Tetrahedron, 1965, Vol. 21, pp. 101 to 113. Pergamon Press Ltd. Printed in Northern Ireland

TERPENES—XII[1]

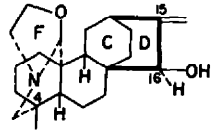
STUDIES IN THE CONVERSION OF PODOCARPIC ACID TO ATISINE

N. N. GIROTRA and L. H. ZALKOW[2]
Department of Chemistry, Oklahoma State University

(*Received* 15 *June* 1964; *in revised form* 20 *July* 1964)

Abstract—Podocarpic acid (IV), a previously synthesized diterpene, has been converted into a mixture of dienes which react with maleic anhydride to give two crystalline adducts (X and XI). Adduct XI was shown to possess the same carbon skeleton as atisine (I), a diterpenoid alkaloid, by its conversion to the hydrocarbon (XXI). Hydrocarbon XXI has recently been synthesized from maleopimaric acid, the Diels-Alder adduct of the diterpene levopimaric acid and maleic anhydride, and has been directly related to atisine. Structure X is tentatively suggested for the second adduct on the basis of its reactions and from studies of the NMR spectra of its various transformation products. The synthesis of XI provides a molecule of correct stereochemistry, containing the bicyclo(2.2.2)-octane C,D ring system of atisine and, in addition, it contains a β-C-4 substituent which would allow introduction of the nitrogen-containing E ring by previously described methods, but it does not possess a ready means of introducing the C-15 methylene group and C-16 hydroxyl group of atisine.

ATISINE (I), a diterpenoid alkaloid of the aconite group, was first described and named in 1877,[3] but it was not until 1937 that the correct molecular formula, $C_{22}H_{33}NO_2$, was determined.[4] The correct structure was only recently deduced by Wiesner *et al.*,[5]



I

after pioneering chemical work by Jacobs *et al.*[3,6] Several excellent reviews describe the earlier work.[3,7–9] The stereochemistry of atisine was determined by the exhaustive work of Pelletier[3,10] and Edwards[9] *et al.* and finally the absolute configuration was arrived at by Djerassi and Vorbrueggen.[11]

[1] This work was generously supported by the National Science Foundation (GP-233). A portion of the work described herein has appeared in a preliminary form, L. H. Zalkow and N. N. Girotra, *Chem. & Ind.* 704 (1964).

[2] To whom inquiries should be sent.

[3] S. W. Pelletier, *Tetrahedron* **14**, 77 (1961).

[4] A. Lawson and J. E. C. Topps, *J. Chem. Soc.* 1640 (1937).

[5] K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954).

[6] W. A. Jacobs, *J. Org. Chem.* **16**, 1593 (1951).

[7] K. Wiesner and Z. Valenta, "*Progress in the Chemistry of Organic Natural Products* Vol. XVI; p. 26. Springer-Verlag, Vienna (1958).

[8] E. S. Stern in *The Alkaloids, Chemistry and Physiology* (Edited by R. H. F. Manske and H. C. Holmes) Vol. VII p. 473. Academic Press, New York (1960).

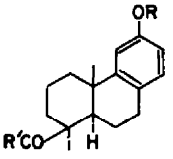
[9] D. Dvornik and O. E. Edwards, *Tetrahedron* **14**, 54 (1961).

[10] S. W. Pelletier, *Experientia* XX, 1 (1964).

[11] H. Vorbrueggen and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 2990 (1962).

A large number of workers[12,13] in many parts of the world accepted the final challenge of atisine chemistry—the total synthesis of the compound itself and at this time two elegant syntheses have been recorded in preliminary form.[14,15] An examination of the structure of atisine (I) reveals that it possesses two unique features not present in steroids, where otherwise a great deal of total synthetic experience is available to draw upon. These features are the nitrogen containing E ring with its fused oxazolidine F ring and the bicyclo(2.2.2)octane C,D ring system.

Edwards and Ap Simon[16] provided a direct means of introducing a nitrogen atom between the C-4 and C-10 methyl groups to give the E ring, which involved photolysis of O-methyl podocarpic azide (II) to give a cyclic lactam which was reduced to the corresponding amine. This method has also been applied to a model compound



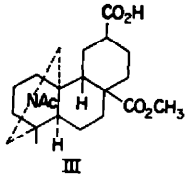
II R=CH_3, R'=N_3
IV R=H, R'=OH

in which the acyl azide was located at C-10 rather than at C-4[17] and the recently reported total synthesis of atisine by Masamune[15] utilized this procedure The second approach used to construct the E ring has involved ring closure, by chemical means, of *cis* functionalized substituents at C-4 and C-10. Iwai *et al.*[18] used a Mannich reaction in this manner and Wiesner *et al.*[19] used an intramolecular acylation. The recent total synthesis by Japanese workers[14] involved a ring closure between a C-4 aldehydo group and a C-10 amido group. Wiesner[20] demonstrated several years ago that the cyclic amino E ring of the related Garrya alkaloids could be readily converted into the oxazolidine F ring and Jacobs and Pelletier[21] applied the method in the atisine series. In both of the reported syntheses[14,15] the final compounds synthesized, in each case, did not contain the F ring of atisine since the further conversions of these intermediates to atisine had already been accomplished earlier.[21-23] In fact, the construction of the F ring of atisine was first partial synthetic accomplishment.

A number of ingenuous methods have been used in synthetic approaches to the bicyclo(2.2.2)octane C,D ring system of atisine. Pelletier and Parthasarathy[22]

[12] Much of the recent synthetic work can be found in references given by A. A. Othman and N. A. J. Rogers, *Tetrahedron Letters* No. 20, 1339 (1963).
[13] R. E. Ireland, *Record of Chemical Progress* **24**, 225 (1963) and Refs therein.
[14] W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, *J. Amer. Chem. Soc.* **85**, 2342 (1963).
[15] S. Masamune, *J. Amer. Chem. Soc.* **86**, 290 (1964).
[16] J. W. ApSimon and O. E. Edwards, *Canad. J. Chem.* **40**, 896 (1962).
[17] W. L. Meyer and A. S. Levinson, *Proc. Chem. Soc.* 15 (1963).
[18] I. Iwai, A. Ogiso, and B. Shimiza, *Chem. & Ind.* 1288 (1962).
[19] J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Weisner, and C. M. Wong, *Tetrahedron Letters* 869 (1962).
[20] K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, *Chem. Ber.* **86**, 800 (1953).
[21] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4144 (1956).
[22] S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters* No. 4, 205 (1963).
[23] S. W. Pelletier, *Chem. & Ind.* 1116 (1958).

