[CONTRIBUTION NO. 1361 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Constitution of Cativo Gum[1]

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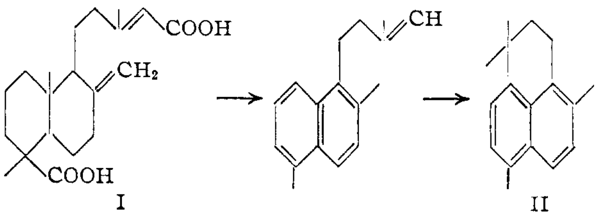
Cativo gum consists principally of mono-unsaturated cativic acid, $C_{20}H_{34}O_2$, and its corresponding ester, cativyl cativate. The structure and stereochemistry of this acid have been determined by the establishment of common identity between one of its degradation products and one derived from manoöl. The position of unsaturation in cativic acid and its ease of isomerization are also shown.

Cativo gum is the oleoresinous exudate of the cativa tree, *Prioria copaifera*, Griseb., found in the rain forests indigenous to Central America. A single report of chemical consequence bearing on the constitution of this resinous material was prepared by Kalman,[3] in which the gum which he examined was observed to consist mainly of an easily esterifiable, unsaturated, liquid acid, $C_{20}H_{34}O_2$, and a neutral fraction assumed to be the corresponding ester, cativyl cativate. This acid of seemingly diterpenoid character was of interest to us because of its unique feature of being readily esterifiable under Fischer–Spier conditions, in contrast to most of the diterpenic acids which contain highly hindered, tertiary carboxyl groups. An acid of this molecular weight and type existing in a liquid state also intrigued us. A sample of the gum with which Kalman worked was made available to us,[4] and with this the initial experiments of Kalman were reproduced. Only by starting with authentically fresh "cativo" were we able to obtain homogeneous, *crystalline* cativic acid, m.p. 82°, and it was with this latter specimen that its structure was determined.[5]

Cativic acid is precipitated by cyclohexylamine from a petroleum ether solution of the extremely viscous, green-brown, sirupy cativo gum. Regeneration of the free acid from this salt with boric acid (or 2% hydrochloric acid) gives the pure substance, $[\alpha]^{26}\mathrm{D}\ -6.54^\circ$. Perbenzoic acid titration of duplicate samples of cativic acid in chloroform gave values of 0.95 and 0.89 double bond per molecule, and one mole equivalent of bromine was absorbed by another portion of the acid in the same solvent. Its methyl ester, $[\alpha]^{30}\mathrm{D}\ -7.16^\circ$,[6] was reduced smoothly and quantitatively in ether by lithium aluminum hydride to the colorless liquid cativyl alcohol which proved to be similar to the alcohol resulting from the alkaline hydrolysis or lithium aluminum hydride reduction of Kalman's cativyl cativate, thereby establishing the relationship of the alcoholic moiety of the ester to cativic acid.

Consideration of the molecular formula, $C_{20}H_{34}O_2$, together with the fact that cativic acid is mono-unsaturated led to the conclusion that the acid is bicyclic and thence to a survey of the naturally occurring bicyclic diterpenes of known structure: manoöl, manoyl oxide, ketomanoyl oxide, sclareol and agathenedicarboxylic acid (I).[7] The latter substance is likewise unique among the diterpenic acids in having one readily esterifiable carboxylic acid group. The weakness of conjectural argument based upon this analogy was removed in part by the isolation of 1,2,5-trimethylnaphthalene from the selenium dehydrogenation of methyl cativate. More significant, however, was the identification of the principal product of this dehydrogenation of cativic *acid*, 1,1,4,7-tetramethylphenalan (II), accounting as it does for 17 of the original 20 carbon atoms. In parallel fashion agathenedicarboxylic acid is dehydrogenated under similar conditions to II, the major product.[8] The synthesis of II has been described recently by Büchi and Pappas[9] who have suggested a mechanism for its formation from I involving an intermediate naphthalene derivative.[10] The formation of II from cativic acid encouraged us to believe that the arrangement of carbon atoms in cativic



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[1] Taken from the doctoral dissertation submitted by F. W. Grant, Jr., to the Faculty of the Graduate School, Yale University, 1954. A preliminary communication of the structure of cativic acid appeared in THIS JOURNAL, **76**, 5001 (1954).

[2] Monsanto Chemical Co., Dayton 7, Ohio.

[3] N. L. Kalman, THIS JOURNAL, **60**, 1423 (1938).

[4] We are indebted to Mr. C. G. Harford of the Arthur D. Little Co., Inc., Cambridge, Mass., for this sample which represented the remainder of Kalman's original material.

