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DIHYDROAROMATIC COMPOUNDS IN THE DIELS–ALDER REACTION—I

A MODEL FOR ATISINE SYNTHESIS

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Abstract—The Diels–Adler reaction between 6-methoxy-1,2,3,4,7,8-hexahydronaphthalene and ethyl acrylate has been used to effect an entry into the field of 2,4a-ethanodecahydronaphthalene compounds. Transformations leading to 3-methylene-2,4a-ethanodecahydronaphthalene, a model for rings B, C and D of atisine, are described.

THE 1,4-dihydroaromatic compounds obtained by the metal in ammonia reduction of a wide range of aromatic substrates, have, until recently,[1] been little investigated as starting materials for Diels–Alder syntheses. The present paper describes one of a series of such applications which have been studied, the synthetic objective in this case being the tricyclic olefin (V), a model for rings B, C and D of the diterpene alkaloid, atisine. Some of the results of these investigations have been briefly reported elsewhere.[2]

The equilibration of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (I) with potassamide in liquid ammonia[3] or with potassium t-amyloxide in t-amyl alcohol,[4] gave a mixture containing up to 70% of the homoannular conjugated dienol ether (II).[5] This mixture always contained some aromatic material, in spite of stringent precautions to exclude air. Reaction of this material, without further purification, with ethyl acrylate at elevated temperatures gave a moderate yield of the isomeric esters (III and IV, R = Et), in the ratio of 3:1 as estimated by GLC analysis and NMR spectroscopy (see below).

The modest yields in this reaction, coupled with the chance observation that the equilibrium I ⇌ II could be initiated by heating in a glass vessel, led us to investigate the use of the unconjugated dienol ether I directly in the Diels–Alder reaction, with the expectation that the conjugated isomer II, produced *in situ*, could be removed efficiently by reaction with ethyl acrylate, thus avoiding the production of aromatic compounds by side reactions. When I was heated in a sealed tube with ethyl acrylate, a high yield of the mixed esters (III and IV, R = Et) was obtained. Similar *in situ*

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[1] A. J. Birch and P. Hextall, *Austral. J. Chem.* **8**, 96 (1955); A. J. Birch, D. N. Butler and J. B. Siddall, *J. Chem. Soc.* 2939, 2941 (1964); W. Kernick and N. A. J. Rogers, Unpublished work; K. L. Rabone and N. A. J. Rogers, *Chem. and Ind.* 1838 (1965); A. J. Birch and J. S. Hill, *J. Chem. Soc.* (C), 419 (1966).

[2] A. A. Othman and N. A. J. Rogers, *Tetrahedron Letters* 1339 (1963).

[3] A. J. Birch, E. M. A. Shoukry and F. Standafield, *J. Chem. Soc.* 5376 (1961).

[4] R. B. Bates, R. H. Carrighan and C. E. Staples, *J. Amer. Chem. Soc.* **85**, 3030 (1963).

[5] cf. N. A. J. Rogers and A. Sattar, *Tetrahedron Letters* 1311 (1964).

isomerizations and Diels–Alder reactions have been investigated and will be reported later.[6]

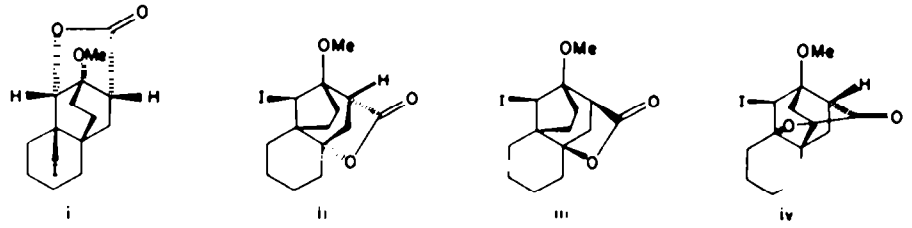
The esters (III and IV, R = Et) were found to be stable to the conditions of the Diels–Alder reaction, and indeed were not interconverted, even at much higher temperatures. They are therefore formed by kinetically controlled processes, and it follows from the Arrhenius equation[7] that the proportion of the more readily produced isomer in the product (III, see below), should be increased at lower temperatures. In practice it was only found possible to increase the amount of *endo*-isomer III in the product to 80% by conducting the reaction under reflux for an extended period of time.