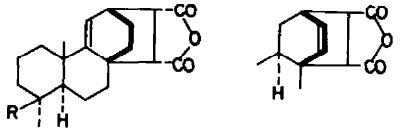
accomplished a partial synthesis of atisine by reconverting III, a degradation product of atisine, into atisine by homologation of the free carboxyl group followed by



III

Dieckman cyclization and then further transformations to introduce the C-15 and C-16 substituents. The Masamune[15] total synthesis involved the synthesis of III from Garryine[7] which was also synthesized.[24] Ireland and Bell[25] used an acid-catalyzed aldol type condensation, and the total synthesis of Nagata *et al.*[14] utilized a displacement reaction. The final approach reported for the syntheses of the C,D ring system has involved the Diels-Alder reaction,[12,26-28] and it is this method which is described in detail in this communication.

We visualized a synthesis of atisine beginning with podocarpic acid, (IV). The rationale for selecting podocarpic acid was as follows: (a) it had been totally synthesized[29] and possessed the required *trans* A,B ring fusion, (b) it possessed a carboxyl group at C-4 *cis* to the bridgehead methyl group at C-10, which had already been used to construct the nitrogen-containing E ring by Edwards *et al.*,[16] and (c) the aromatic C ring of podocarpic acid had been reduced earlier[30] to give an α,β-unsaturated ketone (V) which we visualized could be converted into a diene useful for construction of the C,D ring system by the Diels-Alder reaction. Of course, any synthesis beginning with podocarpic acid would lead, if successful, to the enantiomer of natural atisine. The major uncertainty in this synthetic approach involved the nature of the C ring diene produced. To be useful, this diene must be either $\Delta^{8,11}$ or a $\Delta.^{8(14),12}$ Since the various dienoic resin acids were known to give a single Diels-Alder adduct[31] of the desired type, the path undertaken appeared to offer promise. It should also be noted that ultimately an α-hydrogen atom would have to be introduced at C-9 and a means of introducing the D-ring methylene and hydroxyl groups would be required. It was anticipated that all of these requirements would be met by a $\Delta^{8,11}$ diene or by a $\Delta^{8(14),12}$ diene possessing a C-9 α-hydrogen atom. In either case a dienophile, such as maleic anhydride, would be expected to enter from the less-hindered α-side to give



VI a VI b

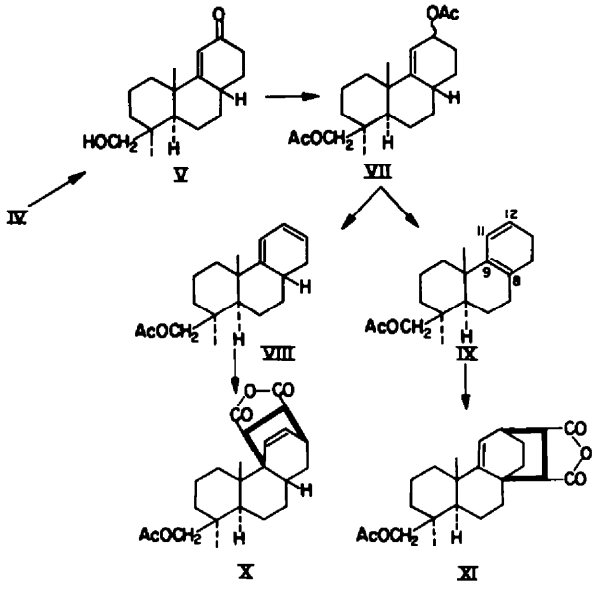
(VIa or VIb). Again, hydrogenation of VIa would be expected to proceed from the less hindered α-side to give the desired C-9 α-hydrogen. Both VIa and VIb would

[24] S. Masamune, *J. Amer. Chem. Soc.* **86**, 290 (1964).
[25] R. A. Bell and R. E. Ireland, *Tetrahedron Letters* 269 (1963).
[26] W. A. Ayer, C. E. McDonald and G. G. Iverach, *Tetrahedron Letters* 1095 (1963).
[27] L. H. Zalkow and N. N. Girotra, *J. Org. Chem.* **28**, 2037 (1963).
[28] L. H. Zalkow and N. N. Girotra, *J. Org. Chem.* **29**, 1299 (1964).
[29] E. Wenkert and A. Tahara, *J. Amer. Chem. Soc.* **82**, 3229 (1960).
[30] R. H. Bible, Jr. and R. R. Burtner, *J. Org. Chem.* **26**, 1174 (1961).

possess anhydride groupings on the necessary bridge for introduction of the D-ring methylene and hydroxyl groups of atisine. Oxidative decarboxylation of the anhydride moiety, after hydrogenation of the double bond, as previously described[27,28] for a similar compound obtained from levopimaric acid, would give the D-ring olefin and the further conversion of such an olefin to the D-ring of atisine with its C-15 methylene group and C-16 hydroxyl group of required stereochemistry has been described by Bell and Ireland.[25] In actual fact, the desired diene (IX) was obtained but it gave an unexpected Diels-Alder adduct.

The α,β-unsaturated ketone (V), previously described by Bible and Burtner,[30] was reduced with sodium borohydride and the resulting diol acetylated to give the diacetate (VII) as a viscous oil which was pyrolyzed in a dynamic system at ~300°. The resulting mixture of dienes (VIII and IX), was treated with maleic anhydride in refluxing xylene and gave two crystalline adducts (X and XI) in approximately 30% and 12% yields respectively.

Anhydride (XI), which crystallized first, showed a single vinylic proton in its NMR spectrum, and the C-10 methyl group showed no shielding by the D-ring double bond.[32,27] Methanolic diazomethane converted XI into the dimethyl ester (XII), which resisted all attempts at hydrogenation. Saponification of XII gave the hydroxy diacid (XIII) which was acetylated to give XIV. The carboxyl groups in XIII and XIV are presumed to be *trans*, epimerization occurring during saponification as observed in similar cases.[27,33] Treatment of XIV with lead tetraacetate in an attempt to effect oxidative bisdecarboxylation[27] failed to yield the desired product containing a bicyclo



