[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Structures of the Triterpenes Friedelin and Cerin[1,2]

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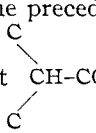
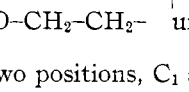
The chemical and physical data leading to the assignment of structure XXXVII to friedelin and to the formulation of cerin as 2α-hydroxyfriedelin are presented.

The substituents of cork have been the subject of numerous researches for the past 150 years, and over this period a considerable number of pure substances have been isolated and characterized.[3] The structures of all of these compounds have been elucidated with the exception of two related triterpenes, friedelin and cerin, which have posed the most formidable structural problem. Although a number of investigators, commencing with Chevreul in 1807,[4] carried out the isolation of the friedelin–cerin mixture from cork, it remained for Drake[5] and his students to establish the formulas of friedelin and cerin and to carry out the pioneering structural studies.[6] The work of Drake and his colleagues established a number of important facts. Friedelin possesses the molecular formula $C_{30}H_{50}O$ and is a saturated pentacyclic ketone. It can be converted to enol esters, carbonyl derivatives and to the saturated parent hydrocarbon friedelane. Cerin is α-hydroxyfriedelin[7] and the hydroxyl group is secondary. Clemmensen reduction of cerin affords friedelane, reaction of cerin with phosphorus tribromide gives a bromoketone which is converted to friedelin upon reduction,[6] and oxidation of cerin affords a dicarboxylic acid $C_{30}H_{50}O_4$ without loss of carbon.[6] Chromic acid oxidation of friedelin affords a keto acid, friedelonic acid, $C_{30}H_{50}O_3$ without loss of carbon[8] which, together with the preceding data, indicates the presence of the unit  in friedelin. Dehydrogenation (by means of selenium at 315°) of one of the epimeric secondary alcohols derived by reduction of friedelin affords 1,2,7-trimethylnaphthalene, 1,2,8-trimethylphenanthrene and 1,8-dimethylpicene.[9] The formation of the last product, which contains all but six of the carbon atoms in friedelin, is especially significant since this substance is also formed from the pentacyclic triterpenes of the α- and β-amyrin series.[10]

Following the early work of Drake, Ruzicka and his co-workers[11,12] carried out a sequence of oxidative degradations on friedelin. Oxidation of friedelin gave the C_{30} dicarboxylic acid previously obtained from cerin, which was converted by pyrolysis to a C_{29} saturated ketone, norfriedelanone. Oxidation of norfriedelanone with selenium dioxide in glacial acetic acid at reflux yielded an unsaturated C_{29} ketone, norfriedelenone and more drastic oxidation with selenium dioxide in dioxane at 200° afforded an α,β-unsaturated 1,2-diketone which was regarded as a C_{29} substance and termed "norfriedelendione." Further oxidation of the unsaturated 1,2-dione led to a C_{25} saturated tetracyclic ketone and a C_{26} β,γ-unsaturated acid.[13]

From these data it is apparent that friedelin and cerin belong to a new class of pentacyclic triterpenes differing from the known α-amyrin, β-amyrin and lupeol types. The present work was undertaken to determine the structures of these triterpenes and their relationship to the known classes.

The starting point for the present work was the assumption that friedelin possesses partial carbon skeleton I as indicated by the formation of 1,8-dimethylpicene by dehydrogenation with selenium under conditions which do not promote drastic rearrangement.[14] The assumption was also made that the unit –CH–CH–CO–CH_2–CH_2–C is present in friedelin as proposed by the Swiss workers[11] on the basis of the preparation of norfriedelendione. We were able to establish easily the presence of the –CH–CO–CH_2–CH_2– unit in friedelin from the finding that norfriedelanone, the C_{29} ketone obtained by pyrolysis of the anhydride of the C_{30} dicarboxylic acid described above, exchanges three hydrogens for deuterium in the presence of excess deuterium bromide in methylene chloride solution. The assumption of partial carbon skeleton I and the presence of the  unit limits the oxo function of two positions, C_1 and C_3. Proof of the

(1) Submitted to the Organic Division of the American Chemical Society in March, 1955, and presented at the 14th National Organic Symposium, Abstracts, p. 81. Preliminary communications: THIS JOURNAL, **77**, 3667, 3668 (1955).

(2) Taken from the Ph.D. dissertation of Joseph J. Ursprung, University of Illinois, 1955.

(3) For a review see I. Ribas-Marques, *Chemie et Industrie (Paris)*, **68**, 333 (1952).

(4) (a) M. Chevreul, *Ann. Chim.*, **62**, 323 (1807); **96**, 141 (1815); (b) Ch. Friedel, *Bull. soc. chim.*, [3] **7**, 164 (1892); (c) V. H. Thoms, *Pharm. Zent.*, **39**, 699 (1898); (d) C. Istrati and A. Ostrogovich, *Compt. rend.*, **128**, 1581 (1899).

(5) N. L. Drake and R. P. Jacobsen, THIS JOURNAL, **57**, 1570 (1935).

(6) For a brief summary of this work see, N. L. Drake, Abstracts Ninth National Organic Symposium, p. 7.

(7) N. L. Drake and S. A. Shrader, THIS JOURNAL, **57**, 1854 (1935).

(8) N. L. Drake and W. P. Campbell, *ibid.*, **58**, 1681 (1936); N. L. Drake and J. K. Wolfe, *ibid.*, **61**, 3097 (1939).

(9) N. L. Drake and W. T. Haskins, *ibid.*, **58**, 1684 (1936).

(10) See D. H. R. Barton in Rodd, "Chemistry of Carbon Compounds," Elsevier Pub. Co., New York, N. Y., 1953, p. 726.

(11) L. Ruzicka, O. Jeger and P. Ringnes, *Helv. Chim. Acta*, **27**, 972 (1944).

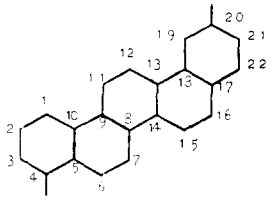
(12) G. W. Perold, K. Meyerhans, O. Jeger and L. Ruzicka, *ibid.*, **32**, 1246 (1949).

(13) For a more complete summary of the reactions and degradative studies which have been carried out on friedelin see Elsevier, "Encyclopedia of Organic Chemistry," Vol. XIV, Elsevier Publishing Co., New York, N. Y., 1940, p. 588, and Vol. XIV, Supplement.

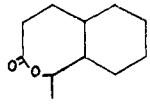
(14) Pl. A. Plattner in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 21.

location of the oxygen at C_3, which seemed most reasonable for biosynthetic reasons,[15] was obtained in a number of ways.

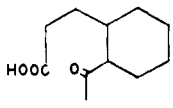
Oxidation of friedelin with peracetic acid proceeds to give a lactone, $C_{30}H_{50}O_2$ (II),[8] carbonyl absorption 1737 cm.$^{-1}$, which is converted by further oxidation with chromic acid to the known keto acid friedelonic acid, $C_{30}H_{50}O_3$ (III).[8] This process is far superior to the earlier method of preparing the C_{30} keto acid by direct chromic acid oxidation of friedelin. Oxidation of friedelonic acid with warm peracetic acid results in the loss of two carbon atoms with the formation of a six-membered lactone (IV), $C_{28}H_{46}O_2$, carbonyl absorption 1740 cm.$^{-1}$, indicating that an acetyl group is present in friedelonic acid which is lost as acetic acid during the oxidation. Peracetic acid attack in the normal Baeyer–Villiger reaction would produce an acetate from a methyl ketone. Lactonization of the acetoxy acid could then occur *via* a carbonium ion or the hydroxy acid produced by hydrolysis.



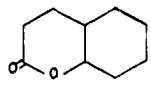
I



II

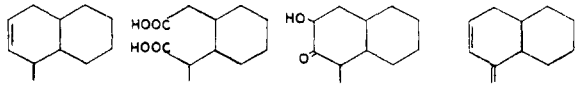


III



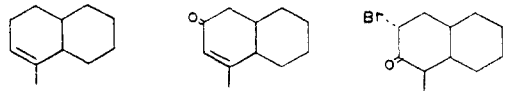
IV

A second piece of evidence for the presence of the carbonyl function at C_3 adjacent to a methyl group at C_4 was obtained starting with an olefin "friedelene" which had been prepared previously from friedelin[8] by reduction with sodium–amyl alcohol to friedelanol, esterification of the alcohol with benzoyl chloride and pyrolysis of the benzoate. Proof that this friedelene is the Δ^2-olefin V was obtained in several ways: (1) oxidation with potassium permanganate gave the known C_{30} dicarboxylic acid VI, (2) the same olefin is formed in excellent yield by Wolff–Kishner reduction elimination of cerin (VII),[16,17] and (3) the same olefin is formed by pyrolysis of either epimeric benzoate, excluding a Δ^3-structure if only *cis*-elimination can occur as seems likely. In addition the ultraviolet absorption of this friedelene indicates that the double bond is disubstituted.[18] Bromination of Δ^2-friedelene gives a stable dibromide which undergoes dehydrobromination with alkali to form a conjugated diene, the ultraviolet spectrum of which (λ_{max} 241 mμ, log ϵ 4.3) indicates a nonhomoannular, s-*trans* arrangement of the double bonds which requires an exocyclic double bond. These data, together with the occurrence of absorption at 878 cm.$^{-1}$ in the infrared characteristic of a terminal methylene group, make it apparent that the diene has the partial structure VIII which necessitates the location of the carbonyl function at C_3 in friedelin. Further evidence for the location of the oxygen at C_3 in friedelin follows from the data presented below. In the course of this work on Δ^2-friedelene and in connection with the



V VI VII VIII

data on brominated friedelin derivatives which follow, it became of interest to prepare Δ^3-friedelene, and this was accomplished in two steps from friedelin as follows. Whereas reduction of friedelin with sodium–alcohol produces friedelanol, reduction with lithium aluminum hydride yields the epimeric alcohol which has been designated as epifriedelanol.[6,19] From the methods of synthesis it is clear that the hydroxyl function in friedelanol and epifriedelanol is equatorial and axial, respectively, and, hence, these substances are designated as friedelanol (ax) and friedelanol (eq), respectively, in the following discussion. Treatment of friedelanol (ax) with *p*-toluenesulfonyl chloride pyridine at reflux affords an olefin which is different from Δ^2-friedelene and to which the Δ^3-structure IX is assigned. Oxidation of this olefin with sodium dichromate–acetic acid forms the same α,β-unsaturated ketone as is obtained from Δ^2-friedelene, presumably Δ^3-friedelen-2-one (X) (λ_{max} 237 mμ, log ϵ 4.1), indicating that the two olefins have the same carbon skeleton. The ultraviolet absorption of the new olefin in the region 205–220 mμ is much more intense than that of Δ^2-friedelene and indicates that the double bond is trisubstituted.