[5] The assistance of Mr. H. Rowe of the United Fruit Co., Boston, Mass., and the Maritrop Trading Corp. in obtaining this resin for our use is gratefully acknowledged.

[6] Diazomethane was used since Fischer conditions promoted isomerization.

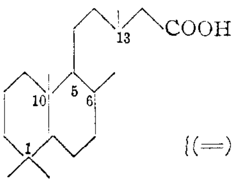
[7] These are discussed in detail by D. H. R. Barton in J. L. Simonsen's "The Terpenes," Vol. III, Cambridge Univ. Press, 1952.

[8] L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, **13**, 1402 (1930).

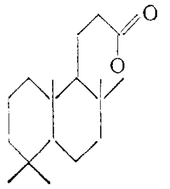
[9] G. Büchi and J. J. Pappas, THIS JOURNAL, **76**, 2963 (1954), whom we thank for an infrared spectrum of synthetic II for direct comparison with our product.

[10] Since little is known about the mechanism of selenium dehydrogenation, we can but infer the possible origin of II from cativic acid. The fact that dehydrogenation of methyl cativate yields 1,2,5-trimethylnaphthalene as the principal product permits the tentative conclusion that ring closure by the side chain is preceded by a decarboxylation. Since the decarboxylation of esters is considerably more difficult than that of free acids [*cf.* M. S. Newman and T. S. Bye, *ibid.*, **74**, 905 (1952)], with the exception of tertiary carboxylic acids and their esters [L. Ruzicka and Fr. Balas, *Helv. Chim. Acta*, **7**, 875 (1924)], this added resistance in the present case apparently is sufficient to result in cleavage of rather than closure by the side chain. Thus it appears also that the dehydrogenation is followed by ring closure by the side chain at the *peri* position of the naphthalene derivative. It is not unlikely, therefore, that the aromatic alkene is also the intermediate in the dehydrogenation of cativic acid. The cyclization of this intermediate is analogous to the acid-catalyzed intramolecular ring closures of various phenylalkenes investigated by M. T. Bogert, D. Davison and P. M. Apfelbaum, THIS JOURNAL, **56**, 959 (1934).

acid constituted another example of the "phytol isoprene rule," *i.e.*, regular "head-to-tail" progression, as are the other bicyclic terpenes of known structure. Provisional structure III was now drawn for cativic acid.



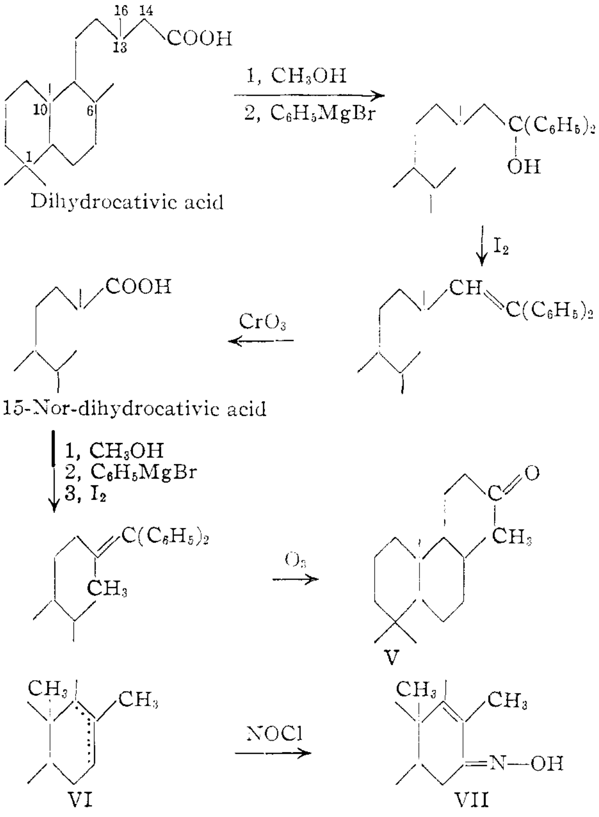
III



IV

Dehydrogenation of cativic acid with palladium-charcoal produced yet a third hydrocarbon, 1,2,5,6-tetramethylnaphthalene, which heretofore has appeared but twice in the diterpene literature (see below).[11] This shortage is undoubtedly due to past dehydrogenations in this field being done either with sulfur or selenium. However, 1,2,5,6-tetramethylnaphthalene is a common dehydrogenation product of numerous triterpenes, but in these cases an adjacent C-2 hydroxyl group may facilitate rearrangement of the retropinacolone type.[12] Lederer, *et al.*,[13] have shown that ambreinolide (IV), sclareol and tetrahydrosqualene give this same naphthalene as the sole product. There can be no doubt, therefore, that cativic acid, like these latter substances of known structure, has undergone rearrangement during palladium-charcoal dehydrogenation. The general utility of this catalyst in the structural elucidation of compounds having ring-substituted *gem*-dimethyl groups is thus indicated by these examples.