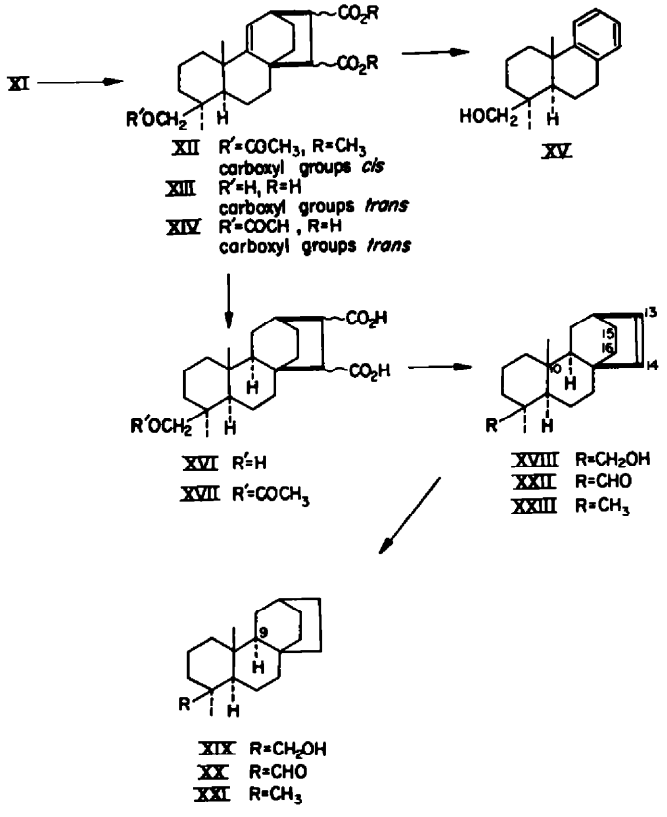
(2.2.2)octane C,D ring system. The product obtained, after saponification, has been assigned structure XV on the basis of its IR, uv and NMR spectra and apparently arises in a reverse Diels-Alder reaction of the intermediate bicyclo(2.2.2)octadiene;

[31] Sir John Simonsen, *The Terpenes* Vol. 3. Cambridge University Press (1952).
[32] W. A. Ayer, C. E. McDonald and J. B. Stothers, *Canad. J. Chem.* **41**, 1113 (1963).
[33] L. H. Zalkow and N. N. Girotra, *J. Org. Chem.* **28** 2033 (1963).

the driving force for the retro Diels-Alder reaction being the stability of the aromatic ring produced.

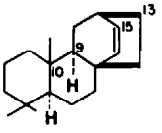
The hydroxy diacid (XIII), in contrast to XII, was readily hydrogenated to yield XVI, hydrogen being absorbed from the less hindered α-side. Acetylation gave XVII which was smoothly decarboxylated to give, after hydrolysis, the alcohol (XVIII). The NMR spectrum of XVIII showed the C-10 methyl group to be highly shielded (δ 0·53) by the spatially close C-13 double bond; in addition, the spectrum clearly showed the presence of two vinylic protons. That structure (XVIII) was indeed correct and *ipso facto* structure XI, was demonstrated by the further conversion of XVIII to hydrocarbon (XXI), the latter having been prepared previously from maleopimaric acid, the Diels-Alder adduct of levopimaric acid and maleic anhydride.[26,27] The stereochemistry at C-9 in maleopimaric acid is well established[32,34] and the hydrogen atom at C-9 in XVI–XXIII is therefore known to be α. In addition, XXI has been shown to be enantiomeric with the hydrocarbon of identical structure obtained by degradation of atisine.[26]

Alcohol XVIII was converted into alkene (XXIII) by chromic anhydride oxidation to give XXII followed by Wolff-Kishner reduction. That the double bond in XXIII and therefore in XVIII was located at C-13 and not at C-15 was clearly shown by comparison of XXIII with XXIV, the latter having been recently synthesized from maleopimaric acid.[27] In the NMR spectrum of XXIII the C-10 methyl signal appeared



[34] L. H. Zalkow, R. A. Ford and J. P. Kutney, *J. Org. Chem.* **27**, 3535 (1962) and Refs. therein

at δ 0·57, whereas in XXIV it appeared at δ 0·82, thus indicating that in XXIII the double bond was close enough to shield the C-10 methyl group. This unfortunate situation makes it difficult to introduce the C-15 methylene and C-16 hydroxyl groups



XXIV

of atisine into XVIII. Alkene XXIV has been used as an intermediate for the further introduction of these groups[25,28] but, again unfortunately, XXIV is derived from a precursor possessing an α-C-4 carboxyl group, which prevents ready introduction of the nitrogen-containing E ring of atisine.

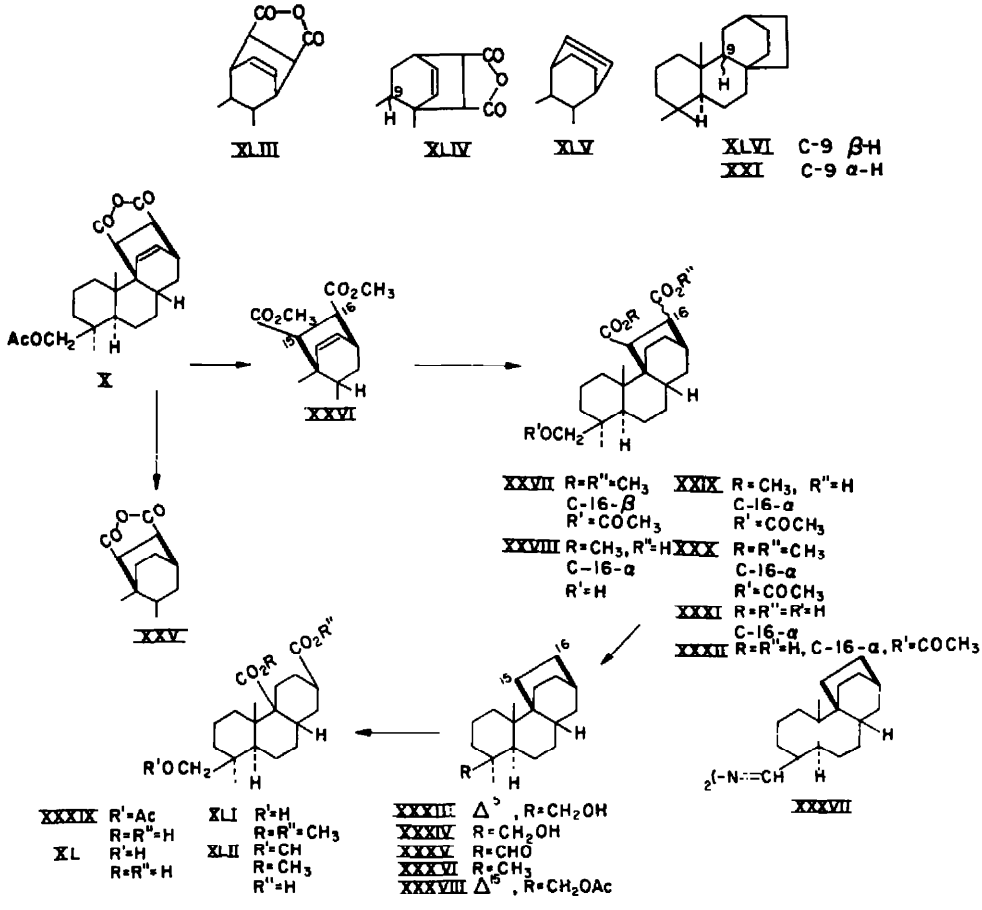
Thus, we are faced, at this time, with the rather awkward situation of being able to synthesize the carbon skeleton of atisine from both podocarpic acid and from levopimaric acid but each pathway has a built-in deficiency. As mentioned earlier, it is surprising that XI was produced in the first place, since it must arise from diene precursor (IX) by attack of the dienophile, maleic anhydride, from the more-hindered top (β) side. This preference for attack from the β-side must arise by some sort of directing influence by the β-C-4 acetoxy group, since in the case of the resin acids only the product arising from attack on the α-side is obtained.