IX X XI

The presence of a methyl group at C_5 was shown in the following way. Direct bromination of friedelin with one mole of bromine in chloroform produces a 2-bromo derivative XI in which the bromine possesses the axial orientation, as is indicated by infrared and ultraviolet data (carbonyl absorption 1710 cm.$^{-1}$, 311 mμ; *cf*, corresponding values for friedelin: 1708 cm.$^{-1}$, 295 mμ).[20,21] The location of bromine at C_2 in this product was proved by successive treatment with sodium borohydride and zinc–acetic acid to yield Δ^2-friedelene.

By heating to 160° friedelin can be converted to an enol benzoate which is mostly the Δ^2-isomer.

(15) See L. Ruzicka, A. Eschenmoser and H. Heusser, *Experientia*, **9**, 357 (1953).

(16) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949), has reported that Wolff–Kishner reduction of cerin affords the saturated hydrocarbon friedelane. Using the same conditions employed by Huang-Minlon, we are able to detect only Δ^2-friedelene as the reduction product.

(17) For similar reduction elimination reactions see N. J. Leonard and S. Gelfand, *ibid.*, **77**, 3269, 3272 (1955).

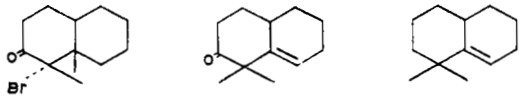
(18) Using the method of P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(19) Epifriedelanol has also been isolated from natural sources: P. R. Jeffereies, *ibid.*, 473 (1954); T. Bruun, *Acta Chem. Scand.*, **8**, 71 (1954).

(20) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(21) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

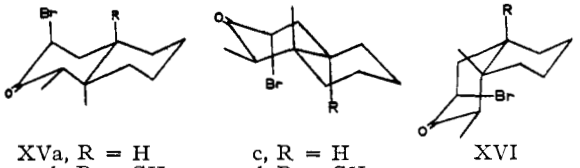
At higher temperatures (180–190°), however, a product which is largely the Δ^3-enol benzoate is formed. Bromination of this high temperature enol benzoate produces the 4-bromo derivative of friedelin XII. The axial orientation of bromine in this bromoketone is apparent from spectral data (carbonyl absorption 1715 cm.$^{-1}$, 310 mμ) and the location of bromine at C_4 follows from conversion in two steps to Δ^3-friedelene. Both bromoketones undergo debromination with zinc–acetic acid–ether to yield friedelin.[22] Whereas 2-bromofriedelin is relatively inert to silver acetate in acetic acid solution at steam-bath temperature, the 4-bromo isomer is readily dehydrobrominated to an unconjugated unsaturated ketone which is not isomerized to a conjugated structure by prolonged treatment with strong acid. In addition, the ultraviolet absorption of this substance indicates that the double bond is probably trisubstituted. The production of the non-conjugated non-isomerizable ketone from 4-bromofriedelin indicates that migration of an alkyl group, most probably methyl, from C_5 to C_4 has occurred during the dehydrobromination process and on this basis the formulation XIII is suggested. Wolff–Kishner reduction of XIII gives an unsaturated hydrocarbon XIV, different from Δ^2- and Δ^3-friedelenes and not isomerizable by heating at reflux with dilute ethanolic sulfuric acid. The stability of the olefin XIV to isomerization as well as its ultraviolet absorption indicates that the double bond occupies the position indicated.



XII XIII XIV

At this point it became possible to draw several conclusions as to the stereochemistry of ring A in friedelin. First of all, friedelan-2,3-dione which is prepared by gentle hydrolysis of 2-ketofriedelin enol benzoate, is not isomerized by prolonged treatment with acid indicating that the A/B ring fusion in friedelin is not susceptible to change by epimerization at C_{10} *via* the Δ^2,1:10-dienediol. This finding indicates that the A/B fusion cannot be *cis* with an equatorial hydrogen at C_{10}. Since, as will be brought out later, there must be a hydrogen at C_{10}, one of the two possible *cis* A/B fusions can be ruled out.

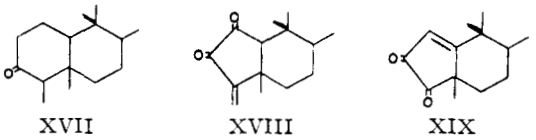
Further stereochemical evidence can be gained from 2- and 4-bromofriedelin. The asymmetric center at C_2 in 2-bromofriedelin is not epimerizable with hydrogen bromide under conditions which result in further bromination, and, hence, the axial orientation of bromine in 2-bromofriedelin is the stable one. This finding rules out all but one of remaining stereochemical possibilities for the A/B fusion, XV and XVI. In structure XV C_2 would be epimerizable if R = CH_3, but not if R = H,[23] so that only the latter possibility is acceptable. In structure XVI C_2 would be epimerizable to a more stable configuration regardless of whether R = H or CH_3, and so both of these possibilities are inadmissible. Friedelin must, therefore, have a *trans*-A/B juncture with a hydrogen at C_{10}.



XVa, R = H
b, R = CH_3
c, R = H
d, R = CH_3
XVI

The change in molecular rotation due to axial bromine at C_2 (ΔM_D −651°) is opposite in direction to that due to axial bromine at C_4 (ΔM_D + 614°). The sign of these shifts taken together with molecular rotation data on axial α-bromoketosteroids of known absolute configuration[24] reveals that bromine is α-oriented in both 2- and 4-bromofriedelin and that the methyl at C_5 is β and the hydrogen at C_{10} is α, *i.e.*, of the two structures of different absolute configuration XVa and XVc only XVc is acceptable using this criterion.

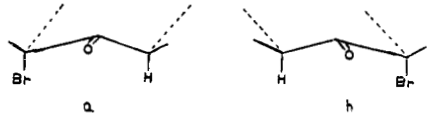
As mentioned earlier Ruzicka and co-workers[11,12] obtained a saturated C_{25}-ketone and an unsaturated C_{26}-acid, both tetracyclic and of unknown structure, by oxidation of the unsaturated 1,2-diketone which they designated as norfriedelendione, $C_{29}H_{44}O_2$. The structures of these two tetracyclic degradation products follow from the data which have been presented concerning the A ring and their mode of formation. Furthermore, it was possible to use these degradation products to probe still further into the structure of the friedelin molecule. The tetracyclic ketone and unsaturated acid were made readily available by the development of an expeditious preparation of "norfriedelendione" involving dichromate oxidation of friedelin enol benzoate to 2-ketofriedelin enol benzoate followed by vigorous oxidation with selenium dioxide (dioxane, 200°). The structure of the "norfriedelendione" of Ruzicka which follows from our partial structure XVII for friedelin and from the molecular formula $C_{29}H_{44}O_2$ is XVIII. It has been pointed out by Spring, *et al.*,[25] that structure XIX, a bisnorfriedelendione requiring a formula $C_{28}H_{42}O_2$, fits the analytical data[11] as well as XVIII. We have been able to obtain support for the bisnor structure XIX by deuterium exchange studies with deuterium bromide–methylene chloride. On the basis of structure XVIII one hydrogen should be replaceable by deuterium with hydrogen bromide,



XVII XVIII XIX

(22) See E. J. Corey and R. A. Sneen, THIS JOURNAL, in press.
(23) E. J. Corey, *ibid.*, **76**, 175 (1954).

(24) An axial bromine in the unit (a) makes a levorotatory contribution whereas that in the mirror-image unit (b) makes a dextrorotatory contribution.



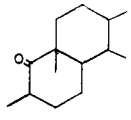
a b

For example, ΔM_D for 5α-bromo-6-ketocholestanyl acetate is −645° while that for 7α-bromo-6-ketocholestanyl acetate is +269°.

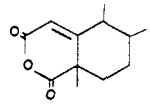
(25) G. B. Brownlie, F. S. Spring, R. Stevenson and W. S. Strachan, *Chem. and Ind.*, 1156 (1955).

whereas with structure XIX none of the hydrogens should be exchangeable. In fact no exchange did take place between the unsaturated 1,2-diketone and hydrogen bromide even after a contact time of several days, thus confirming structure XIX.[26]

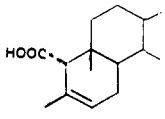
The formulation of the tetracyclic C_{25} saturated ketone follows reasonably from XIX (or the previously accepted XVIII) only if there is a hydrogen at C_{10} in friedelin and is that expressed by partial structure XX. This substance is formed from bisnorfriedelendione by oxidation with hydrogen peroxide to form the six-membered cyclic anhydride XXI followed by ozonolysis and digestion of the ozonide with boiling water. It contains only one α-hydrogen as is shown by deuterium exchange experiments (1.0 deuterium atoms per molecule introduced with excess deuterium bromide in carbon tetrachloride). This fact together with the presence of a methyl group at C_5 in friedelin locates the oxygen function at C_{10} (original numbering, see I) and, further, indicates the presence of a methyl group at C_9. The formation of the C_{25} ketone can be rationalized as proceeding from the ozonide *via* the β-keto acid with a carboxyl substituent at C_5 alpha to the 10-ketone.



