc. of water) and stirring the mixture at 135° with a Hershberg tantalum stirrer. The yield in this step (with 80-g. batches) was better, averaging 80%, and the over-all yield of pure dehydroabietic acid from the crude acid sodium salt was the same as that previously reported using pure salt (43%).

Acetylation of Methyl Dehydroabietate.—By the previous method,[3] 46.7 g. of the ester gave 33.0 g. of **methyl 6-acetyldehydroabietate** (m. p. 133.5–134°) in the first crop of crystals (prisms) from ether, and the mother liquor afforded 5.3 g. more of this substance, m. p. 132–134° (total yield 75%) and 3.8 g. (7%) of the substance, m. p. 119.5–120° (needles), which is now recognized as a complex.

Isolation of Methyl 8-Acetyldehydroabietate.—One gram of the complex, m. p. 119.5–120°, was refluxed for four hours with 0.5 g. of hydroxylamine hydrochloride in 2.5 cc. of pyridine and 5 cc. of alcohol and the mixture was poured into water and extracted with ether. After washing with dilute acid and with sodium bicarbonate solution and drying the solvent was evaporated and the product crystallized from ether–petroleum ether. Two kinds of crystals were deposited simultaneously and a mechanical separation could be accomplished rather easily. There was obtained in all 0.35 g. of fine needles of the oxime of methyl 6-acetylabietate, m. p. 151.5–152°, identified by

(9) All melting points are corrected. Microanalyses by Lyon Southworth, with the exceptions noted.

mixed melting point determination, and 0.28 g. of methyl 8-acetyldehydroabietate. This substance crystallizes in clusters of diamond-shaped tablets and melts on rapid heating at about 133°, resolidifies above this temperature, and remelts sharply at 153–153.5°; $[\alpha]^{25}D$ + 40° (1.0% in alcohol). The substance contains no nitrogen.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.47; H, 9.03. Found: C, 77.69; H, 9.02.

The substance exists in two forms which are easily interconvertible. When the above low-melting tablet form was heated in a test-tube at 140° it melted and resolidified; on immersing this material in a capillary tube in a bath at 140° it showed no change and melted sharply at 153–153.5°. This high-melting form was then melted on a watch glass and cooled rapidly to room temperature, giving a glass. When seeded with the low-melting form and warmed slightly, crystals were formed which melted when immersed in a bath at 137°, or sintered at 132° when heated slowly, and then showed the higher m. p.

For proof of structure 0.1 g. of the 8-acetyl compound was heated with 1 cc. of concentrated nitric acid and 2 cc. of water at 190° for twenty hours and the resulting clear yellow solution evaporated to dryness. The residue was dissolved in hot water and caused to crystallize by adding concentrated nitric acid, giving a product, m. p. 236–238° with gas evolution. This was identified as **prehnitic acid** (1,2,3,4-acid) by conversion with excess diazomethane to the tetramethyl ester, which crystallized from methanol as colorless needles, m. p. 130–130.5°, giving no depression when mixed with an authentic sample.[10] We can confirm Smith and Carlson's[11] observation concerning the purple color which this ester acquires on exposure to light and the recovery of colorless material on recrystallization.

The **oxime of methyl 6-acetyldehydroabietate** exhibits an interesting property in forming what appears to be a molecular compound with glacial acetic acid. On shaking 0.55 g. of the oxime with 2 cc. of this solvent at room temperature the substance dissolved completely in a few seconds and the complex then promptly separated. After bringing this into solution by heating and then allowing crystallization to proceed slowly, there was obtained 0.45 g. of product, m. p. 121.5–122.5°, $[\alpha]^{25}D$ + 76° (1.4% in alcohol). The m. p. is not changed by recrystallization.

Anal. Calcd. for $C_{23}H_{33}O_3N \cdot CH_3CO_2H$: C, 69.58; H, 8.64; neut. equiv., 431.5. Found: C, 69.70; H, 8.83; neut. equiv., 431.

The free oxime is recovered on neutralization or on heating the complex for some time at 125°.