Structure X is tentatively suggested for the second crystalline Diels-Alder adduct obtained from the mixture of C-ring dienes and maleic anhydride as mentioned earlier. The NMR spectrum of X showed two vinylic protons (δ 6·30), and of particular interest was the appearance of one methyl singlet (C-10) at the unusually low field of δ 1·4, the other methyl singlet (C-4) appeared in the usual place (δ 0·97). Hydrogenation of X gave XXV, the NMR spectrum of which still showed a methyl signal at low field (δ 1·26) indicating that the observed deshielding could not have arisen entirely from the double bond. Treatment of X with methanolic diazomethane gave dimethyl ester XXVI which was readily hydrogenated to give XXVII. When XXVII was refluxed with 5% sodium hydroxide the half-acid ester XXVIII was obtained, which on reacetylation gave XXIX, and on further treatment with ethereal diazomethane XXX was obtained. The latter diester was shown to be isomeric with XXVII by thin-layer chromatography and by NMR. In XXVIII, XXIX and XXX the two D ring carboxyl groups can, therefore, be assumed to be in the more stable *trans* arrangement, but since the C-10 methyl groups in XXVII, XXVIII, XXIX and XXX appear in essentially the same position in their respective NMR spectra it can be assumed that it is the C-16 and not the C-15 carboxyl group that is epimerized in the conversion of XXVII to XXVIII. It also follows, from an examination of molecular models, that the C-15 carboethoxy group is more hindered than the C-16 one and hence would be more resistant to saponification.

Vigorous alkaline saponification of XXVII gave the diacid (XXXI) which after acetylation to give XXXII was oxidatively decarboxylated to give the alkene (XXXIII). The NMR spectrum of XXXIII showed two sharp methyl singlets at high field (δ 0·87 and 0·90), indicating no shielding or deshielding of the C-10 methyl group by the double bond, and in addition, two vinylic protons were present. Alkene XXXIII was converted into the saturated hydrocarbon (XXXVI) by catalytic hydrogenation to

XXXIV, then oxidation to XXXV with chromic anhydride in pyridine and finally Wolff-Kishner reduction. In the NMR spectrum of XXXVI the three methyl groups at C-4 and C-10 appeared as sharp singlets at δ 0·85 (6 protons) and δ 0·89 (3 protons). Hydrocarbon XXXVI was found to be different from the previously prepared hydrocarbon (XXI) in m.p. and IR and NMR spectra. In addition to XXXVI, a second product isolated in the Wolff-Kishner reduction of XXXV was found to be the dimeric product XXXVII.

That the carbon skeleton of X, and hence all its derivatives (XXV–XXXVIII), is probably correct, follows from the structure of acetate VII which on pyrolysis in the absence of double bond rearrangement would yield VIII which in turn would give Diels-Alder adduct X. In addition, the following observations support the assigned structures. Anhydride X was shown by NMR to contain *two* vinylic protons. In addition to X only structures XLIII and XLIV are consistent with this observation. If XLIII had been correct instead of X then olefin XXXIII would possess structure

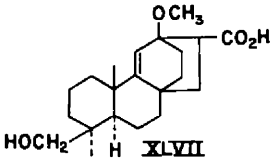


LXV; but XXXIII, after acetylation to give XXXVIII was ozonized to give a diacid (XXXIX) which after esterification to XLI, gave on vigorous alkaline hydrolysis a half-acid ester (XLII). This is consistent with structures X and XLIV, each of which would give rise to one tertiary carboxyl group in the above sequence of reactions, but

not consistent with structure XLIII which would be expected to give rise to two unhindered secondary carboxyl groups. If X had been represented by XLIV, then hydrocarbon XXXVI would have had structure XXI or it would be represented by XLVI, the C-9 epimer of XXI. But, as mentioned above XXXVI was found not to be identical with XXI and if XLVI had been correct then XLIV would have possessed a β-hydrogen atom at C-9. An examination of Dreiding models clearly indicates that in such a case the observed deshielding of the C-10 methyl group by the carbonyl group could not occur. Thus we are left only with structure X.

The hydrogen atom at C-8 in X is assigned the β-configuration because it is known[30] to have this configuration in V from which X was prepared, and because an examination of Dreiding models reveals that had this hydrogen been α, the deshielding of the C-10 methyl group by an anhydride carbonyl group could not occur. In addition, if the C-8 hydrogen were α the double bond in XXXIII would have deshielded the C-10 methyl group, but this was not observed. The NMR observations also indicate that the anhydride moiety in X is *anti* to the double bond—an exception to the much used Alder rule.[35] It is interesting to note that this Diels-Alder adduct also arises by attack of the dieneophile from the *more hindered* β (top) side of the diene.

Othman and Rogers[12] have also mentioned a synthetic approach to atisine from podocarpic acid but have given no details. The workers do, however, state that their Diels-Alder adduct, XLVII, is obtained in impractically poor yield and they do not state whether the carboxyl group in XLVII is on the bridge suitable for ultimate introduction of the methylene and hydroxyl groups as present in atisine. After



XLVII

determining the structures of Diels-Alder adducts (X and XI) and noticing that both of these were "abnormal" adducts we re-examined the mother liquor from which crystalline X and XI were obtained to see if any of the "normal" adduct might be present. We have now found a third adduct in this mother liquor and its structure elucidation will be reported in a future communication.

EXPERIMENTAL

M. ps were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. IR spectra were recorded using a Beckman IR-5 spectrophotometer. NMR spectra were recorded with a Varian A-60 NMR spectrometer, using tetramethylsilane as an internal standard ($\delta = 0$). Gas chromatographs were run at 300° using a column 1/8 in. × 5 ft. of 5% SE-30 on acid-washed Chromosorb W with a hydrogen flame detector and a H_2 flow rate of 30 cc/min and a N_2 flow rate of 45 cc/min.