XX

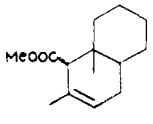


XXI

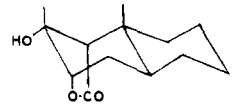


XXII

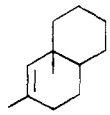
Reaction of bisnorfriedelendione with alkaline hydrogen peroxide results in the loss of two carbon atoms with the formation of the β,γ-unsaturated acid, $C_{26}H_{42}O_2$, XXII. The presence of an unconjugated carboxyl group in the C_{26} unsaturated acid is indicated by its infrared spectrum (unconjugated carbonyl absorption at 1705 cm.$^{-1}$) together with that of the corresponding methyl ester XIII (unconjugated carbonyl absorption 1740 cm.$^{-1}$) and by the formation of a hydroxylactone (formulated as XXIV) with osmium tetroxide.[12] The location of the double bond in XXII in the β,γ-position follows from the ease with which it undergoes decarboxylation upon heating[12] to produce a mixture of isomeric C_{25}-olefins, which probably consists of XXV, the primary product of decarboxylation,[27,28] and XXVI which is formed by isomerization of XXV. Treatment of the olefin mixture with dilute ethanolic sulfuric acid affords the more stable olefin XXVI in pure condition.[12] The ultraviolet absorption of XXVI and also that of the sodium salt of the C_{26} acid XXII indicates that the double bond is trisubstituted in both cases.



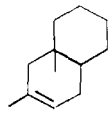
XXIII



XXIV

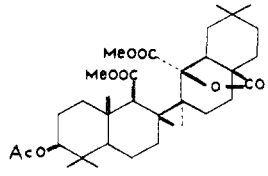


XXV



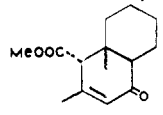
XXVI

This location of the double bond is considerably more stable than the alternative location expressed in XXV as is indicated clearly by the fact that the methyl ester XXIII is not isomerized by treatment with methanolic sulfuric acid, despite the electronic stabilization which would result from a conjugated system. The carboxyl group in the β,γ-unsaturated acid is assigned the axial (α) orientation because of its conversion to the hydroxylactone XXIV which would be expected only for the axial epimer. From the above isomerization experiment it would also appear that the axial orientation of the carboxyl is more stable than the equatorial orientation, a situation which demands that the substituents at the B/C fusion be $8\alpha,9\beta$ (*trans*) or $8\beta,9\beta$ (*cis*) and not $8\alpha,9\alpha$ (*cis*). An analogous stereochemical situation has been observed with acetyloleanolic lactone-11,12-*seco*-dicarboxylic acid methyl ester (XXVII),[29,30] one of the carbomethoxy groups of which can be transposed from the less stable equatorial to the more stable axial orientation by equilibration with base.

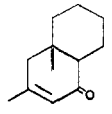


XXVII

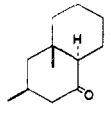
The methyl ester of the C_{26} β,γ-unsaturated acid XXIII was used to gain further structural and stereochemical information in the following way. Oxidation of the ester with sodium dichromate-acetic acid afforded the unsaturated keto ester XXVIII in which the double bond is conjugated with the ketone carbonyl as indicated by its ultraviolet absorption (λ_{max} 247 mμ, log ϵ 3.97) and infrared spectrum (absorption at 1742 and 1670 cm.$^{-1}$ due to nonconjugated ester and conjugated ketone carbonyl groups, respectively). Alcoholysis of the keto ester XXVIII by ethanol-sodium ethoxide yielded the unsaturated ketone XXIX, λ_{max} 248 mμ, log ϵ 3.94, identical to the product which results from dichromate oxidation of the C_{25} olefin XXVI. Hydrogenation of XXIX with palladium-on-charcoal as catalyst gave the saturated tricyclic ketone XXX which contains three α-hydrogens as determined by deuterium bromide-catalyzed deuterium exchange (found 2.9). Consequently there must be a hydrogen attached to C_8 of friedelin.



XXVIII



XXIX



XXX

(26) Evidence has also been obtained for structure XIX by M. Sternburg on the basis of an X-ray crystallographic molecular weight determination, private communication from Dr. G. Ourisson.

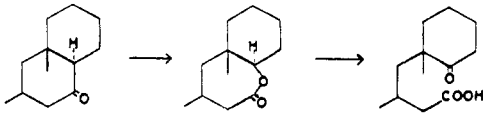
(27) R. T. Arnold, O. C. Elmer and R. M. Dodson, THIS JOURNAL, **72**, 4359 (1950).

(28) D. H. R. Barton and C. W. Brooks, *J. Chem. Soc.*, 257 (1951).

(29) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **19**, 114 (1936).

(30) See also D. H. R. Barton, *Chem. and Ind.*, 664 (1953).

Additional proof was obtained by two-step oxidation of XXX to a keto acid as shown



XXX

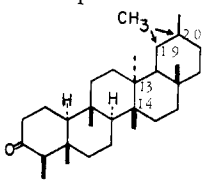
The ketone XXX is not epimerizable at C_8 indicating that the substituents at the B/C ring fusion possess the $8\beta,9\alpha$-orientation and not the $8\alpha,9\beta$-orientation. The *trans*-locking of rings B and C is also indicated strongly by the stability of the double bond between C_5 and C_6 (numbering of structure I) in the C_{26} unsaturated acid XXII, the corresponding methyl ester XXIII and the C_{25} olefin XXVI, since this indicates a *trans*-octalin system for rings B and C.[31] Further evidence that rings B and C, and also rings C and D, in friedelin are *trans*-locked follows from the molecular dimensions ($^1/_4$ unit cell) of friedelan-3α-ol chloroacetate, 16.5 × 6.5 × 6.9 Å. as determined by X-ray single crystal studies.[31,32]

At this point it was possible to locate the four remaining methyl groups in friedelin as follows. Methyl groups must be present at C_{13} and C_{14} since 1,2,7-trimethylnaphthalene (XXXI) and 1,-2,8-trimethylphenanthrene (XXXII) which are formed by dehydrogenation of friedelan-3α-ol[9] (frie-

XXXI XXXII

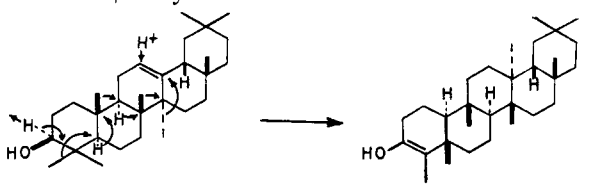
delanol (ax)) can only be accounted for on this basis. In addition the presence of a third methyl group at C_{17} and a fourth at C_{19} or C_{20} are highly probable on biosynthetic grounds[15] because of the probable common genesis of friedelin and the other pentacyclic triterpenes from squalene.

These considerations led us to the expanded formula XXXIII for friedelin and made clear a most interesting relationship between friedelin and



XXXIII
XXXVI, CH_3 at C_{20}

α-amyrin or β-amyrin since XXXIII may be derived from the amyrin structures by a sequence of 1,2-shifts of methyl groups and hydrogen atoms away from ring A and toward ring E, as is illustrated for β-amyrin



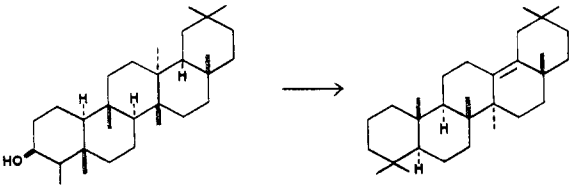
β-Amyrin friedelin (enol)

(31) *Cf.* methyl iodoacetyloleanolate, 16.1 × 6.3 × 7.7 Å.

(32) A. M. Abd El Rahim and C. H. Carlisle, *Chem. and Ind.*, 279 (1954).

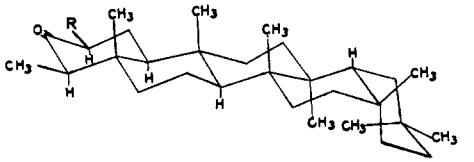
Such a relationship was shown, in fact, to exist by the discovery of a direct correlation of friedelin with β-amyrin.

Treatment of friedelan-3β-ol (XXXIV), in which the hydroxyl group is axial with a variety of acidic reagents causes a multi-group rearrangement which affords the known olean-13(18)-ene (XXXV), identified by m.p. and mixture m.p. with an authentic sample, by conversion to the corresponding epoxide and also by conversion to the known and easily recognized olean-11,13(18)-diene. The rearrangement also proceeds well with Δ^3-friedelene and somewhat less readily with Δ^2-friedelene, the optimum results (55% yield) so far having been obtained from (ax) friedelan-3β-ol and hydrogen chloride in phenol at 110°.



XXXIV XXXV

The conversion of the friedelin derivatives mentioned above to olean-13(18)-ene proves the location of methyl groups at C_{17} and C_{20} as in β-amyrin and, together with the degradative work, establishes structure XXXVI for friedelin, which is complete except for the orientation of the hydrogen at C_{18}.[33,34] The biosynthetic pathway for the conversion of β-amyrin into friedelin illustrated above provides an indication that the hydrogen at C_{18} possesses the β-orientation (D/E *cis*) as in β-amyrin[35] and α-amyrin[36,37] which is confirmed by a 2-dimensional Fourier X-ray analysis on friedelan-3α-ol chloro- and bromoacetates (see Experimental for preparation) made in these laboratories by Dr. I. H. Riley which will be reported separately (see Fig. 1). Structure XXXVII is therefore proposed for friedelin. The formulation



XXXVII, friedelin, R = H
cerin, R = OH

of cerin as 2β-hydroxylfriedelin follows from the location of the hydroxyl and from the fact that the hydroxyl is very easily acylated or sulfonated (equatorial orientation).

The interesting structural relationship between friedelin and the other known pentacyclic triter-

(33) The rearrangement of Δ^2-friedelene to olean-13(18)-ene was carried out at E. T. H., Zurich, after our structure XXXVI was communicated thereto (April, 1955) and has subsequently been reported, H. Dutler, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **38**, 1268 (1955).

(34) This structure has also been adopted by Spring, *et al.* (reference 25, *cf.* Spring, *et al.*, *Chem. and Ind.*, 686 (1955), and by G. Ourisson and T. Takahashi, *ibid.*, 1155 (1955).

(35) D. H. R. Barton and N. J. Holness, *J. Chem. Soc.*, 78 (1952).

(36) E. J. Corey and J. J. Ursprung, THIS JOURNAL, **78**, 183 (1956).

