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THE STRUCTURE OF LAMERTIANIC ACID

A NEW DITERPENIC ACID[1]

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Abstract—A new diterpene acid, lambertianic acid, has been isolated from the oleoresin of the sugar pine tree, *Pinus lambertiana* Dougl. The acid has been shown to have structure III making it the optical antipode of daniellic acid. Spectral features of these two furanoditerpene acids are discussed.

AN EXTENSIVE study of the neutral portions of the oleoresins of pine trees (genus Pinus) has been reported by Mirov.[3] Through the cooperation of Dr. Mirov, the oleoresins of some of the pine species of the subgenus Haploxylon were made available to us in order to investigate the nature of the acids present in the materials. The oleoresin of *Pinus lambertiana* Dougl., or sugar pine, has now been investigated The terpentine fraction of this material has been studied previously and it has been found to consist mainly of D-α-pinene.[3]

The bulk of the acids of the oleoresin was precipitated as cyclohexylamine salts Those acids which formed soluble salts were removed from the filtrate, after acidification, by extraction with potassium hydroxide. The crude acid fraction from this latter extraction crystallized and after several recrystallizations of the solid from hexane, pure lambertianic acid was obtained in a yield of 9%, based upon starting resin.

Analysis of the acid indicated the formula $C_{20}H_{28}O_3$ and the equiv. wt., determined by titration, was 316. The pK_{MCS} was 8·51,[4] indicating an axial carboxyl group flanked by a combination of three 1:3 axial methyl or hydrogen interactions and one α-methyl group.[5] The presence of three double bonds was established by hydrogenation and this fact coupled with the elementary composition indicated the presence of three rings. The IR spectrum showed absorption at 890 cm^{-1}, characteristic of an exocyclic methylene group, and the absorption at 1480 and 870 cm^{-1} established that the remaining two double bonds and oxygen atoms were present as a furan ring.[6] The absence of a maximum above 200 mμ in the UV was in agreement with the presence of a substituted furan.[7] The NMR spectrum displayed three multiplet bands, each indicating one hydrogen, at τ 2·78, 2·93, and 3·87, confirming the presence

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[2] U.S. Public Health Service Postdoctoral Fellow, 1963–1964.

[3] N. T. Mirov, *Composition of Gum Terpentines of Pines*. Forest Service Technical Bulletin No. 1239, U.S. Department of Agriculture, Superintendent of Documents, U.S. Government Printing Office, Washington, D.C.

[4] The authors wish to thank Dr. W. Simon and Mr. C. Pascual (E.T.H., Zurich) for these data.

[5] P. F. Sommer, C. Pascual, V. P. Arya and W. Simon, *Helv. Chim. Acta* **46**, 1734 (1963).

[6] T. Kubota, *Tetrahedron* **4**, 68 (1958).

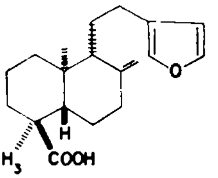
[7] K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy and N. Viswanathan, *Helv. Chim. Acta*, **44**, 1040 (1961).

of two α and one β hydrogen on a furan ring. In addition, the characteristic absorption at τ 5·15 and 5·45 for the two exocyclic vinyl hydrogens was found. Finally, sharp methyl singlets at τ 8·90 and 9·40 established the presence of two quaternary methyl groups, the lower field methyl most likely being attached to the carbon atom holding the carboxyl group.[8]

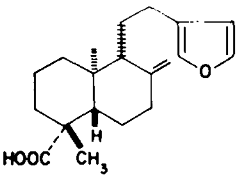
The analytical and spectral data established that lambertianic acid was a bicyclic diterpene acid containing a β-substituted furan ring. Two such acids have been previously reported, they are polyalthic acid (I)[7] and daniellic acid (II).[9] Both acids possess the so-called "wrong" configuration, i.e., a configuration which is the mirror image of the more common resin acids. The m.p. (127°) and the rotation ([α] +55°) of lambertianic acid suggested that this new acid might be the optical antipode of daniellic acid (m.p. 130°, [α] −58°). A comparison of their NMR spectra (Table 1) did substantiate such a structural assignment. However, daniellic acid has been reported[9] to have an UV maximum at 225 mμ whereas no such maximum was displayed by lambertianic acid. The NMR and UV (ε_{213} 6200) spectral features of polyalthic acid,[7] on the other hand, agreed well with those of lambertianic acid but the two materials possessed different physical properties. Since no sample of daniellic acid was available for direct comparison, further investigation of the structure of lambertianic acid was carried out.