Synthesis of ketone (V)

O-Methylpodocarpinol was synthesized according to the method of Zeiss *et al.*,[36] starting from podocarpic acid, which in turn was isolated from rimu resin.[37]

The α,β-unsaturated ketone (V) was prepared by the reduction of O-methylpodocarpinol with lithium and t-butyl alcohol in a mixture of tetrahydrofuran and liquid ammonia.[30]

[35] K. Alder and G. Stein, *Angew. Chem.* **50**, 510 (1937).

[36] H. H. Zeiss, C. E. Slimowitz and V. Z. Pasternak, *J. Amer. Chem. Soc.* **70**, 1981 (1948).

[37] I. R. Sherwood and W. F. Short, *J. Chem. Soc.* 1006 (1938).

Preparation of diacetate (VII)

A solution of 20·3 g of the ketone (V) in 650 ml ethanol was heated to reflux and treated with a solution of 12·6 g $NaBH_4$ in 150 ml 80% ethanol. The stirred mixture was refluxed for 2 hr, cooled and cautiously acidified with 6N HCl. Dilution with 1800 ml water gave an oily material which was extracted into ether. The organic layer was washed successively with water, dil. NaOH aq and water, and then dried ($MgSO_4$). Removal of the solvent yielded the glassy diol, 20·1 g, λ_{max}^{KBr} 2·95, 6·07 and 9·7 μ.

Acetic anhydride (30 ml) was added to a solution of 21 g crude diol in 120 ml anhydrous pyridine and the mixture was stirred at room temp for 20 hr. After the addition of 200 ml ether, the reaction mixture was washed successively with water, cold 5% HCl aq and water. The organic layer was dried ($MgSO_4$) and evaporated to yield 27·5 g viscous diacetate (VII), λ_{max}^{film} 5·73, 5·88, 6·08 and 9·05 μ.

Pyrolysis of diacetate VII

Preparation of dienes VIII and IX. A solution of 1·52 g VII in 20 ml anhydrous benzene was pyrolysed by dropwise addition into a column packed with glass helices, maintained at 300–310°, under a steady stream of dry N_2. The addition took approximately 30 min and the compound was allowed to stay in the hot column for an additional 30 min. The cooled column was washed with benzene and the washings washed with cold 5% $NaHCO_3$ aq and water respectively. The organic layer was dried ($MgSO_4$) and evaporated to yield 1·26 g of the oily mixture of dienes (VIII and IX), λ_{max}^{EtOH} 265 (ϵ = 3380) and 276 mμ (ϵ = 2800).

Preparation of Diels-Alder adducts (X) *and* (XI)

A solution of 28·14 g diene mixture and 15 g maleic anhydride, in 80 ml xylene, was refluxed for 6 hr in an atmosphere of N_2. After addition of 100 ml ether, the cold yellow solution was repeatedly extracted with water to remove the unreacted maleic anhydride. During this process solid XI (2·73 g) m.p. 245–250°, appeared in the organic phase and was collected by filtration. Recrystallization from benzene gave the analytical sample of XI, m.p. 251–252°, λ_{max}^{KBr} 5·42, 5·62 and 8·0 μ, NMR ($CDCl_3$) δ 0·91 (3 protons), 0·99(3), 2·02(3), 4·08 (doublet, 1 proton), 4·27 (doublet, 1 proton) and 5·81 (doublet, 1 proton). (Found: C, 71·41; H, 7·75. $C_{30}H_{30}O_5$ requires: C, 71·47; H, 7·82%).

The filtrate was dried ($MgSO_4$) and removal of a major portion of the solvent yielded a viscous liquid which could be crystallized after the addition of a small amount of ether. After several hr standing at 5°, crystalline X was collected and dried, 7·16 g, m.p. 180–194°. The filtrate after removal of the solvent yielded 21·3 g of a gummy mass, λ_{max}^{film} 5·42, 5·61, 5·78 and 8·1 μ.

Repeated crystallization of a small sample of X, from heptane–benzene afforded the analytical sample, m.p. 213·5–214·5°, λ_{max}^{KBr} 5·42, 5·62, 5·78 and 7·92 μ, NMR ($CDCl_3$) δ 0·97(3), 1·40(3), 2·01(3), 3·87 (doublet, 1 proton), 4·28 (doublet, 1 proton) and 6·30 (doublet, 2 protons). (Found: C, 71·18; H, 7·61. $C_{28}H_{30}O_5$ requires: C 71·47; H, 7·82%).

Since the fractional crystallization method proved to be a lengthy and laborious process for the isolation of X, it was found more convenient to isolate it in the form of its dimethyl ester. A suspension of 7 g crude X, m.p. 180–194°, in 50 ml ether and 50 ml methanol was treated with excess ethereal diazomethane. Evaporation of the solvent and recrystallization twice from methanol yielded 5·1 g dimethyl ester (XXVI), m.p. 169–170°, λ_{max}^{KBr} 3·28, 5·27, 5·79, 6·08, 8·05, 8·15 and 14·08 μ, NMR ($CDCl_3$) δ 0·96(3), 1·21(3), 2·05(3), 3·53(3), 3·55(3), 3·88 (doublet, 1 proton), 4·36 (doublet, 1 proton) and 6·44 multiplet, 2 protons). (Found: C, 69·38; H, 8·48. $C_{32}H_{36}O_6$ requires: C, 69·41; H, 8·39%).

Preparation of dimethyl ester XII

An excess of ethereal diazomethane was added to a suspension of 0·19 g XI in 15 ml methanol and 15 ml ether. After standing overnight the reaction mixture, after evaporation of the solvent, yielded 2·1 g gummy dimethyl ester (XII) which could be crystallized from dil. acetic acid only after long standing, m.p. 73–76°, λ_{max}^{KBr} 5·72, 6·1 and 8·12 μ; NMR (CCl_4) δ 0·86(3), 1·00(3), 1·99(3), 3·50(3), 3·53(3), 4·08 (doublet, 1 proton), 4·30 (doublet, 1 proton) and 6·08 (doublet, 1 proton).

A number of attempts to hydrogenate XII at atmo. press. were unsuccessful.