(37) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

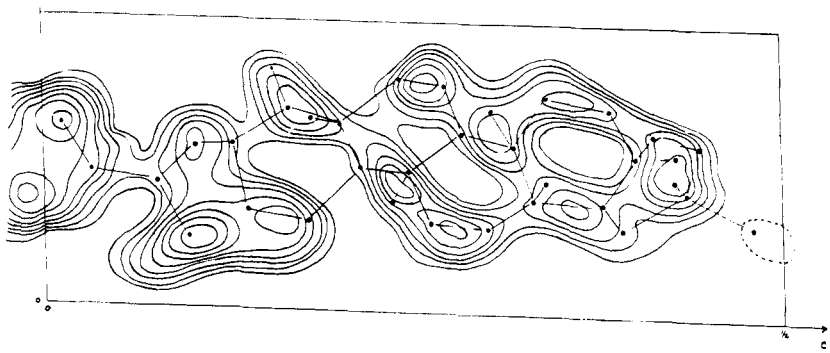


Fig. 1.—Electron density map of friedelan-3α-ol chloroacetate.

penes prompts a certain amount of conjecture with regard to its function in the plant. One simple possibility is that friedelin serves to provide a coating of unusually hydrophobic character which protects certain cells of the plant. Such a function is not unreasonable for friedelin and for its derivative friedelan-3β-ol, which also occurs naturally,[19] since these substances are far less soluble in hydroxylic solvents than any of the other known triterpenes, *e.g.*, β-amyrin, α-amyrin and lupeol. On this basis it seems quite reasonable that friedelin should occur where a protective coating might be needed as, for example, in barks, in lichens and as a waxy layer on the exterior of bamboo stalks.[38] It seems especially natural that plants with less dense, more porous bark, such as cork,[39] would develop such a hydrophobic coating during evolution. Thus, the need for a hydrophobic protective coating may have been the factor directing triterpene synthesis beyond β-amyrin and to friedelin during the evolutionary development of such plants. It is also possible that friedelin plays a more chemical role in plant systems, for example, as the precursor of more highly oxygenated, physiologically active substances.

Acknowledgments.—The assistance of Messrs. H. C. Huang, D. F. Joesting and R. G. Schultz in the isolation of friedelin and the preparation of certain intermediates and of others as mentioned in the Experimental is gratefully acknowledged. We are indebted also to the Eli Lilly Company for financial support and to the Armstrong Cork Company and Mr. R. B. Rohrer for supplies of crude cork wax.

Experimental[40]

Isolation of Friedelin.—Friedelin and cerin were isolated from ground cork by the procedure described by Drake and Jacobsen.[5] A more convenient source of friedelin proved to be a black wax provided by the Armstrong Cork Company which had been obtained in the process of making cork board from ground cork under pressure by treatment with superheated steam. The wax is distilled out of the cork by the steam and condenses in the steam exit ducts.

One kg. of finely ground crude cork wax was stirred overnight with 1 gal. of acetone, and the acetone-leached product was collected by suction filtration and washed further with acetone. The dried material so obtained (540 g.) was stirred with 2.3 l. of chloroform overnight and filtered using celite. One-half of the filtrate was passed through a 180 × 7 cm. glass column containing 600 g. of unground Nuchar which had been wetted down with chloroform before being placed in the column. The column was washed with chloroform until no substantial amounts of material were eluted. Liter fractions were taken and a total of 8 liters was collected. A total of 309.8 g. of crude friedelin was obtained in this way from the original chloroform solution. Recrystallization from methylene chloride–ethyl acetate gave *ca.* 200 g. of material which was satisfactory for most purposes, m.p. 250–255°. Further recrystallization afforded pure friedelin, m.p. 267.3–269.5° (vacuum capillary).

3,4-*seco*-Friedelonic Acid (III).—A solution of 5 g. of friedelin in 200 ml. of chloroform was treated with 20 ml. of 40% peracetic acid. After 12 hr. at 65° the chloroform solution was evaporated to a small volume and 50 ml. of acetic acid was added to the mixture. The remainder of the chloroform was removed under vacuum. Dilution with water gave 4.95 g. of a lactone mixture, m.p. 260–275°; infrared$_{max}$ (carbon disulfide) 1737 cm.$^{-1}$.

The crude reaction product was dissolved in one liter of acetic acid. To the stirred solution at room temperature was added 50 ml. of sulfuric acid, 100 ml. of water and 2.5 g. of chromic anhydride. After stirring for 48 hr. the green reaction mixture was treated with methanol and concentrated to *ca.* 150 ml. under vacuum. Slow dilution with water gave 3.9 g. of a green solid which was dissolved in ether and shaken with 10% sodium hydroxide solution. Centrifugation rendered the insoluble sodium salts compact at the interface. After decanting the ether, the aqueous suspension was washed several times with fresh ether and the ether was decanted in the same way after centrifuging. The suspension of sodium salt in water was warmed on a steam-bath for 1 hr. to remove residual ether and then acidified with dilute hydrochloric acid. Heating on a steam-bath served to coagulate the acid which was filtered and crystallized from ethanol–water to give 2.55 g. (48% from friedelin) of 3,4-*seco*-friedelonic acid, m.p. 200–210° dec.; infrared$_{max}$ (carbon disulfide) 1707, 2500–3400 cm.$^{-1}$.

Esterification with diazomethane yielded methyl 3,4-*seco*-friedelonate as colorless needles from methanol, m.p. 158–159°; infrared$_{max}$ (carbon disulfide) 1739, 1700 cm.$^{-1}$ $[\alpha]^{25}D$ +11.8° (*c* 1.098).[11]

C_{28}-Lactone IV.—A solution of 1.5 g. of 3,4-*seco*-friedelonic acid in 15 ml. of chloroform was treated with 20 ml. of 40% peracetic acid. A few drops of sulfuric acid were added and the solution was allowed to stand at room temperature for 15 days. During this time white plates had separated and were filtered and dried. The mother liquors were treated with another 10 ml. of 40% peracetic acid and allowed to stand for a further 6 days. The mixture was diluted with chloroform, extracted with 10% aqueous sodium hydroxide solution, and the chloroform solution was dried and evaporated. This residue along with the plates filtered previously (a total of 490 mg.) was dissolved in methylene chloride, adsorbed on a column of alumina and eluted with methylene chloride. Four crystallizations from methylene chloride–cyclohexane gave colorless, elongated plates of m.p. 228–235°; infrared$_{max}$ (carbon disulfide) 1738 cm.$^{-1}$; $[\alpha]^{25}D$ +9.6° (*c* 0.84).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. C, 80.83; H, 11.07.

Friedelan-3α-ol.[8]—To a boiling solution of 4 g. of friedelin in 300 ml. of amyl alcohol was added, in small quantities, 8 g. of sodium. The solution was refluxed until all the sodium had dissolved, then steam distilled to remove the alcohol. Crystallization of the solid residue from benzene–ethyl acetate gave 3 g. (75%) of colorless, elongated plates of friedelan-3α-ol, m.p. 302–304°; $[\alpha]^{25}D$ +16.2° (*c* 0.68).

Friedelan-3α-ol Benzoate.[8]—To one gram of friedelan-3α-ol dissolved in 45 ml. of boiling, dry pyridine was added 5 ml. of benzoyl chloride. The solution was refluxed for 30 minutes, diluted with 100 ml. of ethanol and the product

(38) F. C. Chang, Ph.D. thesis, Harvard University, 1941.

(39) The bark of *Quercus suber*, Cork Oak.

(40) All melting points are corrected. Molecular rotations were determined in reagent-grade chloroform as the solvent. The ultraviolet spectra were run in 95% ethanol solution unless otherwise designated. We are indebted to Mr. Jozsef Nemeth and associates for microanalyses and to Mr. James Brader for the infrared spectra.

was allowed to crystallize. After filtration, the product was crystallized from ethyl acetate to give 950 mg. (77%) of clear colorless lances, m.p. 250–251°.

Friedelan-3β-ol.—To a solution of 4.5 g. of friedelin in 50 ml. of dioxane heated on a steam-bath was added slowly, with swirling, 3 g. of lithium aluminum hydride. A vigorous reaction occurred. The dioxane solution was held at steam-bath temperatures for 30 minutes during which time the reaction had subsided. Ethyl acetate was added cautiously until excess lithium aluminum hydride was destroyed. The solution was diluted with water, extracted with large quantities of chloroform and the chloroform extract was dried and evaporated to a small volume. Friedelan-3β-ol crystallized from the chloroform as small, glittering plates. A second crystallization gave a pure product, m.p. 283.5–285°; $[\alpha]^{25}D$ +20° (*c* 0.44).[41,42]

Friedelan-3β-ol Benzoate.—Friedelan-3β-ol was benzoylated in the same manner as friedelan-3α-ol. Crystallization of the product from ethyl acetate gave plates of m.p. 252–254°; $[\alpha]^{25}D$ +34° (*c* 0.52).

Δ²-Friedelene (V).—In an atmosphere of nitrogen, 1.069 g. of friedelan-3α-ol benzoate was pyrolyzed at 300° for 2.5 hr. The pyrolysate was dissolved in chloroform and the chloroform solution was washed with 5% aqueous sodium hydroxide, followed by water and dried over anhydrous sodium sulfate. Charcoal was added to the chloroform solution, and the mixture was swirled for a few minutes, filtered through a cotton plug topped with Filter Cel and evaporated to *ca.* 25 ml. To the solution was added 20 ml. of ethyl acetate, and the chloroform was removed under vacuum. Filtration gave 660 mg. of clear, colorless plates. The mother liquors yielded a further 75 mg. of product. One further crystallization from ethyl acetate gave pure Δ²-friedelene, m.p. 257–258°; $[\alpha]^{25}D$ +47.5° (*c* 0.75); no absorption above 205 mμ.

Friedelan-3β-ol benzoate when treated in the same manner gave Δ²-friedelene in 86% yield.

Wolff–Kishner Reduction of Cerin.—A suspension of 200 mg. of cerin in 60 ml. of dry ethanol containing one gram of sodium and 3 ml. of hydrazine hydrate was sealed in a tube and heated to 190° for 5 hr. The reaction mixture was extracted with ether and the ether solution was washed thoroughly with water, dried and evaporated to dryness. Crystallization of the residue from methylene chloride–ethanol gave 160 mg. (86%) of Δ²-friedelene, m.p. 251–252°. A mixed melting point determination with an authentic sample of Δ²-friedelene, prepared by pyrolysis of friedelan-3α-ol benzoate, showed no melting point depression.