TABLE 1. NMR SPECTRA OF FURANO-DITERPENE ACIDS

	τ, ppm				
Compound	H_α-Furan	H_β-Furan	H-Methylene	C_4-CH_3	C_{10}-CH_3
Lambertianic acid	2·78 2·92	3·88	5·16 5·44	8·77	9·40
Methyl lambertianate III	2·72 2·95	3·89	5·15 5·47	8·87	9·52
Daniellic acid I[9]	2·72 2·86	3·80	5·14 5·48	8·78	9·38
Methyl polyalthate II[8]	2·67 2·82	3·75	5·12 5·40	8·86	9·29
Methyl sciadopate X[13]			5·16 5·50	8·83	9·52



I



II

Assuming that lambertianic acid possessed the normal diterpene skeleton, the

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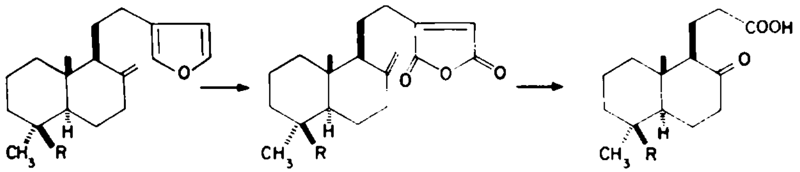
[8] C. A. Hendrich and P. R. Jefferies, *Austral. J. Chem.* **17**, 915 (1964).

[9] J. Haeuser, R. Lombard, F. Lederer and G. Ourisson, *Tetrahedron* **12**, 205 (1961). The NMR data listed in this paper appear to be in error; perhaps due to the use of methylene chloride as the internal standard. The values given in Table 1 are based on tetramethylsilane and were kindly furnished to us by Professor Ourrison.

material could have its carboxyl group at C-10 rather than at C-4 and/or be stereoisomeric at positions C-5 and C-10. That the carboxyl group was at C-4 and not C-10 was indicated, as mentioned earlier, by the absorption of one methyl group at τ 8·87 in the NMR spectrum. In addition, it is known that 4,4-geminal methyl groups in a 10-carboxy resin acid absorb at higher field and are nearly alike (τ 9·10 and 9·20).[10,11] This placement of the carboxyl group was confirmed by degradation of the material.

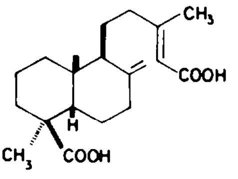


III R = COOH
VI R = CH_2OAc

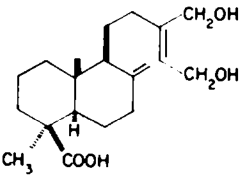
IV R = COOH
VII R = CH_2OAc

V R = COOH
VIII R = CH_2OAc

Lambertianic acid (III) was oxidized at 0° with Jones reagent[12] and the maleic anhydride (IV) was obtained. This result established the presence of a β-substituted furan ring. The anhydride was ozonized in glacial acetic acid and the product worked up oxidatively to yield the ketodiacid (V). This compound (and its dimethyl ester) was shown to be identical with the ketodiacid (and dimethyl ester) derived from agathic acid (IX)[9] by comparison of its m.p., optical rotation and ORD curve, and IR spectrum with a sample kindly supplied by Professor Ourisson. It must be concluded that lambertianic acid possesses the structure III and is, indeed, the antipode of daniellic acid. Thus, the new acid is the first furan diterpene acid found with the so-called "normal" configuration and it belongs to series containing agathic acid (IX) and sciadopic acid (X).[13]



IX



X

The finding of a maximum in the UV spectrum of daniellic acid must have been due to an instrumental error since it is well established that mono-substituted furans do not show a maximum in this region.[7]

In the course of this work, the C-4 carboxyl group was reduced to yield the alcohol VI which was in turn carried through a similar series of reactions to yield VII and VIII. The physical properties of these derivatives are reported in the experimental section.