Hydrolysis of XII

Preparation of XIII. A suspension of 2·98 g XII in a mixture of 25 ml 20% NaOH aq and 25 ml methanol was refluxed 8 hr. The clear reaction mixture was diluted with 150 ml water, made acidic with 6N HCl and then extracted with ether. The organic layer was washed with water and then dried ($MgSO_4$). Evaporation of the solvent yielded 2·41 g crystalline XIII which after recrystallization from ethyl acetate–methanol gave m.p. 251–253° (2·2 g). The analytical sample was obtained by further recrystallization from ethyl acetate–methanol and gave m.p. 253–255°, λ_{max}^{KBr} 2·90, 5·86 and 9·80 μ, NMR (CD_3CO_2D) δ 0·92(3). 1·00(3), 3·61 (doublet, 1 proton), 3·97 (doublet, 1 proton) and 6·08 (doublet proton). (Found: C, 69·29; H, 8·45. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%).

Conversion of XIII to XV

Acetylation of 0·93 g hydroxy diacid XIII with 2 ml acetic anhydride in 5 ml dry pyridine for 10 hr at room temp followed by the usual work up yielded 1·0 g crude amorphous acetate (XIV) which was subjected to the action of lead tetraacetate without further purification.

Acetate XIV (1·0 g) was dissolved in 25 ml anhydrous pyridine at 70° and 1·1 g lead tetraacetate was added to the stirred solution under an atm. of N_2. After 10 min, an additional 1·5 g lead tetraacetate was added and the reaction mixture allowed to reflux for 1·5 hr. The pyridine was removed over a steam bath with a water aspirator and the dark brown residue extracted with ether. The ether extract was washed with water, dried ($MgSO_4$) and evaporated to yield 0·66 g brown gum.

A mixture of 0·66 g of the above described material, 25 ml 15% NaOH aq and 25 ml methanol was heated at reflux for 3 hr. The cooled reaction mixture was diluted with 100 ml water and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to yield 0·17 g brown gum which was chromatographed over 9 g acid-washed alumina (activity III). Elution with 40 ml benzene gave 0·087 g crude gummy XV which was identified only by its spectral properties, λ_{max}^{film} 2·94, 3·28, 9·65 (broad), 13·15 and 13·85μ, λ_{max}^{EtOH} 272 mμ (ϵ = 436), 262 mμ (ϵ = 477), 257 mμ (ϵ = 469), 251 mμ (ϵ = 452) and 209 mμ (ϵ = 4770) and NMR (CCl_4) δ 6·91–7·33.

Preparation of XVII

Hydroxy diacid XIII (1·96 g) was hydrogenated with 0·40 g 5% Pt-C catalyst in 50 ml acetic acid at room temp. Removal of the catalyst by filtration followed by dilution of the filtrate with water and collection of the crystalline solid gave 1·95 g XVI contaminated with its acetate formed from the glacial acetic acid solvent during hydrogenation.

A mixture of the above solid (1·96 g) and 50 ml 5% NaOH aq was heated on a steam bath for 2·5 hr. The cooled reaction mixture was diluted with 150 ml water and made acidic by the addition of 6N HCl. The crystalline product (1·9 g) was collected on a filter, washed with water, and gave on drying m.p. 289–292°. Recrystallization from ethyl acetate–pet ether (60–80°) raised the m.p. of XVI to 291–294°, λ_{max}^{KBr} 2·98, 5·88, 9·0 μ, NMR (CD_3CO_2D) δ 0·72(3), 0·94(3).

A solution of 1·66 g XVI and 2 ml acetic anhydride in 10 ml anhydrous pyridine was stirred at room temp for 10 hr. After the addition of 50 ml ether, the reaction mixture was respectively washed with water, cold 5% HCl aq and water. The organic layer was dried ($MgSO_4$) and evaporated to give 1·94 g glassy mixture of XVII and the mixed anhydride obtained by the interaction of XVII and acetic anhydride. The hydrolysis of the mixed anhydride moiety was effected by refluxing 1·94 g of the above mixture in a solution of 15 ml water and 30 ml dioxane for 7 hr. The cooled reaction mixture after dilution with 100 ml water gave 1·8 g (97·3%) crystalline XVII, m.p. 216–220°. The analytical sample was obtained by crystallization from ethyl acetate–pet ether (60–80°) and gave m.p. 218–220°, λ_{max}^{KBr} 2·90, 3·08, 5·75, 5·88 and 8·05 μ. (Found: C, 68·06; H, 8·86. $C_{23}H_{34}O_6$ requires: C, 67·95; H, 8·43%).

Preparation of XVIII

Diacid XVII (0·76 g) was dissolved in 30 ml anhydrous pyridine, maintained at 70°, and 0·8 g lead tetraacetate added to the stirred solution under an atm of N_2. After 10 min an additional 0·8 g lead tetraacetate was added and the reaction mixture refluxed for 1·5 hr. The pyridine was removed on the steam bath with a water aspirator and the dark brown residue extracted into ether. The ether extract was washed with water, dried ($MgSO_4$) and evaporated to give 0·56 g gummy dark brown substance.

A solution of 0·56 g of the above material in 20 ml 10% NaOH aq and 50 ml methanol was refluxed for 2 hr. The cooled reaction mixture was diluted with 100 ml water and extracted with ether. The

ether extract was washed with water and dried ($MgSO_4$). Removal of the solvent gave 0·27 g semi-solid which was chromatographed over 24 g acid-washed alumina (activity III). Elution with 100 ml benzene gave 0·116 g (22·6%) alkene (XVIII), m.p. 131–133°. The analytical sample was obtained by recrystallization from methanol and gave m.p. 133–135°, λ_{max}^{KBr} 2·95, 3·29, 6·10, 9·72, 13·85 and 14·28 μ, NMR ($CDCl_3$-CS_2) δ 0·53(3), 0·91(3), 2·47 (multiplet, 1 proton), 3·31 (doublet, 1 proton), 3·66 (doublet, 1 proton), 5·81 (quartet, 1 proton) and 6·03 (quartet, 1 proton). (Found: C, 82·16; H, 11·10. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·01%).

Preparation of XIX

Hydrogenation of XVIII (0·13 g) in 10 ml ethyl acetate with 0·025 g 5% Pt-C catalyst at atm. press. followed by removal of the catalyst by filtration and evaporation of the filtrate yielded a quantitative amount of the saturated alcohol (XIX), m.p. 143–145°. The analytical sample obtained by recrystallization from methanol had m.p. 146–147°, λ_{max}^{KBr} 2·95 and 9·7 μ, NMR ($CDCl_3$-CS_2) δ 0·91(3) 0·93(3), 3·43 (doublet, 1 proton) and 3·76 (doublet, 1 proton). (Found: C, 82·22; H, 11·57. $C_{19}H_{32}O$ requires: C, 82·54; H, 11·66%).