Permanganate Oxidation of Δ²-Friedelene.—A suspension of 700 mg. of powdered Δ²-friedelene and 1.19 g. of powdered potassium permanganate in 150 ml. of acetic acid was stirred at room temperature for 18 hr. Sodium bisulfite was then added to remove excess permanganate and the solution was diluted with water. The precipitated solid was filtered, dissolved in ether and the ether solution was extracted with 10% aqueous sodium hydroxide. Acidification of the alkaline extract gave a small amount of acid which was esterified with diazomethane. The ester was crystallized from ethanol to give 80 mg. of methyl 2,3-*seco*-friedelandicarboxylate, m.p. 174–176°. No melting point depression was observed when it was admixed with an authentic sample of methyl 2,3-*seco*-friedelandicarboxylate obtained by oxidation of cerin. The neutral fraction from the oxidation yielded 245 mg. of starting material.

Isofriedelene.—A solution of 14 g. of Δ²-friedelene in one liter of chloroform was saturated with dry hydrogen chloride gas. The solution was allowed to stand overnight at room temperature. The chloroform was removed, and the dried solid was chromatographed on alumina which had previously been activated at 330° under vacuum for 6 hr. The mixture of olefins was placed on the column with pentane which also eluted an isomeric friedelene which, after several crystallizations from methylene chloride–ethanol, melted at 218–219°; no ultraviolet absorption above 205 mμ, indicating a disubstituted double bond.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.75; H, 12.64.

Benzene–pentane (1:1) eluted the remaining 13 g. as Δ²-friedelene, m.p. 254–257°. When this was again treated with hydrogen chloride in chloroform another gram of isofriedelene was obtained.

Hydrogenation of isofriedelene in a mixture of cyclohexane and acetic acid (1:1) in the presence of Adams catalyst gave mainly Δ²-friedelene by isomerization of the double bond, m.p. 248–250°; no melting point depression when admixed with an authentic sample of Δ²-friedelene. A small amount (*ca.* 8%) of isofriedelene was recovered from the reaction mixture.

We regard both isofriedelene and friedelene as Δ²-olefins which are epimeric at C_4.

Δ²-Friedelene Epoxide.—A solution of 200 mg. of Δ²-friedelene in 20 ml. of chloroform was treated with an excess of perbenzoic acid. The solution was allowed to stand at room temperature for 7 days, evaporated to dryness and the solid residue was washed with ethanol. Crystallization from methylene chloride–ethanol gave 145 mg. (70%) of epoxidized Δ²-friedelene, m.p. 275–285°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.89; H, 11.68.

Isofriedelene Epoxide.—A yield of 135 mg. (65%) of isofriedelene epoxide from 200 mg. of isofriedelene was obtained using the above procedure. The oxide crystallized as fine needles of m.p. 218–230° from ethanol.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.11; H, 11.71.

2α,3β-Dibromofriedelane.—A solution of 30 mg. (0.0005 mole) of bromine in 3 ml. of methylene chloride was added to a suspension of 205 mg. (0.0005 mole) of Δ²-friedelene in 5 ml. of methylene chloride, and the mixture was swirled. The Δ²-friedelene dissolved immediately and fine needles began to separate. After the addition of 10 ml. of ethanol the methylene chloride was removed on a steam-bath. Long silky needles separated, were filtered and recrystallized four times from methylene chloride–ethanol to give 220 mg. of 2α,3β-dibromofriedelane, m.p. 217–218° dec.; $[\alpha]^{25}D$ −27.6° (*c* 1.015).

Anal. Calcd. for $C_{30}H_{50}Br_2$: C, 63.91; H, 8.65. Found: C, 63.38; H, 8.84.

Δ²,⁴-Friedeladiene (VIII).—To a solution of 300 mg. of 2α,3β-dibromofriedelane in 20 ml. of dioxane was added 1 g. of potassium hydroxide dissolved in 20 ml. of ethanol, and the solution was refluxed for 7 hr. The reaction mixture was diluted with water, extracted with ether and the ethereal extract was evaporated. Crystallization of the residue four times from methylene chloride–ethanol gave 60 mg. (28%) of Δ²,⁴-friedeladiene, m.p. 240–244°; infrared_{max} (Nujol) 878 $cm.^{-1}$; ultraviolet_{max} (cyclohexane) 241 mμ (log ε 4.3); $[\alpha]^{25}D$ +48.4° (*c* 0.805).

Anal. Calcd. for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 87.84; H, 12.32.

2,3-*seco*-Friedelandicarboxylic Acid (VI).—A solution of 106 mg. of chromic anhydride and 500 mg. of cerin in a mixture of 40 ml. of acetic acid and 25 ml. of carbon tetrachloride was shaken at room temperature for 6 hr. A further 86 mg. of chromic anhydride in 4 ml. of acetic acid was added and shaking was continued for 48 hr. The resulting violet solution was treated with a few drops of methanol and concentrated under vacuum to *ca.* 10 ml. Dilution with water gave, after filtration, 465 mg. of a slightly purple solid, m.p. 240–265°. The solid was stirred with 6 ml. of ice-cold chloroform, filtered and washed with another 5-ml. portion of ice-cold chloroform. Crystallization of the chloroform insoluble material from ethyl acetate yielded 275 mg. (52%) of pure 2,3-*seco*-friedelandicarboxylic acid, m.p. 288–290° dec.; infrared_{max} (Nujol) 1707, 2500–3500 $cm.^{-1}$; $[\alpha]^{25}D$ +21.4° (*c* 1.078).[11]

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.64. Found: C, 75.66; H, 10.56.

Dimethyl 2,3-*seco*-Friedelandicarboxylate.[11]—To a solution of 65 mg. of 2,3-*seco*-friedelandicarboxylic acid dissolved in the minimum amount of ether was added an ethereal solution of diazomethane until a yellow color persisted. After 2.5 hr. at room temperature the ether was evaporated and the residue was crystallized several times from chloroform–methanol to a constant melting point of 178.5–180°; infrared_{max} (chloroform) 1728 $cm.^{-1}$; $[\alpha]^{25}D$ +9.8° (*c* 1.02).[11] The yield of purified dimethyl 2,3-*seco*-friedelandicarboxylate was 62 mg. (90%).

2,3-*seco*-Friedelandicarboxylic Acid Anhydride.[11]—A solution of 200 mg. of 2,3-*seco*-friedelandicarboxylic acid in

(41) J. J. Lander and W. J. Svirbely, THIS JOURNAL, **66**, 235 (1944).
(42) T. Bruun and P. R. Jefferies, *Acta Chem. Scand.*, **8**, 1948 (1954).

5 ml. of acetic anhydride was heated on a steam-bath for 1 hr. The large, stout needles, which separated from the solution on cooling, were filtered and washed with petroleum ether. One further crystallization from acetic anhydride gave 158 mg. (82%) of pure 2,3-*seco*-friedelandicarboxylic acid anhydride of m.p. 270–272° dec.; infrared$_{max}$ (Nujol) 1755, 1802 cm.$^{-1}$; $[\alpha]^{25}D$ +74.6° (*c* 0.912).[11]

Norfriedelanone.[11]—Pure 2,3-*seco*-friedelandicarboxylic acid anhydride (1.5 g.) was heated above its melting point in an atmosphere of nitrogen. Vigorous evolution of carbon dioxide began immediately. When no further evolution of gas was apparent, the mixture was cooled and the pale yellow solid was crystallized from ethyl acetate to give 1.22 g. (90%) of glittering white plates, m.p. 234–236°. Several crystallizations from ethyl acetate and finally from ethanol raised the melting point to 239–240°; infrared$_{max}$ (carbon disulfide) 1738 cm.$^{-1}$; $[\alpha]^{25}D$ −83.7° (*c* 1.53)[11]; 2,4-dinitrophenylhydrazone, m.p. 258–259°.

Deuterium Exchange with Norfriedelanone.—A solution of 75 mg. of norfriedelanone, m.p. 239–240°, in 170 ml. of 0.22 *M* deuterium bromide in methylene chloride was maintained at room temperature in the dark in a glass-stoppered flask for 8 days. The solution was evaporated under reduced pressure and the residue was freed of traces of deuterium bromide by evaporation under reduced pressure with benzene. Recrystallization from methylene chloride–heptane gave 62 mg. of pure deuterated norfriedelanone, m.p. 238.5–239.5 (undepressed upon admixture with starting material) containing 6.2 excess atom per cent. deuterium (analysis by Mr. J. Nemeth using the falling drop method[43]) which corresponds to 2.97 deuterium atoms per molecule.

Norfriedelenone.[11]—A mixture of 300 mg. of norfriedelanone and 60 mg. of selenium dioxide in 20 ml. of acetic acid was refluxed for 2 hr. The precipitated selenium was filtered. The filtrate was diluted with water, extracted with ether and the ether extract washed thoroughly with 10% aqueous sodium hydroxide solution. Drying, evaporation of the ether and crystallization of the residue from methylene chloride–ethanol gave 160 mg. of norfriedelenone, m.p. 258–260°. Two recrystallizations raised the melting point to 260–261°; infrared$_{max}$ (carbon disulfide) 1700, 1647, 875 cm.$^{-1}$; ultraviolet$_{max}$ 253 mμ (log ε 4.2)[11]; $[\alpha]^{25}D$ −108° (*c* 0.85).[11]

Δ^3-Friedelen-2-one (X).—To a solution of 200 mg. of Δ^2-friedelene in 20 ml. of glacial acetic acid was added 250 mg. of sodium dichromate dihydrate. The solution was held at 95° for 7 hr. A small amount of methanol was added to destroy excess dichromate, and the hot solution was diluted slowly with water to complete crystallization. The white product was filtered, crystallized once from methylene chloride–methanol and twice from ethyl acetate to give 120 mg. (58%) of Δ^3-friedelen-2-one as clear, colorless leaves of m.p. 289–291°. Several recrystallizations from methylene chloride–ethanol followed by sublimation raised the melting point to 292–294°; infrared$_{max}$ (carbon disulfide) 1670, 1618 cm.$^{-1}$; ultraviolet$_{max}$ 237 mμ (log ε 4.13); $[\alpha]^{25}D$ +39° (*c* 1.055).