Hydrolysis of the product gave a mixture of the acids (III and IV, R = H), which could only be separated by very careful chromatography on silica gel. The separation could easily be followed by NMR spectroscopic analysis of the chromatographic fractions, and integration of the two vinyl proton signals (*δ* 5·71-*endo*; *δ* 5·92-*exo* ppm).

The structures of the two adducts were established in the following way. That III and IV were related as an *endo–oxo* pair was readily demonstrated by equilibration of the methyl esters using potassium t-butoxide in t-butanol.[8] The equilibrium constant for this reaction slightly favoured the *endo*-isomer III. This and other equilibria in this series will be reported in detail elsewhere.[9]

The *endo*-configuration of the carboxyl group in the more abundant product was suggested by the products of hydrogenation (see below), and established by a study of the NMR spectra of the acids and their methyl esters.* Thus the two acids exhibited vinyl proton signals at *δ* 5·67 and 5·78 ppm respectively, while the corresponding methyl esters exhibited methyl signals at *δ* 3·53 and 3·64 ppm respectively. The high-field signals (*δ* 5·67 and 3·53 ppm) can be assigned to the *endo*-isomers, shielding of the methyl protons by the double bond, and of the vinyl proton by the carbonyl group being anticipated.[11] This situation is illustrated in Fig. 1.

* The reported[9] formation of an iodolactone from III, to which the structure i was assigned, cannot be regarded as evidence for an *endo*-configuration of the carboxyl group, since the *exo*-isomer IV has been shown to give a product with very similar properties under the same conditions. It seems most likely that the structures of these two iodolactones are ii and iii, arising by rearrangement.[10] It is of interest that the IR spectrum of the mother liquors from iodolactonization of the *endo*-acid III suggested the presence of a *δ*-lactone (1780 cm^{-1}), possibly iv.



i ii iii iv

[6] K. L. Rabone, M. A. Qasseem, W. Kernick and N. A. J. Rogers, Unpublished work.
[7] A. A. Frost and R. G. Pearson, *Kinetics and Mechanism* 2nd Ed., p. 23. J. Wiley, New York (1961).
[8] A. C. Cope, E. Cinganek and N. A. LeBel, *J. Amer. Chem. Soc.* **81**, 2799 (1959).
[9] R. Newstead, M. A. Qasseem and N. A. J. Rogers, Unpublished work.
[10] cf. C. D. der Nooy and C. S. Rondestvedt, *J. Amer. Chem. Soc.* **77**, 3583 (1955).
[11] cf. A. H. Kapadi and S. Dev, *Tetrahedron Letters* 1171 (1964); O. L. Chapman, H. G. Smith and R. W. King, *J. Amer. Chem. Soc.* **85**, 806 (1963).

The single vinyl proton signal at δ 5·67 ppm, and the retention of the methoxyl group on treatment with acid, essentially confirm the position of the double-bond and the angular methoxyl group. The position of the double bond was further confirmed by an independent chemical method, before the availability of NMR facilities. Thus, treatment of the acid (III, R = H) with osmium tetroxide resulted in the formation of a glycol to which the structure IX was assigned by analogy with the results of hydrogenation (see below). Further oxidation with lead tetraacetate yielded a single product, the (nujol) IR spectrum of which suggested the lactol

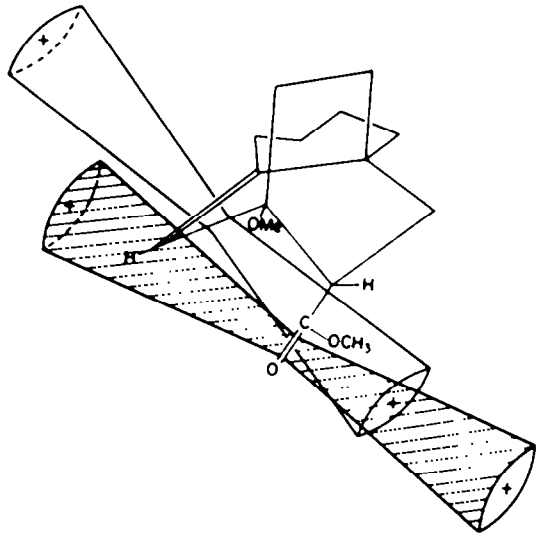


FIG. 1.

structure XI. The solution IR spectrum suggested that this compound was in equilibrium with the open chain compound X. The certain identification of the six-membered ring carbonyl group was made difficult by the possible presence of a carboxylic acid absorption in the same region of the spectrum. The above degradative procedure was therefore repeated on the corresponding primary alcohol XIII, when the IR spectrum of the product unambiguously indicated the presence of saturated carbonyl (1705 cm^{-1}) and aldehyde (1735 cm^{-1}), the low intensity of the latter absorption suggesting the intervention of the hemiacetal form XV.