Conversion of XIX *into* XXI

Alcohol XIX (0·010 g) in 2·5 ml anhydrous pyridine was added to a mixture of 0·15 g CrO_3 and 2·5 ml anhydrous pyridine. After stirring for 1·5 hr, the mixture was poured into ice-water and extracted with ether. The ether extract was washed with cold 5% HCl aq and then with water. The organic layer was dried ($MgSO_4$) and evaporation yielded 0·090 g crude aldehyde (XXII) which was subjected to the following reaction without further purification.

A mixture of 0·085 g XXII, 5 ml diethylene glycol and 1 ml 95% hydrazine was heated at 110–120° for 1·5 hr. Potassium hydroxide, 1 g, was added to the cooled reaction mixture and the mixture was then refluxed for 6 hr. Excess hydrazine and water were distilled out until the temp of the residue reached 220°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine, 0·5 ml, was again added to the residue and refluxing continued for an additional 8 hr. The reaction mixture, distillate and ether washing were combined, added to water, 20 ml, and the entire mixture extracted with ether. The ether extract was thoroughly washed with water and then dried ($MgSO_4$). Evaporation of the ether gave 0·07 g oil which was chromatographed over acid-washed alumina (activity III). Elution with 20 ml pet. ether (60–80°) yielded 0·040 g XXI, which on repeated recrystallization from methanol yielded 0·015 g m.p. 86–87°, identical in every respect with the tetracylic hydrocarbon synthesized from maleopimaric acid.

Preparation of XXIII

A solution of 0·075 g XVIII in 1·5 ml anhydrous pyridine was added to a mixture of 0·090 g CrO_3 and 1 ml anhydrous pyridine. After stirring at room temp for 1 hr, the mixture was poured into ice-water and extracted with ether. The extract was washed with 5% HCl aq then water and finally dried ($MgSO_4$). Evaporation of ether yielded 0·065 g crude XXII which was used in the following reaction without further purification.

A mixture of 0·065 g crude XXII and 0·4 ml 95% hydrazine in 4 ml diethylene glycol was heated at 110–120° for 2 hr under an atm. of N_2. After cooling, KOH (0·4 g), was added and the mixture refluxed for 10 hr. The turbid solution was poured into water (20 ml) and extracted with ether. The ether extract was dried ($MgSO_4$), evaporated and the residue chromatographed over 5 g acid-washed alumina (activity III). Elution with 20 ml pet ether (60–80°) yielded 0·030 g solid which after repeated recrystallization from methanol yielded 0·010 g pure olefin (XXIII), m.p. 71–73°, λ_{max}^{KBr} 3·29, 6·1, 13·8 and 14·28 μ, NMR (CCl_4) δ 0·57(3), 0·80(3), 0·87(3), 3·85 (multiplet, one proton), 5·75–6·2 (multiplet, 2 protons).

Preparation of XXV

The adduct X (0·15 g) was hydrogenated in 15 ml acetic acid in the presence of 0·030 g 5% Pt-C catalyst at room temp. The uptake of H_2 was over within 25 min. The filtrate obtained after the removal of the catalyst was diluted with 100 ml water and collection of the solid on a filter afforded a quantitative yield of XXV, m.p. 251–252°. The analytical sample obtained by recrystallization from benzene had the same m.p., λ_{max}^{KBr} 5·42, 5·62, 5·78 and 7·95 μ, NMR ($CDCl_3$) δ 0·97(3), 1·26(3), 2·05(3),

3·94 (doublet, 1 proton), 4·33 (doublet, 1 proton). (Found: C, 71·41; H, 8·31. $C_{23}H_{32}O_5$ requires: C, 71·10; H, 8·30%).

Preparation of XXVII

A solution of 0·19 g XXVI in 20 ml acetic acid was stirred under an atm. of H_2 with 0·050 g 5% Pt-C catalyst at room temp. After 1 hr, when the uptake of H_2 had ceased, the catalyst was filtered off and the filtrate diluted with water. The crystalline product was collected on a filter and washed with water. A quantitative yield of pure diester (XXVII), m.p. 169–170°, was obtained on drying under vacuum. Recrystallization from methanol did not change the m.p., λ_{max}^{KBr} 5·7, 8·01 and 8·08 μ, NMR ($CDCl_3$) δ 0·94(3), 1·13(3), 2·08(3), 3·62(6), 3·88 (doublet, 1 proton) and 4·35 (doublet, 1 proton) (Found: C, 69·01; H, 8·60. $C_{25}H_{38}O_6$ requires: C, 69·09; H, 8·81%).

Preparation of XXVIII

A suspension of 0·10 g XXVII in 5 ml methanol and 10 ml 10% NaOH aq was refluxed for 6·5 hr. The cooled alkaline solution was made acidic with 6N HCl. The crystalline product was collected on a filter and washed with water. Dry XXVIII, obtained in quantitative yield, gave m.p. 209–211°. The analytical sample, recrystallized from aqueous methanol, showed m.p. 211–212°, λ_{max}^{KBr} 2·89, 5·79, 5·9, 8·05 and 9·75 μ, NMR (CD_3CO_2D) δ 0·96(3), 1·16(3) and 3·66(3). (Found: C, 66·55; H, 9·28. $C_{22}H_{34}O_5$. H_2O requires: C, 66·80; H, 9·17%).

Preparation of XXX

Acetylation of XXVIII with acetic anhydride and pyridine at room temp provided acetate XXIX which showed m.p. 155–156° after recrystallization from hexane–ethyl acetate, λ_{max}^{KBr} 2·89, 3·08, 5·72, 5·78, 5·88 and 8·06 μ, NMR (CCl_4) δ 0·92(3), 1·17(3), 1·98(3) and 3·63(3). (Found: C, 68·85; H, 8·78. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·62%).

Treatment of XXIX with etheral diazomethane gave XXX as a viscous gum which could not be crystallized, λ_{max}^{film} 5·72, 5·78 and 8·2 μ, NMR (CCl_4) δ 0·91(3), 1·16(3), 1·98(3), 3·64(3) and 3·68(3).

Preparation of XXXI

A suspension of 3·5 g XXVII in 50 ml 25% methanolic NaOH aq was refluxed for 30 hr. The cold reaction mixture was diluted with 100 ml water and made acidic with 6N HCl. The solid precipitate was taken up in ethyl acetate, the organic layer washed with water then dried ($MgSO_4$) and finally evaporated to yield 2·89 g crystalline XXXI which after recrystallization twice from a mixture of ethanol and ethyl acetate gave m.p. 270–277°, 2·5 g. After two further recrystallizations from the same solvent it showed m.p. 296–300° (dec), λ_{max}^{KBr} 2·94, 3·13, 5·83 and 9·8 μ.