Anal. Calcd. for $C_{30}H_{48}O$: C, 85.24; H, 11.08. Found: C, 85.08; H, 11.19.

Friedelan-2-one.—A solution of 100 mg. of friedelan-Δ^3-ene-2-one in 30 ml. of ethyl acetate which had previously been distilled from Raney nickel was hydrogenated in the presence of palladium-on-charcoal (5%) for 7 hr. After removing the catalyst the solution was concentrated to *ca.* 5 ml. The white needles which separated were filtered, washed with methanol and dried to give 92 mg. of friedelan-2-one, m.p. 286–292°; infrared$_{max}$ (carbon disulfide) 1712 cm.$^{-1}$. When admixed with a pure sample of Δ^3-friedelen-2-one a large melting-point depression was observed. Further crystallization did not change the melting point. The analytical sample was sublimed at 270° (0.01 mm.).

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.36; H, 12.19.

Δ^3-Friedelene (IX).—A solution of 1 g. of friedelan-3β-ol and 1 g. of *p*-toluenesulfonyl chloride in 50 ml. of dry pyridine was heated at reflux for 4 hr. and then concentrated to dryness under reduced pressure. The residue was dissolved in methylene chloride–ether, shaken with aqueous hydrochloric acid (0.5 *N*) and the organic layer was evaporated. Recrystallization of the residual solid from benzene afforded large colorless prisms of Δ^3-friedelene, m.p. 268–269°.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.80; H, 12.06.

The ultraviolet end absorption in ethanol due to the double bond corresponded in intensity to that shown by α- and β-amyrins, which possess trisubstituted double bonds, and is much more intense than Δ^2-friedelene or Δ^2-cholestene.

Oxidation of 150 mg. of Δ^3-friedelene with 150 mg. of sodium dichromate dihydrate in benzene–acetic acid (1:1) at reflux for 3 hr. afforded Δ^3-friedelene-2-one (95 mg.), m.p. 291–292°, identical with a sample prepared from Δ^2-friedelene as described above.

Friedelin-enol Benzoate. (A).—A mixture of 900 mg. of friedelin and 7 ml. of benzoyl chloride was heated for 30 minutes at 160°. The cooled solution was diluted slowly, while shaking, with 200 ml. of ethanol and the crystals were allowed to separate for 0.5 hr. Filtration gave a slightly yellow powder which, on crystallization from ethyl acetate–chloroform, yielded 750 mg. (67%) of friedelin-enol benzoate, m.p. 260–263°[5]; infrared$_{max}$ (Nujol) 1727 cm.$^{-1}$. This product is regarded as the Δ^2-enol benzoate.

(B).—Three grams of friedelin in 20 ml. of benzoyl chloride was heated to 180° (internal temperature) for 3 hr. The product was isolated as described in part A, yield 3.1 g., m.p. 268–275°. Further recrystallization from methylene chloride–ethyl acetate raised the m.p. to 280–281.5°, infrared$_{max}$ (CS_2) 1728 cm.$^{-1}$.

Anal. Calcd. for $C_{37}H_{54}O_2$: C, 83.71; H, 10.26. Found: C, 83.80; H, 10.09.

From bromination experiments it is apparent that the high melting enol benzoate is largely the Δ^3-isomer.

2α-Bromofriedelin (XI).—A solution of 1.28 g. of friedelin in 50 ml. of chloroform was treated with 1 ml. of a saturated solution of hydrogen bromide in chloroform followed by a solution of 0.55 g. of bromine in 5 ml. of chloroform. The decolorization of bromine was almost instantaneous. The chloroform was evaporated under reduced pressure and the residue was recrystallized from methylene chloride–ethyl acetate to give 0.74 g. of colorless crystals, m.p. 209° dec. Further recrystallization from methylene chloride–ethyl acetate and methylene chloride–heptane afforded pure material, m.p. 210° dec., $[\alpha]^{25}D$ −140°, infrared$_{max}$ 1710 cm.$^{-1}$, ultraviolet$_{max}$ 311 mμ. This substance was not isomerized by treatment with hydrogen bromide in chloroform for 12 hr. at 25°.

Anal. Calcd. for $C_{30}H_{49}OBr$: C, 71.26; H, 9.65; Br, 15.81. Found: C, 71.07; H, 9.65; Br, 15.38.

2α,4α-Dibromofriedelin.—This substance was prepared by the procedure given above using two equivalents of bromine, m.p. 203–204° dec., $[\alpha]^{25}D$ −60.4°, infrared$_{max}$ 1712 cm.$^{-1}$, ultraviolet$_{max}$ 332 mμ (both bromines axial).

Anal. Calcd. for $C_{30}H_{48}OBr_2$: C, 61.64; H, 8.27; Br, 27.34. Found: C, 61.70; H, 8.32; Br, 27.20.

4α-Bromofriedelin (XII).—To a solution of 3.9 g. of the high melting friedelin enol benzoate, m.p. 275–278° (see above, mainly the Δ^3-isomer) and 1 g. of pyridine in 35 ml. of methylene chloride at 0° was added a solution of 1.21 g. of bromine in 10 ml. of methylene chloride. Bromine absorption was essentially instantaneous and after 5 minutes at 0°, the solution was concentrated under reduced pressure, and the product was crystallized by adding ethyl acetate and driving off the methylene chloride on a steam-bath. The crude product (3.1 g.) was recrystallized from methylene chloride–ethyl acetate to give almost pure material, 2.4 g., m.p. 191–192° dec. Further recrystallization from methylene chloride–heptane afforded analytically pure material, m.p. 196–197° dec., $[\alpha]^{25}D$ +90.5°, infrared$_{max}$ 1715 cm.$^{-1}$, ultraviolet$_{max}$ 310 mμ.

Anal. Calcd. for $C_{30}H_{49}OBr$: C, 71.26; H, 9.65; Br, 15.81. Found: C, 70.44; H, 9.38; Br, 15.70.

Conversion of 2α-Bromofriedelin to Δ^2-Friedelene.—To a solution of 300 mg. of 2α-bromofriedelin in 25 ml. of dioxane was added 300 mg. of sodium borohydride dissolved in absolute ethanol. After storage at room temperature for 4 hr., the solution was filtered and the excess borohydride was destroyed by addition of acetic acid. The filtrate was evaporated under reduced pressure and the residue was taken up in ether–methylene chloride and washed with saturated salt solution. Evaporation of the organic solvent and recrystallization from methylene chloride–ethanol gave

(43) A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1942).

crude bromohydrin, m.p. 220–230°, which gave a positive Beilstein test and showed hydroxyl but no carbonyl absorption in the infrared. This material was refluxed with a suspension of zinc dust (500 mg.) in acetic acid (10 ml.) for 1 hr. The hot solution was decanted and evaporated under reduced pressure. The residue was dissolved in ether–methylene chloride and washed with dilute sodium hydroxide solution followed by saturated salt solution. Evaporation of the solvent and filtration of the residue dissolved in cyclohexane solution through alumina yielded 170 mg. of pure Δ^2-friedelene, m.p. 255° undepressed upon admixture with an authentic sample.

Conversion of 4α-Bromofriedelin to Δ^3-Friedelene.—A solution of 300 mg. of 4α-bromofriedelin in chloroform (5 ml.) was treated with a solution of 200 mg. of sodium borohydride in ethanol at room temperature for 40 minutes. The crude product was isolated by acidification with acetic acid, evaporation and extraction and was further treated with zinc dust (1 g.), sodium acetate (100 mg.) and acetic acid (10 ml.) at 80° for 4 hr. The olefin, isolated as described above for Δ^2-friedelene, had m.p. 266–268°, undepressed by admixture with an authentic sample of Δ^3-friedelene.

Friedelan-2,3-dione.—A solution of 1 g. of friedelan-2,3-dion-3-enol benzoate and 5 g. of potassium hydroxide in one liter of methanol was refluxed for 3 hr. The reaction mixture was diluted with ether, the ether solution was washed thoroughly with water, dried and evaporated to dryness. The crystalline residue was chromatographed on a column of alumina. Benzene eluted 170 mg. of a crystalline norketone, m.p. 215–217°; infrared_{max} (carbon disulfide) 1735 cm.$^{-1}$. Ethyl acetate eluted 305 mg. of friedelan-2,3-dione, m.p. 267–269°; ultraviolet_{max} 275 mμ (log ε 4.06).[11] This diketone gives a dark brown color when treated with ferric chloride. Treatment of the diketone with hydrogen bromide in methylene chloride under nitrogen for three days at 25° did not change this product, m.p. and mixture m.p. 267–269°.

Conversion of 4α-Bromofriedelin to the Rearranged Ketone XIII.—To a hot solution (85°) of 600 mg. of silver acetate in 220 ml. of acetic acid was added 1.35 g. of 4α-bromofriedelin with stirring and heating was continued for 45 minutes. Filtration, evaporation of the acetic acid under reduced pressure and recrystallization from methylene chloride–ethyl acetate afforded 550 mg. of prisms, m.p. 246–247.5°. Further recrystallization raised the m.p. to 247–248°, $[\alpha]^{25}D$ −48.6°, infrared_{max} 1710 cm.$^{-1}$, ultraviolet_{max} 290 mμ. The ketone remains unchanged after heating with 5% hydrogen chloride in acetic acid for 6 hr. at 100°.

Anal. Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 84.87; H, 11.20.

Wolff–Kishner reduction of 100 mg. of XIII with 30 ml. diethylene glycol, 0.5 g. potassium hydroxide and 1 ml. of hydrazine hydrate at 200° for 2 hr. afforded after chromatography over alumina and recrystallization from methylene chloride–acetone 61 mg. of the unsaturated hydrocarbon XIV, m.p. 221–222°, $[\alpha]^{25}D$ −5.6°, yellow color with tetranitromethane, ultraviolet end absorption indicative of tri- or tetra-substituted double bond.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.59; H, 11.86.