Beckmann Rearrangement of the Oxime of Methyl 6-Acetyldehydroabietate and Hydrolysis.—A solution of 0.5 g. of the oxime in 2 cc. of warm glacial acetic acid was cooled, treated with 1 cc. of acetic anhydride, and saturated with dry hydrogen chloride. The reaction product soon began to separate in the form of colorless plates, and after twenty-four hours this was collected, washed with acetic acid and dried; yield 0.5 g., m. p. 179–183°. This apparently is a mixture of the $ArNHCOCH_3$ and $ArCONHCH_3$ compounds in which the former predominates, but separation at this point by crystallization is not practical. The yield and character of the mixture was the same in larger runs (40 g.) and on using three times the specified quantities of acetic acid and anhydride.

For partial hydrolysis facilitating a separation of products, the crude, undried material from 37.1 g. of oxime was refluxed for one hour with 250 cc. of acetic acid and 125 cc. of 6 *N* hydrochloric acid; the solution was poured into 1.5 liters of cold water and the colorless precipitate was collected and combined with that obtained by neutralizing the acid liquor with alkali. The total moist solid was stirred with excess alkali and extracted with ether, and after separation of the ether layer the alkaline liquor was acidified with acetic acid, giving 3.0 g. of an **acid mixture B,** which subsequently was worked up as described below. The ethereal solution (800 cc.) was dried, concentrated to a volume of about 200 cc., and saturated with dry hydrogen chloride. The precipitated material, washed with ether and air dried at 50°, weighed 35 g. and will be referred to as **mixture A.** This consists largely of the hydrochloride of methyl 6-aminodehydroabietate but contains a sufficient amount of the unhydrolyzed acetate of this amine to interfere with the isolation of the amine in a pure, crystalline condition unless removed by further hydrolysis. The presence of the acetate was ascertained on submitting mixture A to diazotization. On dissolving the diazonuim salt in water an insoluble residue remained, and when purified by distillation and crystallization from methanol this formed flat needles, m. p. about 90°, having the characteristics of the 6-acetylamino ester described below. It is odd that this acetate should be carried down from an ethereal solution by hydrogen chloride, but this behavior was noted with an analytical sample prepared from the pure amine as described below.

Methyl 6-Aminodehydroabietate (VII).—A solution of 5 g. of the partially hydrolyzed mixture A in 40 cc. of acetic acid and 20 cc. of 6 *N* hydrochloric acid was refluxed for four hours, cooled, and poured into a solution of 36 g. of sodium hydroxide in 400 cc. of water. The liberated amine was extracted with ether (saving the **alkaline liquor C,** see below) and after drying and concentrating the solution it was obtained crystalline; the yield of satisfactory material was 2.9 g. (62%, based upon the oxime). Crystallized from ether–petroleum ether, it formed diamond-shaped plates, m. p. (evacuated capillary) 137–137.5°, $[\alpha]^{25}D$ +81° (1% in alcohol).

Anal. Calcd. for $C_{21}H_{31}O_2N$: C, 76.54; H, 9.48. Found: C, 76.36; H, 9.33.

The **hydrochloride** was prepared by saturation of an ethereal solution of the amino ester with dry hydrogen chloride. For crystallization 0.25 g. of the salt was warmed with 2–3 cc. of 6 *N* hydrochloric acid and enough alcohol to bring the material into solution at the boiling point. The substance separated as colorless leaves which sintered at about 160° and melted at about 250°, dec.; $[\alpha]^{25}D$ +61° (1% in alcohol). Immersed in a bath at 245°, the sample melted with loss of water, resolidified and melted at 250–260°, dec. The substance, dried at 80° and 9 mm., appears to be a monohydrate; after heating at 245° and evacuating the capillary the product remained unmelted at 290°.

(10) Fieser and Peters, THIS JOURNAL, **54**, 4347 (1932).

(11) L. I. Smith and Carlson, *ibid.*, **61**, 288 (1939).

Anal. Calcd. for $C_{21}H_{32}O_2NCl \cdot H_2O$: C, 65.69; H, 8.93. Found: C, 65.47, 66.06; H, 8.77, 8.70.

The salt was also isolated from mixture A by crystallization from acid-alcohol and showed the same characteristics on heating.

6-Aminodehydroabietic Acid.—The alkaline liquor C mentioned above on acidification with acetic acid gave 1.1 g. (24% from the oxime) of this acid as a white solid. Crystallization from alcohol gave pure material separating in laths, m. p. (vacuum) 214.5–215°; $[\alpha]^{25}D$ + 82° (1% in alcohol).