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[10] J. W. ApSimon, O. E. Edwards and R. Howe, *Canad. J. Chem.* **40**, 630 (1962).
[11] W. H. Ayer, C. E. McDonald and J. B. Stothers, *Canad. J. Chem.* **41**, 1113 (1963).
[12] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).
[13] M. Sumimoto, Y. Tanaka and K. Matsufugi, *Tetrahedron* **20**, 1427 (1964).

EXPERIMENTAL[14]

Isolation of lambertianic acid (III). To a stirred solution of 100 g oleoresin from *Pinus lambertiana* Dougl. in 300 ml ether there was slowly added a solution of 40 ml cyclohexylamine in 300 ml ether. The mixture was allowed to stand at room temp until the precipitation was complete. The amine salts were removed by filtration and washed well with ether. The filtrate and the washings were combined, the combined ethereal solution washed with cold 10% H_3PO_4aq, and finally with cold water until the wash solution was neutral to Universal indicator paper. The ether was removed under red. press. and the residue dissolved in 100 ml hexane. The hexane solution was extracted with 2 × 50-ml portions 3% KOH in 50% aqueous MeOH solution. The alkaline extracts were washed with 3 × 50-ml portions hexane, acidified with cold 30% H_3PO_4, and extracted with 2 × 75-ml portions ether. The aqueous phase was discarded and the ether fractions combined. The ethereal extract was washed well with water, 2 × 50-ml portions of a sat NaClaq, and dried over Na_2SO_4. The ether was removed under red. press., the residue dissolved in 60 ml hexane, and the solution cooled to 0–5°. Crystallization was initiated by scratching the walls of the flask with a glass rod. The solid was recrystallized several times from hexane, yield 6·5 g; m.p. 124·5–125·5°; $[\alpha]_D^{22}$ +55·0° (*c* 3·0, 95% EtOH). Concentration of the mother liquors gave an additional 3 g crystalline acid. Chromatography of lambertianic acid over silica gel G (elution with 1% ether in benzene) raised the m.p. to 126·5–127·5°. (Found: C, 75·79; H, 8·73; Neut. Equiv. 316. $C_{20}H_{28}O_3$ (316·42) requires: C, 75·91; H, 8·92%.)

The IR spectrum showed absorption at 1695 cm^{-1} (carboxyl), 1656 and 890 cm^{-1} (exocyclic methylene), and 1480 and 870 cm^{-1} (furan). The NMR spectrum showed absorption at τ 9·40 and 8·90 (angular methyl hydrogens), two broad bands at τ 5·45 and 5·15 (vinyl hydrogens), and multiplets at τ 3·87, 2·93 and 2·78 (furan hydrogens). The UV spectrum showed strong end absorption (ε_{200} 10,000, 95% EtOH). The pK_{MCS} was 8·51.[4]

The methyl ester of lambertianic acid was prepared by treating an ethereal solution of the acid with excess ethereal solution of diazomethane at 0°. The oily methyl ester could not be obtained crystalline. The IR spectrum showed a shift in the carbonyl absorption from 1695 cm^{-1} to 1735 cm^{-1}. The NMR spectral values are listed in Table 1. The mass spectrum showed a parent peak at m/e 330; other prominent peaks were m/e 189, 121 and 81.