Provisional structure III was verified by a two-stage Barbier–Wieland degradation of dihydrocativic acid. The product of the first stage was an easily esterifiable carboxylic acid and that of the second, a methyl ketone whose infrared spectrum was consistent with the methyl ketone structure V. This ketone proved to be the same as that previously reported from the degradation of manoöl.[13a] This identity was confirmed by comparison of infrared spectra, mixed melting point and optical rotations of the semicarbazone derivatives.[14] This rotational agreement relates dihydrocativic acid structurally and stereochemically through manoöl to the di- and triterpenes.[15]

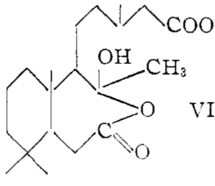


V

VI

VII

The location of the double bond of cativic acid in the ring system was shown by the absence of cleavage fragments on ozonolysis and by the absence of exocyclic methylenic absorption in the infrared spectrum of cativic acid. The crystalline ozonolysis product[16] gave a positive iodoform test, and this led to the conclusion that the double bond terminates at a tertiary ring carbon atom bearing a methyl group. The partial, ambiguous structure VI may then be written for cativic acid in which either a tetra- or a trisubstituted double bond is possible.



VIII

Methyl cativate, arising from the reaction of cativic acid and diazomethane, undergoes reaction smoothly with nitrosyl chloride in chloroform at

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[11] R. Schwyzer, H. G. Biswas and P. Karrer, *Helv. Chim. Acta* **34**, 652 (1951). Dr. T. G. Halsall of the Dyson Perrins Laboratory, Oxford, has kindly sent us a pre-publication copy of their (with Dr. J. D. Cocker) manuscript on the structure of labdanolic acid in which the platinum-charcoal dehydrogenation of 15-hydroxylabd-8(20)-ene also yields this tetramethylnaphthalene; *J. Chem. Soc.*, 4262 (1956).

[12] L. Ruzicka, M. W. Goldberg and K. Hoffman, *Helv. Chim. Acta*, **20**, 325 (1937); L. Ruzicka, H. Schellenberg and M. W. Goldberg, *ibid.*, **20**, 791 (1937).

[13] E. Lederer, F. Marx, D. Mercier and G. Perot, *ibid.*, **29**, 1354 (1946); E. Lederer, D. Mercier and G. Perot, *Bull. soc. chim.*, [5] **14**, 345 (1947).

[13a] J. R. Hosking and C. W. Brandt, *Ber.*, **68**, 1311 (1935). Their sequence of reactions was repeated using a sample of pure manoöl most generously forwarded to us by Dr. F. J. T. Grigg, Director of The Dominion Laboratory, Wellington, New Zealand.

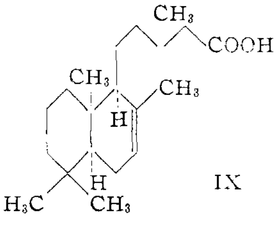
[14] We are at a loss to account for the discrepancy between the optical rotation of this derivative and that prepared by T. G. Halsall and J. D. Cocker (reference 11) from labdanolic acid in spite of the fact that complete agreement is found in all other areas of comparison of cativic acid derivatives and degradation products with those of labdanolic acid (see Experimental).

[15] This result leads to the conclusion also that the hydrogenation of cativic acid and manoöl took the same stereochemical course *or* that the rotational contribution of the asymmetric center involved at C-6 is very small. Analogous situations arose in the hydrogenations performed in relating ambreinolide and manoöl, L. Ruzicka, O. Durst and O. Jeger, *Helv. Chim. Acta*, **30**, 353 (1947), in the partial synthesis of ambreinolide, H. R. Schenk, H. Gutman, O. Jeger and L. Ruzicka, *ibid.*, **35**, 817 (1952), and in the conversion of labdanolic acid to V, reference 14.

[16] This substance, $C_{20}H_{34}O_5$, separated from solution during the course of the ozonization. Its infrared absorption bands at 3.02, 5.77 and 5.90 μ together with its chemical behavior permit the provisional representation VIII.