Anal. Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27. Found: C, 76.29; H, 9.09.

The **hydrochloride** was prepared by passing dry hydrogen chloride into an ethereal solution of the amino acid and crystallized from a mixture of alcohol and 6 *N* hydrochloric acid. It is unmelted at 295°.

Anal. Calcd. for $C_{20}H_{30}O_2NCl$: C, 68.26; H, 8.59. Found: C, 68.06; H, 8.63.

6-Methylamidodehydroabietic Acid (Va).—The 3 g. of the acid mixture B separated after partial hydrolysis of the rearrangement product on crystallization from aqueous alcohol afforded 2.7 g. of material melting in the range 210–240°. About one-third of this was found to consist of 6-aminodehydroabietic acid, which was dissolved by extraction of the solid with 150 cc. of boiling ether in two portions, precipitated from the ethereal extract with hydrogen chloride, reconverted to the amino acid (0.8 g.), crystallized from alcohol, giving 0.7 g. of pure material (2% yield from the oxime).

A little of the amide-acid (0.2 g.) was recovered from the remaining ether solution by extraction with alkali and precipitation with acid, and this was combined with the material which did not dissolve in the ether (1.5 g.). Crystallization of the total V from aqueous alcohol gave 1.5 g. (4% from the oxime) of shiny leaves, m. p. 253–254°, and the fully purified substance melted at 254–255°; $[\alpha]^{25}D$ +82° (0.9% in alcohol).

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.90; H, 8.74; N, 3.93; neut. equiv., 358. Found: C, 74.30, 73.77; H, 8.78, 8.38; N (Kjeldahl), 4.12; neut. equiv., 359.

6-Carboxydehydroabietic Acid (IX).—A solution of 0.2 g. of the amide-acid V in 5 cc. of *n*-butyl alcohol containing 0.5 g. of potassium hydroxide was refluxed for four hours, the solvent was removed by steam distillation, and the clear aqueous solution remaining was acidified with hydrochloric acid, giving 0.2 g. of an amorphous white solid which did not melt at 280°. This remained undissolved when boiled with 15 cc. of alcohol, but on adding a few cc. of water it dissolved readily. After adding more water at the boiling point the solution became turbid and on cooling the dibasic acid separated as the monohydrate in the form of colorless needles (0.18 g.). The sample was further purified by crystallization from aqueous acetone and gave $[\alpha]^{25}D$ +71° (0.9% in 80% alcohol).

Anal. Calcd. for $C_{21}H_{28}O_4 \cdot H_2O$: C, 69.59; H, 8.33; neut. equiv., 181. Found: C, 69.41; H, 8.54; neut. equiv., 181.

Acetylation of Methyl 6-Aminodehydroabietate.—The **diacetyl derivative** was obtained by heating the amine recovered from 0.5 g. of the hydrochloride with 5 cc. of acetic anhydride at the boiling point for a few minutes Water was added and the mixture warmed to hydrolyze the excess reagent, cooled, and the product extracted with ether. Crystallization from ether–hexane and then from methanol yielded 0.25 g. of the pure derivative in the form of thick prisms, m. p. 150–151°; $[\alpha]^{25}D$ +75° (1.7% in alcohol).

Anal. Calcd. for $C_{25}H_{35}O_4N$: C, 72.60; H, 8.53. Found: C, 72.78, 72.40; H, 8.47, 8.82.

The **monoacetyl compound (IV)** was made by allowing a solution of 0.3 g. of the free amine in 5 cc. of pyridine and 2 cc. of acetic anhydride to stand at 35–40° for two days and pouring the mixture into 30 cc. of water containing excess hydrochloric acid. The oily product soon solidified and was crystallized twice from methanol. The substance forms characteristic flat needles but does not melt normally or sharply. At 93–95° it changes gradually to a transparent but very viscous liquid which does not flow to the bottom of the capillary. The rotation was $[\alpha]^{25}D$ +79° (1.0% in alcohol).

Anal. Calcd. for $C_{25}H_{33}O_3N$: N, 3.77. Found (Kjeldahl): N, 3.87.