Hydrogenation of lambertianic acid. To a slurry of 50 mg prereduced Pd–C in 5 ml ethyl acetate there was added a solution of 127 mg lambertianic acid in 15 ml ethyl acetate. The mixture was hydrogenated until the uptake of H_2 ceased, the absorbed volume of H_2 being equiv. to 3 molar equivs. TLC analysis of the residue after removal of the catalyst and solvent showed the presence of one component (R_f 0·41, cyclohexane:ethyl acetate:acetic acid; 34:14:2). The oily perhydrogenated product could not be obtained crystalline. The IR spectrum of the oil showed the loss of absorptions characteristic of an exocyclic methylene group (1656 and 890 cm^{-1}) and the furan system (1480 and 870 cm^{-1}). The NMR spectrum showed the loss of olefinic and furan hydrogens and the appearance of a new doublet at τ 9·10.

Preparation of acid anhydride IV. To a stirred solution of 1·07 g lambertianic acid in 80 ml acetone cooled to 0° there was added, dropwise, 1 ml of 3M CrO_3 in H_2SO_4aq.[12] The mixture was allowed to warm to room temp over a period of 4·5 hr, poured into an ice-water mixture, and the mixture immediately extracted successively with 150, 100 and 50 ml portions ether. The ether fractions were combined and the combined extracts were washed with cold water until the wash solution was neutral to Universal indicator paper. The ethereal solution was then washed with 2 50-ml portions of sat. NaClaq, and it was dried over Na_2SO_4. The solvent was removed under red. press. and the crystalline residue was recrystallized from ether–hexane, yield 950 mg, m.p. 171–172°, $[\alpha]^{25}$ 578 mμ +61°, $[\alpha]^{25}$ 365 mμ +193° (*c* 1·07, dioxan). The IR spectrum showed absorption at 1845 and 1770 cm^{-1} (anhydride), 1695 cm^{-1} (carboxyl), and 1640 and 890 cm^{-1} (exocyclic methylene). The NMR spectrum showed absorption at τ 9·39 and 8·84 (angular methyl hydrogen), τ 5·45 and 5·07 (vinyl hydrogens on exocyclic methylene), and τ 3·42 (vinyl hydrogen on anhydride). (Found: C, 69·60; H, 7·80. $C_{20}H_{26}O_5$ (346·41) requires: C, 69·34; H, 7·56%.)

Preparation of keto diacid V. A solution of 1·9 g IV in 15 ml ethyl acetate and 15 ml glacial acetic acid was cooled to 0° and a stream of O_3 and O_2 (0·07 mmoles O_3/min) was passed through the

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[14] Analyses by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley. The NMR spectral data are relative to tetramethylsilane as an internal standard.

solution for 6 hr. To the cold reaction mixture there was added 10 ml water and 3 ml 30% H_2O_2 and the mixture was allowed to warm to room temp over a 12 hr period. The solvent was removed under red. press. at a temp of 40°, the residue dissolved in 100 ml ether, and the ethereal solution washed with 4 25-ml portions water and 2 10-ml portions of sat. NaClaq. The ethereal solution was dried, the solvent removed under red. press., and the partially crystalline residue recrystallized from ethyl acetate–hexane to yield 900 mg crystalline material, m.p. 188·5–189·0°, $[\alpha]^{22}_{D}$ +3·6°, $[\alpha]^{22}$ 365 mμ −215° (*c* 1·96, 95% EtOH), $[\alpha]^{22}$ 307 mμ −1825° (*c* 0·27, MeOH). The IR spectrum (KBr pellet) showed principal absorption at 3600, 1695, 1450, 1280, 1175 and 1165 cm^{-1}. (Found: C, 64·67; H, 8·26. $C_{16}H_{24}O_5$ (296·35) requires: C, 64·84; H, 8·16%.)

A mixture m.p. of the above keto diacid and an authentic sample (from agathic acid) was undepressed. The mixture m.p. of the above acid with that of its enantiomer (from daniellic acid[15]) was depressed, m.p. 179–183°. The IR and NMR spectra as well as the ORD curve were identical with those of the acid from agathic acid.