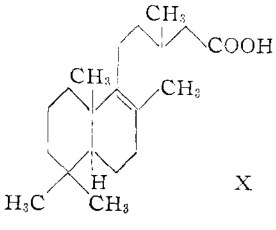
low temperatures. The adduct thus formed (transient blue color) spontaneously undergoes elimination and enolization to the α,β-unsaturated oxime VII, $\lambda_{\max}$ 246 mμ, log ϵ 4.1; 3.07, 5.77 and 6.17μ.[17] Hydrolysis of the oxime gives a ketone having a $\lambda_{\max}$ at 251 mμ, log ϵ 4.1. Formation of the oxime is consistent only with the trisubstituted double bond structure. With the position of unsaturation located and a knowledge of the stereochemistry of manoöl,[18] structure IX is assigned to cativic acid.

The isomeric nature of Kalman's cativic acid was suspected in the early phases of this investigation. The fact that this sirupy acid and its ester make up 95% of the crude cativo gum weight is evidence in itself that the resin contains only one acid, excepting possible double bond isomers. Further evidence was obtained from the palladium–charcoal dehydrogenation of Kalman's acid, which yielded 1,2,5,6-tetramethylnaphthalene as the sole product, a duplication of the result secured with cativic acid. Perbenzoic acid titration, analysis and neutralization equivalence measurement confirmed the mono-unsaturated, monobasic, bicyclic character of Kalman's acid.



IX

Kalman's acid, $[\alpha]^{24}\text{D}$ $-34.1°$, is unaffected by refluxing formic acid; but crystalline cativic acid under the same conditions is transformed into a sirupy, non-crystallizing acid, $[\alpha]^{25}\text{D}$ $-39.1°$, with altered chemical properties and infrared absorption. Cleavage of the crystalline diol, resulting in poor yield from the permanganate oxidation of Kalman's acid, with lead tetraacetate gives a product which still possesses twenty carbon atoms, contains a methyl ketone group and tests negatively for aldehydic activity. These considerations lead to the conclusion that Kalman's acid is an isomeric mixture containing X. Inasmuch as isomerized cativic acid and Kalman's acid exhibit similar infrared spectra, the acid X is a constituent of both.



X

Experimental[19]

Cativic Acid.—Cativo gum (600 g.) was dissolved in 1800 ml. of petroleum ether, b.p. 60–100°, and then filtered to remove wood chips and other foreign solids. This solution, after adding 300 ml. of cyclohexylamine, was warmed and then set aside at 0°. The long-needled clusters which had formed were filtered off and recrystallized several times from petroleum ether and several times from acetone. In this manner there was obtained from 5 kg. of crude resin 1130 g. of the **cyclohexylamine salt** of cativic acid, m.p. 141.5–143°, $[\alpha]^{25}\text{D}$ $-2.88°$.

Anal. Calcd. for $C_{26}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 77.10; H, 11.49; N, 3.68.

Cativic acid was regenerated from the amine salt by shaking an ethereal solution of the salt with saturated, aqueous boric acid solution, or, more efficiently, with 2% hydrochloric acid (no isomerization). This solution was further washed with water and then evaporated *in vacuo* to a clear, colorless sirup which required only one crystallization from aqueous methanol or acetic acid to give an analytically pure specimen of **cativic acid**, m.p. 80–82°, $[\alpha]^{26}\text{D}$ $-6.54°$ (*c* 3.50, α 0.229°), neut. equiv. 303 (calcd. 306).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.36; H, 11.18. Found: C, 78.22; H, 10.92.

The 2-methyl-2-amino-1-propanol salt of cativic acid, m.p. 119.5–121°, was prepared by adding this amine to an ethanolic solution of the acid.

Reaction of cativic acid with diazomethane in dry ether gave **methyl cativate** as a colorless liquid, b.p. 165° (*ca.* 1 mm.), $[\alpha]^{30}\text{D}$ $-7.16°$, $n^{25}\text{D}$ 1.4954. Esterification under Fischer conditions, *i.e.*, absolute methanol and several drops of sulfuric acid, resulted in isomerization, since the ester thus obtained had an altered rotation, +24.7°, but unchanged b.p. and refractive index. Saponification of this ester led to a non-crystallizing acid, $[\alpha]^{23}\text{D}$ $+26.7°$.