6-Acetylaminodehydroabietic acid was prepared from the amino acid (0.4 g.), pyridine (5 cc.) and acetic anhydride (2 cc.). After twenty-four hours at 35°, 100 cc. of water was added and the product slowly crystallized (0.4 g.). One crystallization from methanol gave 0.32 g. of thick hexagonal plates, m. p. 255–256°, $[\alpha]^{25}D$ +80° (1.2% in alcohol).

Anal.[12] Calcd. for $C_{22}H_{31}O_3N$: C, 73.90; H, 8.74; N, 3.93. Found: C, 74.00; H, 8.65; N (Kjeldahl), 3.97.

Methyl 6-Hydroxydehydroabietate (VIII).—One gram of powdered sodium nitrite was added to a stirred mixture of 10 cc. of concentrated sulfuric acid and 5 cc. of water at 0°; the mixture was warmed gradually to 35–40° with stirring until a nearly clear solution resulted. This was cooled to −5° and a solution of 2 g. of methyl 6-aminodehydroabietate in 6 cc. of pyridine was added dropwise with stirring, keeping the temperature below 0°. Sufficient ice and water was added to the thick cream-colored paste to permit good stirring, and after forty-five minutes the volume was made up to about 200 cc., 0.6 g. of urea was added, and stirring was continued for one-half hour. The suspension of the diazonium salt was then poured rapidly into 300 cc. of boiling water and boiling was continued for a few minutes. The phenol separated as a granular precipitate and was collected after cooling. Crystallization from ether–hexane yielded 1.0 g. of diamond-shaped plates, m. p. 157–157.5° and a second crop of 0.5 g., m. p. 156–157°; total yield 68%. Further crystallization did not change the m. p. of the first crop; the rotation was $[\alpha]^{25}D$ +71° (1.2% in alcohol).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.63; H, 9.15. Found: C, 76.32; H, 9.15.

Dehydroabietinol (II).—Methyl dehydroabietate (5 g.) was reduced to the carbinol in dioxane (5 cc.) using copper chromite catalyst (0.5 g.) with hydrogen at 1310–1070 lb. (87–71 atm.) pressure at 250°. After forty-eight hours

(12) Analysis by the Arlington Laboratories.

there was no further absorption of gas. After dilution with water the product was extracted and dried in ether and obtained as a stiff resin consisting largely of the carbinol but containing some unreduced ester. It was refluxed for four hours with 1.5 g. of potassium hydroxide in 15 cc. of *n*-butyl alcohol, the solvent was removed with steam, and the neutral fraction extracted and dried in ether. On distillation the carbinol fraction boiled almost completely at 177° at 1 mm.; yield 3.3 g. (73%). The rotation was $[\alpha]^{25}D$ +53° (2.4% in alcohol).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.87; H, 10.55. Found: C, 84.25; H, 10.91.

Acidification of the alkaline liquor gave 0.6 g. (12.5%) of dehydroabietic acid.

For characterization the carbinol was converted into the 3,5-dinitrobenzoate by warming it with the corresponding acid chloride in benzene–pyridine at 35–40° for seventeen hours. The substance crystallized from ether–hexane in clusters of prisms, m. p. 123–124°.

Anal. Calcd. for $C_{27}H_{32}O_6N_2$: C, 67.49; H, 6.71. Found: C, 67.58; H, 6.87.

6-Aminodehydroabietinol (XI).—A mixture of 3.3 g. of methyl 6-aminodehydroabietate, 1 g. of copper chromite catalyst, and 25 cc. of dioxane was shaken at 200° with hydrogen at 2400–2100 lb. for seventeen hours, when approximately two moles of gas had been absorbed and the reaction was stopped. The solution was filtered through a thin layer of Norite, washed through with methanol, and the colorless solution concentrated to 40–50 cc., and diluted with water while hot. On cooling, the amino alcohol crystallized in long, shining laths, m. p. 135–137°; yield 2.2 g. (73%). From the mother liquor 0.2 g. more of the product (total yield 80%) was obtained after removing the solvent with steam and removing unchanged ester by saponification of the resin (0.78 g.) with potassium hydroxide (1 g.)–*n*-butyl alcohol (10 cc.) by boiling for four hours. The amine was extracted with ether, converted with aqueous acid to the hydrochloride (0.3 g.), recovered, and crystallized from ether–petroleum ether.