Preparation of XXXII

Acetylation of 2·33 g XXXI with acetic anhydride in pyridine at room temp gave 1·8 g (69·5%) acetate (XXXII), m.p. 273–277° (dec) after recrystallization twice from ethyl acetate–hexane, λ_{max}^{KBr} 2·9, 5·71, 5·9 and 8·2.

Preparation of XXXIII

The acetoxy diacid (XXXII; 0·53 g) was dissolved in 30 ml anhydrous pyridine, maintained at 70°, and 0·7 g lead tetraacetate was added to the stirred solution under an atm. of N_2. After 10 min, an additional 1 g lead tetraacetate was added and the reaction mixture allowed to reflux for 1·5 hr. The pyridine was removed on the steam bath with a water aspirator and the dark brown residue extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated to give 0·42 g brown solid.

A suspension of 0·42 g of the above solid in a mixture of 50 ml 5% NaOH aq and 25 ml methanol was refluxed for 2·5 hr. The cold solution was diluted with 100 ml water and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to yield 0·32 g yellow solid which was chromatographed on 24 g acid-washed alumina (activity III). Elution with 75 ml benzene afforded 0·22 g (61·6%) XXXIII, m.p. 120–121°, λ_{max}^{KBr} 3·0, 3·28, 6·18, 9·67 and 14·27μ, NMR (CS_2) δ 0·87(3), 0·90(3), 2·28 (multiplet, 1 proton), 2·8(1), 3·24 (doublet, 1 proton), 3·65 (doublet, 1 proton) and 6·14 (doublet, 2 protons). (Found: C, 83·57; H, 11·07. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·02%).

Preparation of XXXIV

The unsaturated alcohol (XXXIII; 0·2000 g) was hydrogenated with 0·040 g 10% Pd-C catalyst in 15 ml ethanol at atm. press. After 2 hr, the catalyst was filtered off and dilution of the filtrate with water followed by filtration and drying yielded a quantitative amount of alcohol (XXXIV), m.p. 141–142°. The analytical sample, obtained by recrystallization, from methanol showed m.p. 142–143°, λ_{max}^{KBr} 3·0, 9·65 μ; NMR ($CDCl_3$-CS_2) δ 0·85(3), 0·93(3), 3·38 (doublet, 1 proton) and 3·82 (doublet, 1 proton). (Found: C, 82·98; H, 11·59. $C_{19}H_{32}O$ requires: C, 82·54; H, 11·66%).

Preparation of XXXVI

A solution of 0·40 g XXXIV in 8 ml anhydrous pyridine was added to a mixture of 0·50 g CrO_3 in 5 ml anhydrous pyridine and the entire mixture was then strirred for 1 hr. After pouring into ice-water, the solution was extracted with ether, the ether extract washed successively with 5% HCl aq and water, and then dried ($MgSO_4$). The solvent was removed by evaporation and 0·35 g crude aldehyde (XXXV) was obtained, λ_{max}^{film} 3·88 and 5·8 μ.

A mixture of 0·35 g XXXV 1·5 ml 95% hydrazine and 10 ml diethylene glycol was heated at 110–120° for 2 hr. After cooling, 1·5 g KOH pellets were added and the mixture refluxed for 12 hr. The solution was poured into 50 ml ice-water and extracted with ether. The ether extract was washed with water and dried ($MgSO_4$). Removal of the solvent yielded 0·31 g oily product which was chromatographed on 6 g acid-washed alumina (activity III). Elution with 100 ml pet ether (60–80°) yielded 0·24 g oily substance which on addition of a mixture of methanol and ether deposited 0·045 g azine (XXXVII), m.p. 240–242°. The analytical sample was obtained by recrystallization from ethyl acetate and gave m.p. 249–253°, λ_{max}^{KBr} 6·1 μ, NMR (CCl_4) δ 0·72(6), 1·03(6) and 7·75(2). (Found: C, 83·72; H, 10·97. $C_{38}H_{60}N_2$ requires: C, 83·75; H, 11·09%).

After removal of XXXVII, the filtrate was evaporated to give a residue which on distillation (100–105° at 1 mm) yielded 0·160 g (42·5%) oily XXXVI, λ_{max}^{film} 3·43, 7·21 and 7·3 μ, NMR (CCl_4) δ 0·85(6) and 0·89(3). Crystallization of a small sample from methanol–ether yielded crystalline hydrocarbon (XXXVI), m.p. 47–48°. (Found: C, 87·31; H, 12·31. $C_{19}H_{32}$ requires: C, 87·61; H, 12·38%)

Preparation of XXXVIII *and its reaction with ozone*

A solution of 0·135 g unsaturated alcohol (XXXIII) in 2 ml anhydrous pyridine was acetylated with 0·5 ml acetic anhydride as described above. The crude acetate (XXXVIII; 0·144 g) showed m.p. 89–91°, λ_{max}^{KBr} 3·26, 5·73, 6·06, 8·1 and 14·23 μ and was subjected to the action of ozone without further purification.

Ozone was passed at −70° through a 0·14 g sample of XXXVIII dissolved in 20 ml methylene chloride until the solution turned deep blue. One ml H_2O_2 (30%) was then added to the solution and the entire mixture stirred at room temp for 6 hr. The excess peroxide was decomposed with a small amount of 10% Pd-C catalyst. The catalyst was removed by filtration and the filtrate was washed with water and dried ($MgSO_4$). Removal of the solvent yielded 0·16 g crude fluffy XXXIX which was subjected to basic hydrolysis without further purification.

Preparation of XLI *and its partial hydrolysis*

A solution of 0·16 g crude XXXIX in 25 ml 10% NaOH aq and 10 ml methanol was refluxed for 1·75 hr. The cooled solution was diluted with 50 ml water and extracted with ether. The alkaline layer was made acidic with dil. HCl aq and extracted with ether. The latter ether extract was washed with water, dried ($MgSO_4$) and evaporated to yield 0·084 g crude hydroxy diacid (XL), m.p. 215–230°.

A solution of 0·084 g LX in 10 ml ether was treated with an excess of ethereal diazomethane. After 2 hr, evaporation of the solvent yielded 0·087 g amorphous hydroxy dimethyl ester (XLI), NMR (CCl_4) δ 3·68, 3·58 and 3·62.

A solution of 0·087 g crude XLI in 5 ml 5% NaOH aq and 5 ml methanol was refluxed for 1 hr. The cold reaction mixture was made acidic with 6N HCl and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to yield 0·079 g amorphous XLII, NMR ($CDCl_3$) δ 0·91(3), 0·98(3), 3·69(3) and 6·55 (broad, 2 protons, disappears on the addition of D_2O).