Preparation of acetate VI. To a stirred slurry of 1·5 g LAH in 20 ml anhydrous tetrahydrofuran was added, dropwise, a solution of 5·39 g lambertianic acid in 20 ml tetrahydrofuran. The mixture was allowed to stir for 1 hr at room temp and then heated under reflux for 12 hr. The reaction was cooled to 5° and 200 ml anhydrous ether was added. Sat. NH_4Claq was added, dropwise, until the layers separated cleanly, the supernatant liquid decanted, and the residual salts washed well with ether. The combined ethereal solution was washed with 2 × 50-ml portions ice water, 1 × 25-ml portion cold 10% H_3PO_4aq, 2 × 25-ml portions cold water, and 2 × 25-ml portions sat. NaClaq. The ether solution was dried, and the solvent removed under red. press. to yield 5·0 g of a glass which crystallized on the walls of the flask. A small fraction of material was recrystallized twice from hexane and distilled in a molecular still at 150° (0·25 mm), m.p. 69·5–70·0°. The IR spectrum showed absorption at 3600, 1635, 890 and 870 cm^{-1}. The NMR spectrum showed absorption at τ 9·35 and 9·08 (3H singlets); τ 6·75 (1H, doublet, J, 11·0 c/s); τ 6·35 (1H, doublet, J, 11·0 c/s); τ 5·45 and 5·27 (1H, broad singlets); τ 3·87 (1H, multiplet); τ 2·90 and 2·77 (1H, multiplets). (Found: C, 79·41; H, 9·93. $C_{20}H_{30}O_2$ (302·44) requires: C, 79·42; H, 10·00%.)

To a cold, stirred solution of 5·0 g of the above alcohol in 50 ml dry pyridine was added 2·5 g acetic anhydride. The solution was allowed to warm to room temp over a 4 hr period. The solution was poured into ice water and the mixture processed in the usual manner to yield 5·0 g viscous oil which was homogeneous by TLC. The IR spectrum showed bands at 1740, 1625, 890 and 870 cm^{-1}. The NMR spectrum showed absorption at τ 9·39 and 9·15 (3H singlets); τ 8·19 (3H singlet); τ 6·43 (1H, doublet, J, 10 c/s); τ 6·06 (1H, doublet, J, 10 c/s); τ 5·63 and 5·37 (1H broad singlets); τ 4·10 (1H, multiplet); τ 3·19 and 3·05 (1H multiplets).

Preparation of acetate anhydride VII. Following the procedure used for the preparation of IV, 2·5 g of VI was oxidized with 9·4 ml 3M CrO_3 solution. The crude product was recrystallized from ether–hexane, yield 1·73 g, m.p. 75·5–76·0°, [α] 578 mμ +46°, [α] 365 mμ +172° (*c* 1·0, $CHCl_3$). The IR spectrum showed principal bands at 1840, 1775, 1725, 1640, 1250 and 890 cm^{-1}. The NMR spectrum showed absorption at τ 9·29 and 9·05 (3H, singlets); τ 8·03 (3H, singlet); τ 6·25 (1H, doublet, J, 11 c/s); τ 5·80 (3H, doublet, J, 11 c/s); τ 5·60 and 5·11 (1H broad singlets); τ 3·40 (1H). (Found: C, 70·21; H, 7·88. $C_{22}H_{30}O_5$ (374·46) requires: C, 70·56; H, 8·08%.)

Preparation of keto acid acetate VIII. Following the procedure used for the preparation of V, 1·0 g of VII was ozonized and processed in the usual manner. The crude product was chromatographed over silica gel and the desired material crystallized from ethyl acetate–hexane, yield 380 mg, m.p. 132–133°, [α] 578 mμ −26°, [α] 365 mμ −304° (*c* 1·50, 95% EtOH), [α] 307 mμ −2000 (*c* 0·20, MeOH), ν_{max} 1710 cm^{-1}. The NMR spectrum showed bands at τ 9·28 and 8·95 (3H, singlets); τ 7·93 (3H, singlet); τ 6·18 and 5·77 (1H doublets, J, 11 c/s), and τ −·15 (1H). (Found: C, 66·40; H, 8·66. $C_{18}H_{28}O_5$ (324·40) requires: C, 66·64; H, 8·70%.)

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[15] The two authentic samples from agathic and daniellic acids were kindly supplied by Professor G. Ourisson.