These observations are best accounted for in terms of the structure (III, R = H) for the more abundant Diels–Alder adduct, but do not absolutely rule out the presence of a C_4-*endo*-carboxyl group (equilibrium involving structure of type XV. The position of the carboxylic acid group was established in the following way. The structure to be expected on the basis of experience with the Diels–Alder reaction (III, R = H),[12] would lead to two consequences: (i) the related hydroxy ester (XVI, R = OH, R′ = Me) would be expected to show evidence of intramolecular hydrogen-bonding, and (ii) the hydroxy acid (XVI, R = OH, R′ = H) would be expected to be a stronger acid than the corresponding methoxy acid (VI, R = H) by virtue of hydrogen-bonding in the anion. These predictions are illustrated in Fig. 2.

[12] A. Wassermann, *Diels-Alder Reactions* p. 31. Elsevier (1965).

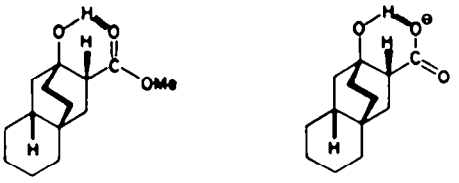


FIG. 2.

At concentrations of the order of 10^{-3} molar in carbon tetrachloride the hydroxy ester showed strong absorption at 3532 cm^{-1} (bonded OH) and weaker absorption at 3593 cm^{-1} (unbonded OH). This result was supported by a study of the NMR spectrum of the hydroxy ester in solution in carbon tetrachloride. This revealed two methyl ester signals, at δ 4·12 and 4·16 ppm, integration suggesting a ratio of about 1:3. This would be in accord with a preponderance of hydrogen-bonded ester groups, the bonding causing slight deshielding of the methyl protons.

The p*K*a's of three related acids (measured in aqueous methanol) are shown in Table 1. The expected trend in acid strength is clearly observed. That this increase

TABLE 1

Acid	p*K*a
XVI, R = R′ = H	6·45
VI, R = H	5·90
XVI, R = OH, R′ = H	5·45
$HO{\cdot}CH_2{\cdot}CO_2H$	3·83*
$MeO{\cdot}CH_2{\cdot}CO_2H$	3·48*

* See Ref. 13.

in acid strength is not associated merely with inductive effects is shown by the last two entries in Table 1.

Hydrogenation of the acid (III, R = H) under atmospheric pressure, led to a single product in high yield. Hydrogenation of the isomeric acid (IV, R = H) on the other hand, gave a low-melting product, which, after esterification with diazomethane revealed the presence of two compounds in about equal proportions on GLC analysis. These findings are fully in accord with the stereochemistry assigned to III and IV. Thus, in the case of the *endo*-isomer III, approach of the double bond to the catalyst surface would be expected to be hindered on the α-face of the molecule by the bulky carboxyl group, hydrogenation therefore leading to the 8a(β)-product exclusively (VI, R = H). The double bond in the *exo*-isomer (IV, R = H) on the other hand, should be equally accessible from either face, hydrogenation therefore leading to approximately equal amounts of the isomers (VII, R = H) and (VIII, R = H). Support for these conclusions was forthcoming from a study of the base-catalysed isomerization of the saturated ester (VI, R = Me), which lead to the production of a new ester, with a retention time on GLC identical with that of one of the products of hydrogenation of the *exo*-unsaturated ester (IV, R = Me).

As a result of these studies, it became clear that 2-methoxy-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid (VI, R = H), was the only one of

* H. Zimmermann, *J. Amer. Chem. Soc.* **78**, 1168 (1956).

the four isomeric saturated acids of this series which would be readily available in a pure condition. Accordingly, the 8a(β)-series was adopted in all further reactions; the ultimate objective of the synthetic scheme being therefore the olefin XXIII rather than V.