Dehydrogenation of Cativic Acid. (a) With Pd-C.—Cativic acid (5.0 g.) and 2.5 g. of 10% Pd-C were heated between 300–320° in an atmosphere of carbon dioxide for 5 hr. The cooled residue was extracted with ether, and the combined extracts were filtered before evaporation to 3.2 g. of a brown, fluorescent sirup. An ethanolic solution of this material was filtered and then treated with an equal volume of ethanol saturated with trinitrobenzene. Purification by crystallization of the crude, orange, crystalline adduct thus formed was slow, and so the hydrocarbon moiety was regenerated by passing a benzene solution of the derivative through a column of alumina. Concentration of the ethanolic mother liquors above gave oily adduct, and this was decomposed on alumina also. Purification of the hydrocarbon by sublimation and recrystallization from aqueous methanol, m.p. 114.5–115°, gave a product which did not depress the m.p. of an authentic sample of **1,2,5,6-tetramethylnaphthalene**[20] and exhibited infrared and ultraviolet spectra superimposable on those of the latter compound. Its **picrate**, m.p. 151–153°, and **trinitrobenzolate**, m.p. 180–181°, were also prepared (lit. m.p.'s 154–156° and 181–182°, respectively).

(b) With Selenium.—Cativic acid (10 g.) and 10 g. of selenium were heated together at 300° under an atmosphere of carbon dioxide for 30 hr. The cooled residue was extracted with ether, and the combined extracts were filtered and evaporated to a dark, fluorescent sirup. This material was fractionally distilled through a small Vigreux column at 1 mm. pressure from which three fractions boiling between 105–140° and totalling 7 g. were obtained. The m.p.'s of the **picrates and styphnates** (136–138° and 153–155°, respectively) prepared from these fractions and of the hydrocarbon, 39–40.5°, resulting from decomposition of the picrate of the middle fraction on a column of alumina and recrystallization from methanol, showed these fractions to be substantially pure **1,1,4,7-tetramethylphenalan**, lit. m.p. 42°. The ultraviolet and infrared spectra reported for this substance[9] were used to confirm the identity of our hydrocarbon.

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[17] This reaction has analogies in the conversion of limonene to carvone oxime, H. Goldschmidt and R. Zurrer, *Ber.*, **18**, 2220 (1885); in the formation of nitrosopinene from α-pinene, J. C. Earl and J. Kenner, *J. Chem. Soc.*, 1269 (1927); and more recently in the preparation of 2-phenylcyclopent-2-enone from 1-phenylcyclopentene, Y. Amiel, A. Löffler and D. Ginsburg, THIS JOURNAL, **76**, 3625 (1954).

[18] This has been established by the relationship of manoöl to abietic acid, O. Jeger, O. Dürst and G. Büchi, *Helv. Chim. Acta*, **30**, 1853 (1947); and to the triterpenes and steroids, W. Voser, M. V. Mijovic, H. Heusser, O. Jeger and L. Ruzicka, *ibid.*, **35**, 2414 (1952).

[19] All melting points are corrected. Optical rotations were measured in 95% ethanol and a 1-dm. tube, ultraviolet spectra in 95% ethanol through a 1 cm. path, infrared spectra in chloroform in concentrations approximating 10%. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

[20] We are indebted to Dr. O. Jeger of the Eidg. Technische Hochschule, Zürich, for providing us with a sample of this substance.

Dehydrogenation of Methyl Cativate.—Methyl cativate (5.0 g.) and 6 g. of selenium were heated at 320° under carbon dioxide for 36 hr. The residue was extracted with ether and then distilled in a small claisen flask at 2 mm. pressure. The first fraction, 0.7 g., boiling between 105–120°, was converted to a **styphnate** and recrystallized from ethanol, m.p. 129–132° (lit. m.p. 129–129.5°). Its parent hydrocarbon was regenerated on alumina in benzene solution and was obtained as a slightly blue oil whose ultraviolet absorption was the same as that reported for **1,2,5-trimethylnaphthalene**.[21] **Its trinitrobenzolate**, m.p. 157.5–159°, and **picrate**, m.p. 135–137°, were also prepared (lit. m.p.'s 159.5–160° and 137–138°).

Methyl Dihydrocativate.[22]—Cativic acid (5.0 g.) in 150 ml. of glacial acetic acid was shaken in an atmosphere of hydrogen at 22° and 758 mm. pressure with freshly prepared Adams catalyst. After 12 hr. the theoretical value of hydrogen was absorbed. The solvent was then distilled off *in vacuo*, and the sirupy residue, when crystallized from methanol at −60°, gave long white needle clusters. However, after filtering cold through a buchner funnel, the crystalline acid began to liquify; but if the acid was transferred quickly to a glass plate before liquification had become complete, it eventually resolidified on standing, m.p. 70.5–71.5°, $[\alpha]^{31}\text{D}$ +25.4° (*c* 1.68), neut. equiv. 308 (308).

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 77.54; H, 11.62.

The 2-methyl-2-amino-1-propanol salt of dihydrocativic acid was also prepared, m.p. 127–128.5°, $[\alpha]^{26}\text{D}$ +22° (*c* 0.207).