The olefin XIV was recovered unchanged after refluxing with a 10% solution of sulfuric acid in ethanol for 2 hr., conditions which suffice for the isomerization of XXV to XXVI.

Friedelan-2,3-dion-3-enol Benzoate.—Over a period of 2 hr. 200 mg. of sodium dichromate dihydrate dissolved in 10 ml. of acetic acid was added to a boiling solution of 500 mg. of friedelin-enol benzoate in a mixture of 40 ml. of benzene and 20 ml. of acetic acid. The resulting solution was allowed to reflux gently for 42 hr. Benzene was removed under vacuum and the acetic acid solution was dissolved in ether. Acetic acid was removed by extraction with 10% aqueous sodium hydroxide solution. After drying, the ethereal solution was concentrated to *ca.* 25 ml., ethanol added and the ether removed completely. White needles, which had separated, were filtered and washed with methanol to give 324 mg. (63%) of friedelan-2,3-dion-3-enol benzoate, m.p. 306–312°. Three further crystallizations raised the melting point to 311–313°; infrared_{max} (carbon disulfide) 1734, 1692 cm.$^{-1}$.

Anal. Calcd. for $C_{37}H_{52}O_3$: C, 81.62; H, 9.62. Found: C, 82.09; H, 9.80.

Bisnorfriedelendione (XIX).—A suspension of 1.495 g. of friedelan-2,3-dione-3-enol benzoate and 3.2 g. of selenium dioxide in 100 ml. of dry dioxane was sealed in a pressure tube and heated at 200° for 13 hr. The selenium was filtered and the dioxane was removed under vacuum. An ether–methylene chloride solution of the residue was washed thoroughly with 10% aqueous sodium hydroxide and dried. After treatment with a small amount of charcoal, the filtered solution was evaporated, and the residue was crystallized from methylene chloride–ethanol to give 725 mg. (65%) of yellow-orange needles of bisnorfriedelenone, m.p. 272–273°; infrared_{max} (carbon disulfide) 1762, 1726, 873 cm.$^{-1}$; ultraviolet_{max} 281 mμ (log ε 4.36); negative ferric chloride test. No deuterium was introduced into XIX by treatment with excess deuterium bromide in methylene chloride at 25° for 10 days (Experiment by W. Coleman).

Bisnorfriedelendicarboxylic Acid Anhydride.[11]—A hot solution of 1.725 g. of bisnorfriedelendione in 180 ml. of acetic acid was treated dropwise with 12.5 ml. of 30% hydrogen peroxide dissolved in 60 ml. of acetic acid. The solution was held at 80° for 1.5 hr. during which time it became colorless. Dilution with water gave a white solid which, when crystallized from methylene chloride–ethanol, gave 1.608 g. (90%) of bisnorfriedelendicarboxylic acid anhydride, m.p. 236–237°; infrared_{max} (carbon disulfide) 1790, 1740, 1625, 873 cm.$^{-1}$; ultraviolet_{max} 220 mμ (log ε 4.0); $[\alpha]^{25}D$ −40.9° (*c* 1.08).

Saturated C_{25}-Ketone XX.—A solution of 180 mg. of norfriedelendicarboxylic acid anhydride in 35 ml. of dry carbon tetrachloride was ozonolyzed at 0–20° for 1 hr. The carbon tetrachloride was removed under vacuum and the residue was boiled with 5 ml. of water for 90 minutes. The water suspension was extracted with ether, and the ether was washed with 10% aqueous sodium hydroxide and dried. Evaporation of the ether and crystallization of the residue from ether–ethanol gave 83 mg. of the C_{25}-ketone, m.p. 180–190°. Several recrystallizations raised the melting point to 207–208°[12]; infrared_{max} (carbon disulfide) 1707 cm.$^{-1}$; $[\alpha]^{25}D$ +38° (*c* 1.10).

Deuterium Exchange with C_{25}-Ketone XX.—A solution of 86 mg. of the C_{25}-ketone in 50 ml. of dry carbon tetrachloride containing deuterium bromide (0.20 *N*) free from hydrogen bromide was allowed to equilibrate at room temperature for 10 days. The carbon tetrachloride was removed under vacuum, the residue was dissolved in ether and the ether solution was extracted with 3% aqueous sodium hydroxide solution. After drying, the ether solution was evaporated and the solid was crystallized from methanol–water. The deuterated ketone was filtered and dried in a high vacuum at 76°. A deuterium analysis by the falling drop method showed 2.5% of the total original hydrogen had been replaced by deuterium. This is equivalent to 1.0 replaceable hydrogen per molecule (deuterium analysis by R. A. Sneen).

Unsaturated C_{26}-Acid XXII.—A refluxing solution of 400 mg. of bisnorfriedelendione in 40 ml. of ethanol was treated dropwise with 10 ml. of 2% ethanolic potassium hydroxide solution. To the orange solution was added slowly 4 ml. of 30% hydrogen peroxide in 7 ml. of ethanol, and the solution was refluxed for 1 hr. under nitrogen. The suspension of sodium salt was acidified, concentrated to a small volume and diluted with water. Filtration yielded 320 mg. of crude acid. Several crystallizations from methylene chloride–ethanol gave 280 mg. of pure acid, m.p. 249–250°; infrared_{max} (carbon disulfide) 1705, 2600–3300 cm.$^{-1}$; ultraviolet_{max} (potassium salt in ethanol) 213 mμ (log ε 3.22); $[\alpha]^{25}D$ −51° (*c* 0.99).

Several attempts were made to isolate the remaining carbon atoms as solid carbonyl derivatives and as an acid with no success.

As the methyl ester of the acid crystallized more readily than the acid itself, in subsequent reactions the acidified alcohol solution, obtained from the reaction, was evaporated almost to dryness, the residue was dissolved in ether and the ether solution was washed thoroughly with 10% aqueous sodium hydroxide and with water. After esterification with diazomethane the ether was evaporated and the ester was crystallized from methylene chloride–ethanol. In one such reaction 14.9 g. of bisnorfriedelendione yielded 12 g. (90%) of the pure ester XLI, m.p. 167–168°; infrared_{max} (carbon disulfide) 1740 cm.$^{-1}$.

C_{25}-Olefin XXVI.—Pure unsaturated C_{26}-acid XXII (500 mg.) was pyrolyzed at 290° for 1.5 hr. in an atmosphere of nitrogen. The pyrolysate was dissolved in 25 ml. of ethanol and 4 ml. of sulfuric acid was added to the solution. After refluxing for 0.5 hr. the solution was diluted with water and the solid which separated was filtered. The dried product was dissolved in methylene chloride and filtered through a column of alumina. Crystallization from methylene chloride–ethanol gave 277 mg. of colorless plates, m.p. 150–155°. Three recrystallizations raised the melting point to 157–159°; $[\alpha]^{25}D$ −19° (*c* 0.89).

Epoxidation of the olefin with perbenzoic acid gave a mixture of epoxides, m.p. 145–150°. On treatment with boron trifluoride etherate, this mixture of epoxides gave a mixture of ketones, infrared_{max} (carbon disulfide) 1705, 1695 $cm.^{-1}$.

Unsaturated Keto-ester XXVIII.—A solution of 3.4 g. of sodium dichromate dihydrate in 125 ml. of acetic acid was added to a solution of 3.4 g. of the ester XXIII in 125 ml. of benzene. The resulting mixture was stirred at 70° for 12.5 hr. The benzene was removed under vacuum and the residual acetic acid solution was diluted with water. An ether extract of this mixture was washed thoroughly with water and 10% aqueous sodium hydroxide. After drying, the ether solution was decolorized with charcoal, filtered and the filtrate was evaporated to dryness. Chromatography on acid-washed alumina gave, eluting with cyclohexane, 440 mg. of the unsaturated ketone XXIX (see below) and 1.72 g. of the unsaturated keto-ester XXVIII. Several crystallizations from methylene chloride–ethanol followed by sublimation gave the analytical sample of keto-ester XXVIII, m.p. 150–151°; infrared_{max} (carbon disulfide) 1742, 1670, 1620 $cm.^{-1}$; ultraviolet_{max} 247 mμ (log ε 3.93); $[\alpha]^{25}D$ −42.7° (*c* 1.64).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.49; H, 10.05.

Unsaturated Ketone XXIX.—A solution of 1.5 g. of unsaturated keto ester XXVIII was refluxed in 300 ml. of dry ethanol containing 2 g. of sodium for 7 hr. under nitrogen. After cooling, the solution was diluted with water and the solid which separated was filtered and dried. Several crystallizations from methylene chloride–ethanol yielded 920 mg. (71%) of the unsaturated ketone, m.p. 191–192°; infrared_{max} (carbon disulfide) 1662, 1617 $cm.^{-1}$; ultraviolet_{max} 248 mμ (log ε 3.95); $[\alpha]^{25}D$ −19.5° (*c* 1.18).

Anal. Calcd. for $C_{25}H_{40}O$: C, 84.21; H, 11.31. Found: C, 84.33; H, 11.38.

Oxidation of the C_{25} olefin XXVI with sodium dichromate dihydrate gave, in small yields, the same unsaturated ketone, m.p. 188–190°; infrared and ultraviolet spectra identical; mixture melting point showed no depression.

Saturated Ketone XXX.—A solution of 920 mg. of the unsaturated ketone XXIX in 30 ml. of ethyl acetate, which had previously been distilled from Raney nickel, was hydrogenated at atmospheric pressure in the presence of 500 mg. of palladium-on-charcoal (5%). The catalyst was filtered and the ethyl acetate was evaporated. Crystallization of the residue from methylene chloride–ethanol gave 916 mg. (99%) of the saturated ketone, m.p. 180–185°. Several recrystallizations followed by sublimation raised the melting point to 195–197°; infrared_{max} (carbon disulfide) 1708 $cm.^{-1}$; $[\alpha]^{25}D$ +42.5° (*c* 1.48).

Anal. Calcd. for $C_{25}H_{42}O$: C, 83.73; H, 11.81. Found: C, 84.02; H, 11.88.