On thorough purification from ether–petroleum ether the amine separated both as flat needles and as leaves of the same m. p. (and mixed m. p.) 139.5–140°; $[\alpha]^{25}D$ +72° (1% in alcohol).

Anal. Calcd. for $C_{20}H_{31}ON$: C, 79.68; H, 10.37. Found: C, 79.97; H, 10.39.

The **hydrochloride** can be purified by crystallization from aqueous hydrochloric acid, forming fine white needles; $[\alpha]^{25}D$ +63° (1.0% in alcohol).

Anal.[12] Calcd. for $C_{20}H_{32}ONCl$: C, 71.08; H, 9.55; Cl, 10.49. Found: C, 71.16; H, 9.49; Cl, 10.35.

The yield in several hydrogenations conducted as above varied from 75 to 85% using pressures from 1000 to 2500 lb. (67 to 167 atm.). The yield was lower at higher temperatures; in one run at 250° ammonia was formed (green color, test with litmus), while in another, using crude starting material, no ammonia was produced but in four and one-half hours the yield of amine was only 45 and 41% of acid was recovered on saponification. A longer reaction time at 200° (forty-eight hours) gave a lower yield (68%).

6-Dimethylaminodehydroabietinol Methyl Ether (XII) Hydrochloride.—A solution of 0.3 g. of 6-aminodehydroabietinol in 10 cc. of dry ether was treated with 5 cc. of methyl iodide and 0.3 g. of silver oxide and refluxed for forty-four hours in a Soxhlet apparatus containing anhydrous sodium sulfate in the thimble to absorb the water formed. During the refluxing two 5-cc. portions of methyl iodide and five 0.3-g. portions of silver oxide were added. The solvent was evaporated and the residue was digested with three 10 to 15-cc. portions of water on the steam-bath. Each aqueous extract was treated while hot with 1 g. of solid ammonium iodide and the resulting gel converted to the crystalline methiodide by heating and shaking. This gave in all 0.45 g. of colorless needles, m. p. 152–152.5° with evolution of gas. For decomposition to the tertiary amine the methiodide was placed in a tube with a constriction providing two compartments and heated in a furnace at 140° and 1–2 mm. pressure, when the amine slowly distilled as a very viscous, clear oil. This was dissolved in ether and treated with dry hydrogen chloride, giving 0.3 g. of the hydrochloride, m. p. (vacuum) 226–227°, with gas evolution. The salt crystallized from a mixture of about equal parts of methanol and 6 *N* hydrochloric acid in the form of colorless laths of the same m. p. (which is somewhat dependent on the rate of heating), yield, 2.7 g. (71%), $[\alpha]^{25}D$ +78° (0.8% in alcohol).

Anal. Calcd. for $C_{23}H_{38}ONCl$: C, 72.70; H, 10.08; OCH_3, 8.17. Found: C, 72.97; H, 10.07; OCH_3, 8.22.[12]

In methylating a 3-g. portion of the amine (eighty hours) it was found expedient during the extraction with water to add 2 g. of silver oxide with each 50-cc. portions of water in order to complete conversion to the water soluble methohydroxide. In this case the methiodide contained a small amount of infusible solid but this did not alter the m. p. of the methiodide or interfere with its decomposition, being left as a white, non-volatile residue. The yield of pure hydrochloride was 68%.

6-Hydroxydehydroabietinol (X).—Attempted preparation of this substance by high pressure hydrogenation of methyl 6-hydroxydehydroabietate gave a product which could be obtained only as a gel or an amorphous solid.

A solution of 1 g. of crude 6-aminodehydroabietinol, m. p. 136–137°, in 100 cc. of hot water containing 0.9 cc. of 6 *N* hydrochloric acid was filtered, cooled to 0–5°, and the hydrochloride precipitated as a fine suspension by adding 10 cc. of 6 *N* acid. A solution of 0.24 g. of sodium nitrite in a little water was added all at once. The salt rapidly dissolved and a flocculent, light yellow precipitate separated. After thirty minutes 0.5 g. of urea was added, and in ten minutes more the precipitate (0.3 g.) was removed by filtration and washed with cold water. The cloudy filtrate and wash water (250 cc. in all) was poured into a solution of 400 cc. of 3 *N* sulfuric acid at 85° and heating was continued for twenty minutes. After cooling, the crude phenol was collected as a light yellow resin (0.65 g., 65%). Crystallization from ether–hexane yielded in all 0.42 g. (42%) of faintly yellow prisms, m. p. 180–181.5°, $[\alpha]^{25}D$ +72° (1.1% in alcohol). The behavior on melting is like that of camphor, liquid appearing at the lower temperature indicated and the crystal skeleton disappearing at the higher temperature.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99. Found: C, 79.52; H, 10.25.