Further progress required modification of the angular substituent. Demethylation to yield the hydroxy acid (XVI, R = OH, R′ = HO) was achieved most cleanly using boron trifluoride and acetic anhydride.[14] The use of refluxing hydriodic acid[15] yielded mixtures of the hydroxy acid and the corresponding iodo acid (XVI, R = I, R′ = H). The addition of red phosphorus[16] to the reaction mixture resulted in the formation of the iodo acid alone. Refluxing hydrobromic acid[17] yielded a mixture of the required hydroxy acid and the corresponding bromo acid (XVI, R = Br, R′ = H). Boron trichloride in methylene dichloride,[18] followed by decomposition of the product with methanol, yielded a mixture of the hydroxy ester (XVI, R = OH, R′ = Me) and the chloro ester (XVI, R = Cl, R′ = Me) in high yield. This mixture was used in further reactions.

Prolonged reaction of the mixture with phosphorus pentachloride in dry ether[19] yielded the chloro ester, which was hydrolysed to the corresponding acid (XVI, R = Cl, R′ = H). In view of the drastic conditions involved in some of the transformers described above, the following structural correlations were performed at this stage. Treatment of the chloro, bromo, or iodo acids (XVI, R = Hal, R′ = H) with dilute sodium hydroxide solution, under reflux for extended reaction times[20] resulted in the formation of the hydroxy acid (XVI, R = OH, R′ = H). Esterification with diazomethane, followed by treatment with sodium hydride and then methyl iodide, yielded a mixture of the acids (VI and VII, R = H), in which the latter predominated. It is not clear whether equilibration of the carboxyl group occurred during the reaction of the ester with sodium hydride, or during one of the earlier transformers. In view of the sharp melting points of the hydroxy and chloro acids, the former is believed to be the case.

Reduction of the chloro acid (XVI, R = Cl, R′ = H) with lithium in t-butanol and tetrahydrofuran[21] yielded a low-melting acid, the methyl ester of which revealed the presence of two compounds on GLC analysis.* Partial separation of the acids was achieved by chromatography on silica gel. Equilibration of the methyl esters with potassium t-butoxide in t-butanol[8] showed that they were related as *endo–exo*-isomers. The acids were therefore assigned the structures XVI and XVII (R = R′ = H). A mixture of these acids was used without further purification in all subsequent operations.

* Again, it is not clear at which stage this equilibration occurs, but in light of arguments presented earlier it seems most likely that the prolonged exposure to lithium metal during the reduction step is responsible.