A more satisfactory method of dealing with the hydrogenation product was to make the methyl ester of the acid directly by refluxing a methanolic solution of the acid with a small amount of concentrated sulfuric acid. The usual isolation procedure of the neutral fraction gave a clear, colorless sirup which could be crystallized easily from aqueous methanol as pure **methyl dihydrocativate**, m.p. 43–44°, $[\alpha]^{27}\text{D}$ +23.4° (*c* 1.34).

Anal. Calcd. for $C_{21}H_{38}O_2$: C, 78.20; H, 11.88. Found: C, 78.61; H, 11.36.

Side Chain Degradation of Methyl Dihydrocativate.—Methyl dihydrocativate (7.5 g.) was dissolved in 200 ml. of dry benzene and then added dropwise to a stirred solution of phenylmagnesium bromide in 150 ml. of ether (69.4 g. of bromobenzene and 10.7 g. of magnesium). After refluxing for 8.5 hr., the mixture was poured into a mixture of ice, water and ammonium chloride. Steam was blown through the hydrolyzed mixture for 1 hr. to remove the solvents and the major portion of by-product biphenyl. The organic residue was then taken up in ether and chromatographed on alumina. The remainder of the biphenyl was eluted cleanly with petroleum ether and an ether–petroleum ether eluent was used to clean the column of 8.0 g. of a light tan sirup which did not crystallize but which appeared to be a mixture of the tertiary alcohol **15,15-diphenyldihydrocativ-15-ol** and its dehydration product from the consideration of its ultraviolet (253, 259 mμ) and infrared (2.95, 9.32 μ) spectra. This material was used in the next step without further purification.

This crude mixture (8.0 g.) was dissolved in 100 ml. of dry benzene and refluxed with 0.10 g. of iodine for 3 hr. The cooled solution was diluted with ether and then washed with sodium thiosulfate solution and water before the removal of solvents. The tan sirup remaining was chromatographed on alumina with petroleum ether and eluted with the same solvent to yield 5 g. of the clear, colorless liquid **15,15-diphenyldihydrocativ-14-ene**,[23] $n^{25}\text{D}$ 1.5596, $[\alpha]^{24}\text{D}$ +110° (*c* 4.91), λ_{max} 251 mμ, log ε 3.8.

Anal. Calcd. for $C_{32}H_{44}$: C, 89.65; H, 10.35. Found: C, 89.46; H, 10.39.

The diphenylethylene (2 g.) in 40 ml. of stirred acetic acid was oxidized by the dropwise addition of 2 g. of chromium trioxide dissolved in a minimal quantity of water and diluted with 40 ml. of acetic acid. After the addition the reaction mixture was heated on the steam-bath for 3 hr., and the excess chromic acid was decomposed with methanol. The solution was then poured into a large volume of water, extracted with ether and the combined ether extracts washed with water before separation into neutral and acidic fractions by dilute base extraction. The neutral fraction consisted mainly of benzophenone as shown by the isolation of its 2,4-dinitrophenylhydrazone, m.p. 235–236°, undepressed mixed m.p. Attempts to crystallize the acidic fraction were unsuccessful until it had been purified through its **2-methyl-2-amino-1-propanol salt**, m.p. 149–151° (80% crude acid yield). Regeneration of the acid by shaking an ethereal solution of the salt with dilute hydrochloric acid, washing with water and evaporating the ether layer, resulted in a clear sirup which was crystallized from aqueous methanol as the pure **nor-dihydrocativic acid**,[24] m.p. 89–90°, $[\alpha]^{28}\text{D}$ +51.0° (*c* 0.56), neut. equiv. 300 (294).

Fischer esterification of this acid resulted in the crystalline **methyl nor-dihydrocativate**, m.p. 54.5–55.5°.[25]

Methyl nor-dihydrocativate (6.2 g.) was dissolved in 200 ml. of dry benzene and then added dropwise to a solution of phenylmagnesium bromide made from 7.7 g. of bromobenzene, 1.1 g. of magnesium and 150 ml. of ether. The solution was refluxed for 8.5 hr. and then hydrolyzed in essentially the same manner as that described after the Grignardization of methyl dihydrocativate above. The product was chromatographed on alumina with petroleum ether, and 8.5 g. of crude carbinol was eluted from the column with ether-petroleum ether. Without further purification this alcohol was dehydrated directly with iodine in boiling benzene. Chromatography of the dehydration product on alumina gave a petroleum ether eluate of *ca.* 7 g. which was crystallized from ether–ethanol as small colorless platelets of **15-nor-14,14-diphenyldihydrocativ-13-ene**,[26] m.p. 118.5–119°, λ_{max} 245 mμ, log ε 4.1.