Summary

Pure dehydroabietic acid can be prepared very conveniently by the previous process but starting with Steele's abietic acid. The Friedel and Crafts reaction of the ester with acetyl chloride gives chiefly the 6-acetyl derivative, but this is accompanied by a small amount of the 8-isomer with which it forms a stable molecular compound resolvable by preferential reaction with hydroxylamine.

The oxime of methyl 6-aminodehydroabietate rearranges smoothly on treatment with hydrogen chloride in acetic acid–anhydride and gives chiefly the acetylamine derivative, along with a small amount of the isomeric methyl amide. After suitable hydrolysis, derivatives of these substances can be separated efficiently and pure 6-aminodehydroabietic acid and its ester can be obtained by this route in good yield.

By hydrogenation over copper chromite catalyst methyl dehydroabietate and its 6-amino derivative can be converted smoothly to the carbinols. The amino alcohol on methylation with methyl iodide–silver oxide gives 6-dimethylaminodehydroabietinol methyl ether, which is being tested for possible morphine-like actions. The phenols methyl 6-hydroxydehydroabietate and 6-hydroxydehydroabietinol were prepared from the amines by the diazo reaction; the latter substance has some of the structural features of oestradiol.

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Studies in the Synthesis of the Antirachitic Vitamins. I. The Synthesis of 3-[2′-Methylenecyclohexylidene-1′]-propene-1

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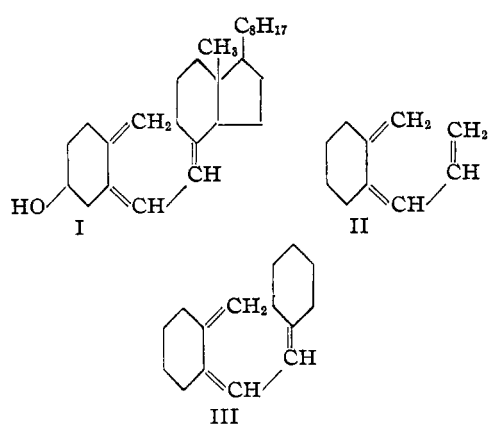
Although the structure of the antirachitic vitamins has been fairly well elucidated, ultimate proof is lacking because they have not yet been synthesized from simple substances. Some time ago we undertook the problem of synthesis, but in view of its complexity we decided first to synthesize the most unstable portion of the vitamin molecule, then to build the other parts together with the necessary functional groups around this portion. The most unstable portion of an antirachitic vitamin, represented by structure I, is that which includes the three conjugated double bonds. This is known to be responsible for the characteristic spectrum of the vitamin and, together with the hydroxyl group and the side chain,[1] contributes to its antirachitic action.

Two of the simplest configurations which represent this portion of the antirachitic molecule are indicated by structures II and III. After a number of attempts on various reactions which would lead to the synthesis of II and III, we have found that in the case of II the reactions outlined by the equations below led to the expected product in fairly good yields. In view of similar work



undertaken in other laboratories,[2,3] we are publishing at present the synthesis of II which will be followed shortly by that of III and other portions of the antirachitic molecule.

The ultraviolet absorption spectra of II and VII have been plotted side by side in Fig. 1. It may be seen readily that the amine VII absorbs rather strongly in the region of 236 mμ. Its extinction coefficient has been calculated to be 10,500, which is of the right order of magnitude

(1) Milas and Milone, unpublished work which indicates that the side chain of the antirachitic vitamins plays an important role.

(2) Aldersley and Burkhart, *J. Chem. Soc.*, 545 (1938).

(3) Dimroth, *Ber.*, **71**, 1333, 1846 (1938); Dimroth and Jonsson, *ibid.*, **71**, 2658 (1938).