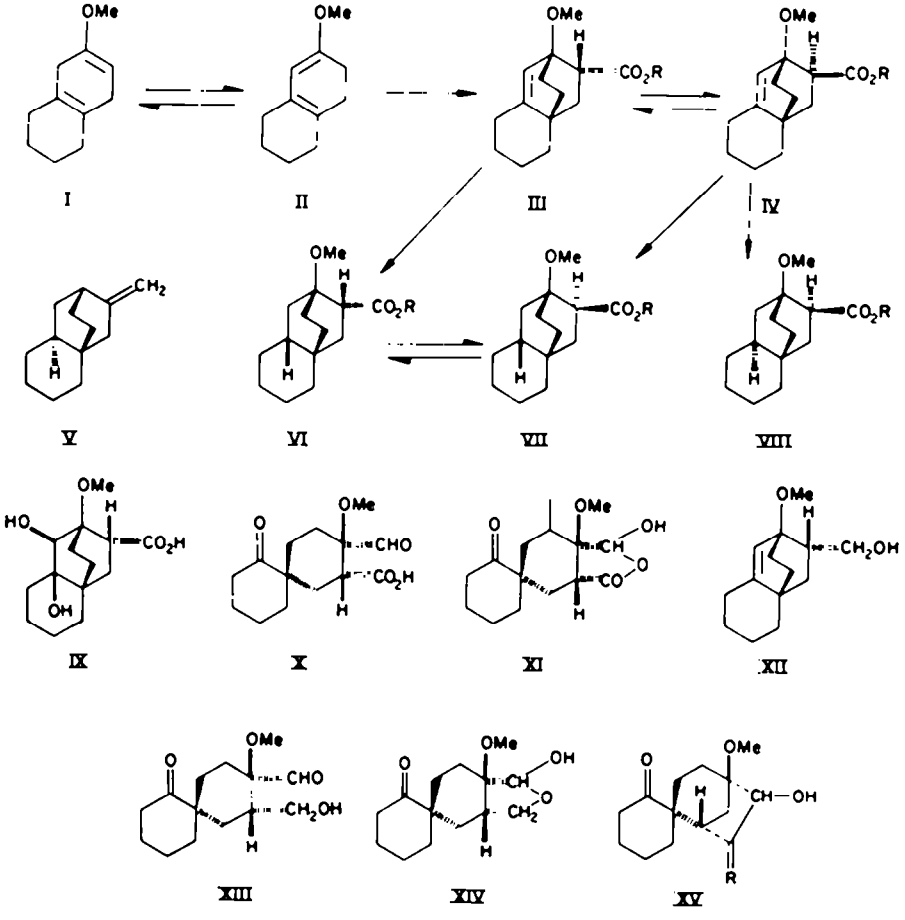
[14] C. R. Narayanan and K. N. Iyer, *Tetrahedron Letters*, 759 (1964).
[15] D. R. Boyed and J. E. Pitman, *J. Chem. Soc.* 87, 1255 (1905).
[16] P. Rabe, *Ber. Dtsch. Chem. Ges.* 37, 1671 (1904).
[17] R. L. Burwell, L. M. Elkin and L. G. Maury, *J. Amer. Chem. Soc.* 73, 2428 (1951).
[18] S. Allen, T. G. Bonner, E. J. Bourne and N. M. Saville, *Chem. and Ind.* 630 (1958).
[19] R. D. Haworth, B. G. Hutley, R. G. Leach and G. Rodgers, *J. Chem. Soc.* 2720 (1962).
[20] J. D. Roberts, W. T. Moreland and W. Frazer, *J. Amer. Chem. Soc.* 75, 637 (1953).
[21] P. G. Gassman and P. G. Pape, *Tetrahedron Letters* 9 (1963).

Three methods were used for the conversion of the acids to the olefin XXIII. These were:

(a) Reduction with lithium aluminium hydride to a mixture of the alcohols (XVIII, R = OH), which with trifluoroacetic anhydride[22] gave the trifluoroacetates (XVIII, R = O·CO·CF_3). Pyrolysis at 400°,[23] followed by column chromatography gave 3-methylene-2(β),4a(β)-ethano-8a(β)-dicahydronaphthalene (XXIII) in moderate yield. The product was homogeneous to GLC apart from a minute trace of impurity of shorter retention time.

(b) Conversion of the acids, through the acid chlorides, to the dimethylamides, followed by reduction with lithium aluminium hydride to the dimethyl amines (XVIII, R = NMe_2). Oxidation to the amine oxides, followed by pyrolysis[8] gave the olefin XXIII in poor yield.

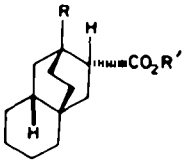
(c) Conversion of the acids to the corresponding acid chlorides, followed by treatment with bromine[24] gave the bromo acid chloride XIX. Hydrolysis with



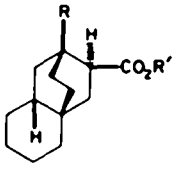
[22] E. J. Bourne, J. C. Tatlow and C. E. H. Tatlow, *J. Chem. Soc.* 1367 (1950).
[23] cf. C. H. DePuy and R. W. King, *J. Amer. Chem. Soc.* **83**, 215 (1961).
[24] H. Kwart and G. Null, *J. Amer. Chem. Soc.* **81**, 2765 (1959).

sodium bicarbonate yielded the hydroxy acid XX. The stereochemistry shown was assigned to these compounds on the basis of the following arguments. Bromination of the acid chloride must proceed via the enol XXIV, in which the (α)-face is seen to be shielded from attack by the carbon atoms of the unsubstituted cyclohexane ring. Base-catalysed hydrolysis of α-halo acids is known in other cases[25] to proceed via an α-lactone intermediate XXV, with consequent retention of configuration. Lithium aluminium hydride reduction of the hydroxy acid XX, followed by periodic cleavage of the resulting glycol XXI gave the ketone, 2(*β*),4a(*β*)-*ethano*-8a(*β*)-*decahydronaphthalene*-3-*one* (XXIII). A Wittig reaction with methylene triphenyl phosphorane[26] gave the olefin XXIII as an oil, homogeneous to GLC.