Deuterium Exchange with Saturated Ketone XXX.—A solution of 65 mg. of the ketone XXX in 100 ml. of dry methylene chloride containing deuterium bromide (0.20 *N*) free from hydrogen bromide was allowed to equilibrate at room temperature for 6 days. The solution was diluted with ether, and the ether solution was quickly extracted with 3% aqueous sodium hydroxide, dried and evaporated. The residue was crystallized from methanol and dried in a high vacuum at 76°. A deuterium analysis by the falling drop method showed 6.9% of the total original hydrogen had been replaced by deuterium. This corresponds to 2.9 replaceable hydrogens per molecule (analysis by R. A. Sneen).

Oxidation of the Ketone XXX.—A mixture of 500 mg. of the ketone and 5 ml. of 40% peracetic acid in 50 ml. of chloroform was held at 50–55° for 16 hr. The solution was concentrated to a small volume, 10 ml. of ethanol added and all the chloroform was removed under vacuum. After filtering and drying, the solid obtained (infrared_{max} (carbon tetrachloride) 1737 $cm.^{-1}$) was suspended in 50 ml. of acetic acid. Ten drops of sulfuric acid and twenty drops of water were added and the suspension was stirred at room temperature for 4 hr. Dilution with water and filtration gave 400 mg. of crude product, which was separated into an acid and a neutral fraction by shaking an ethereal solution of the product with 10% aqueous sodium hydroxide solution. The ether layer gave 68 mg. of starting material on evaporation. After acidification, the aqueous layer was extracted with ether and the ether solution was treated with diazomethane. The ether was evaporated, and the residue was crystallized five times from ethanol to give 253 mg. of the ester as broad, flat laths of m.p. 134–134.5°; infrared_{max} (carbon disulfide) 1737, 1713, 1695 (weak) $cm.^{-1}$; $[\alpha]^{25}D$ +21.1° (*c* 0.855).

Anal. Calcd. for $C_{26}H_{44}O_3$: C, 77.08; H, 10.96. Found: C, 77.38; H, 10.91.

Direct oxidation of the ketone XXX with chromic anhydride in acetic acid gave the acid in small yields. A mixed melting point of the ester with that obtained through the lactone showed no depression and the infrared spectra of the two materials were identical.

Olean-13(18)-ene. (A).—A mixture of 500 mg. of friedelan-3β-ol, 200 mg. of red phosphorus, 1.3 g. of iodine and 30 ml. of dry benzene was heated under reflux for 3 hr. The warm solution was shaken with mercury to remove iodine and evaporated to 5 ml. under vacuum. Methylene chloride was added and the solution was shaken with aqueous sodium bisulfite solution and several times with water. The methylene chloride was evaporated and the solid residue was crystallized from ethanol to give 200 mg. of colorless needles, m.p. 175–180°. Three crystallizations from acetone raised the melting point to 187–188°; ultraviolet_{max} (cyclohexane) 213 mμ (log ε 3.5); $[\alpha]^{25}D$ −12.5° (*c* 0.80); bright yellow coloration with tetranitromethane.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.76; H, 12.37.

An authentic sample of olean-13(18)-ene was prepared from β-amyrin by oxidation, Wolff–Kishner reduction and acid-catalyzed isomerization of the 12,13-double bond to the 13,18-position,[44] m.p. 186–187°; $[\alpha]^{25}D$ −13.9° (*c* 0.79). A mixture melting point with the olefin prepared from friedelan-3β-ol showed no depression. The infrared and ultraviolet spectra of the two olefins were identical. **(B).**—Heating a solution of friedelan-3β-ol in benzoyl chloride at 160–180° for 0.5 hr. gave olean-13(18)-ene in yields which varied considerably, but which were as high as 50%. **(C).**—A mixture of 2.0 g. of friedelan-3β-ol and 12 ml. of phenol, saturated with hydrogen chloride and maintained at saturation by passage of a slow stream of the gas through the reaction mixture, was heated at 110° for 45 minutes. The mixture was cooled, treated with 100 ml. of 10% aqueous potassium hydroxide and extracted with several portions of methylene chloride. The organic layer was filtered and concentrated and the product was crystallized by acetone and boiling off the methylene chloride. Further recrystallization from acetone–methylene chloride afforded pure material, m.p. 185–186°, in 55% yield. **(D).**—A solution of 50 mg. of Δ^3-friedelene in 10 ml. of phosphorus oxychloride to which had been added a small drop of concentrated hydrochloric acid was heated at reflux for 2 hr. Evaporation under reduced pressure followed by recrystallization from acetone gave 26 mg. of olean-13(18)-ene, m.p. 184–185°, undepressed upon admixture with an authentic sample. The same product was obtained under these conditions starting with friedelan-3β-ol.

Conversion of Olean-13(18)-ene to Olean-11,13(18)-diene.—A solution of 200 mg. of olean-13(18)ene from friedelin in 7 ml. of 0.3 *M* perbenzoic acid in chloroform was maintained at 25° for 3 days. The epoxide was isolated by washing the chloroform solution with base after addition of ether, evaporation and crystallization; from methylene chloride–methanol, m.p. 191–195° undepressed upon admixture with an authentic sample prepared from β-amyrin. Treatment of 100 mg. of this oxide from friedelin in methylene chloride solution (5 ml.) with 3 drops of boron trifluoride etherate for 30 minutes followed by evaporation and crystallization from methylene chloride–methanol gave 77 mg. of olean-11,13-(18)-diene, m.p. 217–218°. Further recrystallization afforded pure material, m.p. 219–220° undepressed

(44) K. Takeda, *J. Pharm. Soc. Japan*, **63**, 197 (1943); *C. A.*, **45**, 586 (1951).

upon admixture with an authentic sample, $[\alpha]^{25}D$ −72.4°, ultraviolet$_{max}$ 242, 250, 260 mμ (log ε 4.44, 4.50, 4.31), brown coloration with tetranitromethane.

Anal. Calcd. for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.02; H, 11.91.

Friedelan-3α-ol Chloroacetate.—A solution of 600 mg. of friedelan-3α-ol in 50 ml. of lepidine was cooled until the lepidine just started to crystallize. To this solution was added 1.5 ml. of chloroacetyl chloride dropwise with swirling. The mixture turned dark brown and a precipitate appeared immediately. The mixture was left without further cooling for 0.5 hr., diluted with water and extracted with ether. The ether extract was washed with dilute hydrochloric acid, 1% aqueous sodium hydroxide and water. Charcoal treatment of the ether layer gave a light brown solution which was concentrated to a small volume, 10 ml. of ethanol added and the remaining ether was removed. The small plates which separated were filtered, dried and dissolved in benzene. The benzene solution was filtered through a column of alumina and evaporated to dryness. Crystallization of the residue from methylene chloride–ethanol gave 340 mg. of colorless plates, m.p. 280° dec. Two further crystallizations raised the melting point to 283° dec.; infrared$_{max}$ (carbon disulfide) 1760, 1732 cm.$^{-1}$. This material was satisfactory for X-ray single crystal analysis.

Anal. Calcd. for $C_{32}H_{53}O_2Cl$: C, 76.07; H, 10.58. Found: C, 76.34; H, 10.16.

Friedelan-3α-ol Bromoacetate.—A solution of 750 mg. of friedelan-3α-ol, 2 ml. of bromoacetyl bromide and 2 ml. of pinene in 30 ml. of methylene chloride was heated to reflux for 20 hr. Heptane was added and the methylene chloride was distilled off. Upon cooling the heptane solution deposited 680 mg. of bromoacetate which was purified by copious washing with hexane, passage through a short column of alumina in benzene solution and recrystallization from benzene; 650 mg., m.p. 279°. Recrystallization from *n*-heptane–methylene chloride afforded analytically pure material, m.p. 279°. Samples for X-ray analysis were prepared by recrystallization from benzene.

Anal. Calcd. for $C_{32}H_{53}O_2Br$: C, 69.92; H, 9.72; Br, 14.54. Found: C, 69.99; H, 9.57; Br, 14.41.

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[CONTRIBUTION FROM EXPERIMENTAL THERAPEUTICS, MEDICINAL CHEMICAL, AND VIRAL AND RICKETTSIAL SECTIONS, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Studies with Corticotropin. I. Isolation, Purification and Properties of β-Corticotropin

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Seven active components have been separated by countercurrent distribution of oxycellulose hog corticotropin. The homogenous principal component has been characterized by end group and quantitative amino acid analysis. Two types of intermedin activity present in crude corticotropin preparations were separated.

The isolation, purification and characterization of β-corticotropin have been briefly reported[1] earlier. The results of this investigation are given in detail here and in the following papers.[2,3]

The physiological importance of the hormones of the anterior pituitary gland has been the subject of many papers in the last two decades. It was recognized that certain of these materials were involved in the formation of steroids by the adrenal gland. However, the announcement that ACTH was effective in rheumatoid arthritis[4] stimulated research workers to the efforts which have resulted in the appearance of several hundred reports in the literature of the last six to eight years. Based on our current knowledge, the bulk of this work was carried out using very impure material.

The existence of more than one type of pituitary hormone activity which affected the adrenal cortex was first suggested by Reiss, *et al.*[5] It was later proposed[6] that the two suspected factors be designated the *adrenal weight factor* and the *ascorbic acid factor*. However, this concept has been questioned,[7a] since the apparent separation of the two factors could not be confirmed when the method of administration of the sample was varied. The present work was not designed to resolve this question. Rather, we were interested in preparing a pure, clinically active hormone.

The term "corticotropin activity" as used here refers to response in the adrenal ascorbic acid depletion assay of Sayers, *et al.*[8] We consider the hormonal activity measured by this assay to be significant, since the clinical activity[9] in rheumatoid arthritis appeared to be proportional to the Sayers assay response for "clinical" ACTH, for β-corticotropin and its pepsin degradation product[2] P4.

Early work by Li, *et al.*,[10] and Sayers, *et al.*,[11] led to the conclusion that ACTH isolated from either hog or sheep pituitaries by acid–acetone extraction[12] was a pure protein of molecular weight about 20,000. The peptide character of its active principle was demonstrated by its solubility properties and its inactivation by proteolytic enzymes such as trypsin,[13,14] chymotrypsin,[14] pepsin,[14] and carboxypeptidase.[13] The active principle was sepa-

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