Anal. Calcd. for $C_{31}H_{42}$: C, 89.79; H, 10.21. Found: C, 90.20; H, 10.50.

The nordiphenylethylene (5.0 g.) in 150 ml. of chloroform was ozonized at 0° for 1.5 hr., after which time the effluent gases began to oxidize a solution of potassium iodide in saturated, aqueous boric acid. The solution of the ozonide was then decomposed by adding it dropwise to boiling water. The organic material was extracted from the cooled water with ether, and the residue from the evaporation of the ether extracts was distilled from a small claisen flask, yielding 2.0 g. of distillate boiling over a wide range (130–170°) at 1 mm. This mixture of benzophenone and **15,16-bisnor-dihydrocativ-13-one**[27] was treated in ethanol with semicarbazide hydrochloride and sodium acetate, from which, after two recrystallizations from aqueous methanol, pure **15,16-bisnor-dihydrocativ-13-one semicarbazone** was secured, m.p. 201.5–202.5°, $[\alpha]^{31}\text{D}$ +66.6°[14] (α, 0.242, *c* 0.726 in $CHCl_3$, *l* 0.5).

Regeneration of the ketone was effected by refluxing a mixture of the semicarbazone with three times its weight of oxalic acid in water for 3.5 hr. The cooled solution was made weakly alkaline with aqueous sodium carbonate solution and extracted with ether. The methyl ketone was isolated as a clear, colorless sirup which exhibited absorption bands in the infrared region at 5.85, 7.09, 7.35 and 8.61 μ, as required.[28]

An alternative method of preparing 15,16-bisnor-dihydrocativ-13-one consisted of brominating the acid chloride of dihydrocativic acid, then esterifying with neopentyl alcohol, dehydrobrominating and finally ozonizing the α,β-unsaturated neopentyl ester.

Manoöl was degraded by the procedure of Hosking and Brandt[13] to **15,16-bisnor-tetrahydromano-13-one** whose semicarbazone constants and infrared spectrum were the same, within experimental limits, as those of 15,16-bisnor-dihydrocativ-13-one semicarbazone, m.p. 194–196 (mixed m.p. undepressed), $[\alpha]^{31}\text{D}$ +65.4° (α 0.213°, *c* 0.653, *l* 0.5) in $CHCl_3$.

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[21] E. Heilbronner, U. Fröhlicher and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949).

[22] Properties are the same as those of methyl labdan-15-oate (*cf.* reference 11).

[23] Properties are the same as those of 15,15-diphenyllabd-14-ene (*cf.* reference 11).

[24] Properties are the same as those of 15-norlabdan-14-oic acid (*cf.* reference 11).

[25] This ester is equivalent to methyl 15-norlabdan-14-oate: reference 11.

[26] Properties are the same as those of 5-nor-14,14-diphenyllabd-13-ene (*cf.* reference 11).

[27] This methyl ketone is equivalent to 15,16-bisnor-13-oxolabdane: reference 11.

[28] H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945).

Reaction of Methyl Cativate with Nitrosyl Chloride.—Cold, concentrated hydrochloric acid (0.7 ml.) was added dropwise to a solution of 1 g. of methyl cativate and 1 ml. of amyl nitrite in 5 ml. of chloroform at −60°. The initial yellow color turned to greenish-blue on warming to room temperature, after which time the solvent and excess hydrochloric acid were removed by vacuum distillation without heating. Chromatography of the oily residue in benzene on alumina gave a benzene–ether eluate which crystallized in the receiver after evaporation of the eluent. Recrystallization from aqueous methanol gave 0.64 g. of **methyl iso-(Δ^5)-cativ-7-one oxime**, m.p. 121.5–122°, λ_{max} 246 mμ (log ϵ 4.1); 3.07, 5.77, 6.17 μ.

Anal. Calcd. for $C_{21}H_{35}O_3N$: C, 72.16; H, 10.09; N, 4.01. Found: C, 71.97; H, 10.31; N, 4.24, 3.96.

The crystalline oxime (0.35 g.) was refluxed with 0.27 g. of pyruvic acid in 10 ml. of 50% aqueous acetic acid for 4 hr. The cooled solution was poured into 100 ml. of water, extracted with ether, and the combined extracts were washed with water, 5% aqueous sodium hydroxide solution and water. The ether layer was then evaporated, leaving 0.1 g. of a pale yellow oil which could not be crystallized but which showed expected absorption for a mono-α-, di-β-substituted, α,β-unsaturated ketone, λ_{max} 251 mμ (log ϵ 4.1).[29] Its infrared spectrum showed absorption maxima at 5.77, 6.05 and 6.22 μ.