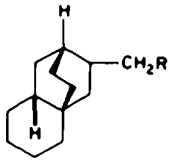
Further aspects of this synthetic approach, of general interest, will be described in subsequent papers. The overall synthetic objectives, however, have been abandoned in light of the recent successfully completed synthetic essays in the diterpene alkaloid field.[27]



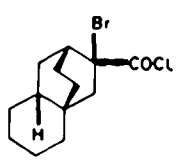
XVI



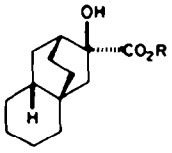
XVII



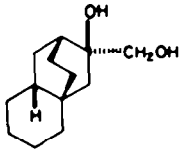
XVIII



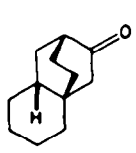
XIX



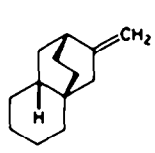
XX



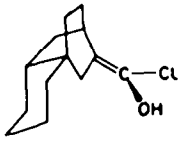
XXI



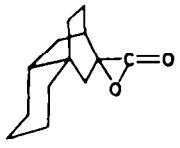
XXII



XXIII



XXIV



XXV

EXPERIMENTAL

All m.ps are uncorrected. NMR spectra were measured on a Varian A-60 spectrometer. GLC analyses were performed on a Pye Argon chromatograph, the stationary phase being polyethylene glycol adipate (PEGA) unless otherwise indicated. Light pet. refers to the fraction boiling between 40 and 60°.

[25] W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* 1208 (1937).

[26] S. Trippett, *Advances in Organic Chemistry, Methods and Results*, Vol. 1, p. 98.

[27] S. Masamune, *J. Amer. Chem. Soc.* **86**, 290, 291 (1964); S. W. Pelletier and P. C. Parthasrathy, *Tetrahedron Letters* 205 (1963); W. Nagata *et al. J. Amer. Chem. Soc.* **85**, 2342 (1963); Z. Valenta, K. Wiesner and C. M. Wong, *Tetrahedron Letters* 2437 (1964); R. W. Guthrie, A. Philipp, Z. Valenta and K. Wiesner, *ibid.* 2945 (1965).

Isomerization of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (I)

(a) To a soln of potassamide (from 40 g P) in liquid NH_3 (2·5 l.), was added a solution of the unconjugated diene (I, 35 g) in dry 1,2-dimethoxyethane (200 ml), the reaction being conducted under dry N_2. A deep red colour was immediately established, and stirring was continued for 1·5 hr. EtOH was then added to destroy the colour, followed by brine until no further violent evaporation occurred. Extraction with ether gave an oil (33 g) which on GLC showed peaks attributable to 6-methoxy-1,2,3,4,7,8-hexahydronaphthalene (II, 76%), the starting material (I, 16%), 6-methoxy-1,2,3,4-tetrahydronaphthalene (3·5%) and 6-methoxy-1,2,3,7,8,9-hexahydronaphthalene (4·5%).[4] The product had λ_{max} 270 mμ (ε_{max} 3280); ν_{max} 1680 and 1625 cm^{-1}, characteristic of the homoannular conjugated diene (II).

(b) To a solution of potassium t-amyloxide (from 2·5 g K) in t-amyl alcohol (50 ml), under dry N_2, was added the hexalin (I, 5 g), and the mixture stirred at 100° for 4 hr. Removal of solvent, and extraction with ether led to the isolation of an oil (4·35 g), of similar composition to that described under (a). The heteroannular diene was not observed using this procedure.

Diels–Alder reaction using the equilibrated dienes

(a) A mixture of the equilibrated dienes (26 g) ethyl acrylate (45 ml), and hydroquinone (1 g) was heated in a sealed tube, at 150°, under N_2, for 36 hr. The volatile materials were removed *in vacuo* and the resulting dark oil distilled to give a nearly colourless product (16 g); b.p. 110–120°/0·1 mm; ν_{max} 1730 (CO_2Et), and 1105 (OMe) cm^{-1}. The NMR spectrum showed signals at δ 5·67 (*endo*-isomer) and 5·78 (*exo*-isomer) ppm, integrating for and *endo–exo* ratio of 3:1. GLC on Apiezon L indicated the presence of two substances in this ratio.