Ozonization of Cativic Acid.—Ozonizations of cativic acid were generally carried out in ethyl acetate solution at −50° in concentrations varying from 10–20%. Similar results described below were obtained in carbon tetrachloride, chloroform, methanol and *n*-pentane solutions up to 0°. The presence or absence of moisture appeared to have little effect on the course of the reaction which was considered complete when the effluent gases passing through the ozonide solution began to oxidize potassium iodide in saturated aqueous boric acid.

The white, crystalline product which separated from solution during the course of the ozonization in *ca.* 30% yield proved to be quite stable, resisting the action of boiling water or hydrogenolysis in the the presence of Adams catalyst in ethanol at room temperature. It was recrystallized from aqueous methanol to m.p. 137–138° dec.: mol. wt. Rast, 343 (354); neut. equiv., 355 (354).

Anal. Calcd. for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 68.03; H, 9.84.

The substance gave positive starch–iodide, iodoform, Schiff, Tollens tests and negative tetranitromethane reaction. It was soluble in sodium bicarbonate and gave no crystalline oxime derivative. The compound showed no ultraviolet absorption but gave infrared bands at 3.02 (hydroxyl), 5.77 and 5.90 μ (carbonyl).

The mother liquors from the crystalline ozonolysis product were concentrated to an orange, intractable oil. This oil yielded no additional information. Decomposition attempts by treatment of the ozonolysis product with boiling water failed to fragment the molecule as shown by the neutralization equivalent of the oily product (300) and the absence of any neutral, water-soluble or low molecular weight acidic products. Attempts to isolate easily volatile degradation products were likewise unsuccessful.

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[29] Calcd. λmax 249 mμ: L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 192.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Structure and Reactions of Gossypol. IV. The Synthesis of Desapogossypol Hexamethyl Ether[1,2]

BY DAVID A. SHIRLEY AND WALTER L. DEAN[3]

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1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-2,2′-binaphthyl has been synthesized and found to be identical with desapogossypol hexamethyl ether, a degradation product of gossypol.

The extensive work of Professor Roger Adams and students on the structure of gossypol, the principal pigment of cottonseed, led to the postulation of structure X for this molecule. While a large amount of evidence was accumulated in support of this structure, an uncertainty remained in the relationship of the positions of the methyl groups and binaphthyl linkage to the positions of the other groups. An alternative possibility was the binaphthyl linkage at the 3,3′-position and the methyl groups in the 2,2′-positions. It was the objective of this research to synthesize desapogossypol hexamethyl ether (VIII) in order to answer this question as well as to provide additional general information on the structure of gossypol. After completion of this work,[4] there was reported the synthesis of a compound corresponding to the one postulated for apogossypol hexamethyl ether (IX) and the identity of the synthetic product with that obtained from gossypol.

The preparation of 3-methyl-6,7-dimethoxy-1-tetralone (I) has been reported in an earlier paper from this Laboratory[5] and by other workers.[6-8] The tetralone was converted to the 2,2-dibromo derivative II in essentially quantitative yield. Dehydrobromination of II with pyridine gave the naphthol III in about 40% yield and methylation in about 70% yield produced 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene. It was found best to carry out the dehydrobromination and methylation in one step using sodium methoxide and methyl sulfate in methanol. This produced V directly from II in about 70% yield. Oxidation of the naphthol III with potassium nitrosyl disulfonate produced the quinone IV which showed an ultraviolet absorption spectrum characteristic of the 1,4-naphthoquinone system. Direct formation of the Grignard reagent of V could not be accomplished, and use of the entrainment method with a large ex-

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[1] A report of work carried out under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Utilization Research Branch of the Agricultural Research Service.

[2] Preceding paper: D. A. Shirley and W. C. Sheehan, *J. Org. Chem.*, **21**, 251 (1956).

[3] From a dissertation presented in December, 1955, by Walter L. Dean to the University of Tennessee in partial fulfillment of the requirements for the Ph.D. degree.

[4] J. D. Edwards and J. L. Cashaw, THIS JOURNAL, **78**, 3224 (1956).

[5] D. A. Shirley and W. L. Dean, *ibid.*, **77**, 6077 (1955).

[6] J. D. Edwards and J. L. Cashaw, *ibid.*, **76**, 6188 (1954).

[7] R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 807 (1938).

[8] W. Borsche and J. Neimann, *Ann.*, **502**, 264 (1933).