(b) A mixture of the dienes (4 g), ethyl acrylate (15 ml) and hydroquinone (250 mg) was refluxed (110°), under N_2 for 48 hr. The product (3 g) exhibited an *endo–exo* ratio of 4:1.

In situ *isomerization and Diels–Alder reaction of the unconjugated hexalin* (I)

(a) A mixture of the methoxy-hexalin (I, 14 g), ethyl acrylate (25 ml) and hydroquinone (0·5 g) was heated in a sealed tube to 155°, uner N_2 for 36 hr. The product, after distillation (16 g), was identical in all respects with the mixture obtained under (a) above.

(b) A mixture of the methoxy-hexalin (I, 15 g), ethyl acrylate (30 ml), and hydroquinone (0·5 g) was heated to 110° under N_2, in a sealed tube for 6 days. The product after distillation (22 g) was identical with that obtained under (b) above.

Hydrolysis of the mixed esters (12·35 g) in aqueous-alcoholic KOH gave a crude mixture of the *endo-* and *exo*-acids as a yellow gum. Careful chromatography on silica gel gave, on eluting with ether–light pet. (1:4) the *exo*-acid (IV, R = H), (1·5 g), m.p. 118–119°, ν_{max} 1700 (CO_2H) and 1105 (OMe) cm^{-1}. The NMR spectrum showed signals at δ 5·92 (broad, vinyl proton) and 3·38 (OMe) ppm. (Found: C, 71·17; H, 8·65. $C_{14}H_{20}O_3$ requires: C, 71·16; H, 8·53%.) The methyl ester of his acid showed a single peak on GLC on Apiezon-L.

Further elution with the same solvent gave a mixture of isomers (1·5 g), and elution with ether–light pet. (1:2) gave the *endo-acid* (III, R = H), (8 g), m.p. 104–104·5°, ν_{max} 1700 (CO_2H) and 1105 (OMe) cm^{-1}. The NMR spectrum showed signals at δ 5·71 (broad, vinyl proton) and 3·34 (OMe) ppm. (Found: C, 70·8; H, 8·2. $C_{14}H_{20}O_3$ requires: C, 71·26; H, 8·53%.) The methyl ester showed a single peak on GLC on Apiezon-L.

Oxidative degradation of the endo-*acid* (III, R = H)

A solution of the acid (III, R = H, 230 mg) and OsO_4 (200 mg) in dry ether (35 ml) and dry pyridine (1·2 ml) was heated under reflux for 1 hr and then left overnight at room temp. The solvents were removed *in vacuo* and the residue shaken with a solution of mannitol (5 g) in 10% KOH (50 ml) for 12 hr. Acidification followed by extraction with ether gave a green crystalline solid. Heating to 100° with aqueous-alcoholic Na_2SO_3 for 0·5 hr, followed by acidification and extraction with ether gave the *acid-glycol* (IX, 134 mg), which was recrystallized from light pet. m.p. 150–152°. (Found: C, 61·21; H, 8·54. $C_{14}H_{22}O_5$ requires: C, 62·2; H, 8·2%.)

This material was dissolved in galcial AcOH (5 g), $(AcO)_4Pb$ (200 mg) added and the solution stirred for 2 days. Removal of the volatile materials *in vacuo*, followed by addition of brine and extraction with ether gave the *spiroundecanone* (XI) as a solid (87 mg); m.p. 160–162°, ν_{max} (CH_2Cl_2)

3500 (OH), 1800 (γ-lactol), 1730 (aldehyde) and 1705 (ketone) cm^{-1}. ν_{max} (nujol) 3275 (OH), 1770 (γ-lactol) and 1700 (ketone) cm^{-1}. (Found: C, 62·36; H, 7·69. $C_{14}H_{20}O_5$ requires: C, 62·67; H, 7·55%.)

Oxidative degradation of the endo*-alcohol* (XII)

The acid (III, R = H, 100 mg) was reduced to XII with LAH. The product (66 mg) was subjected to the reactions described above to yield the *spiroundecanone* (XIII = XIV) as an oil (58 mg); ν_{max} (CH_2Cl_2), 3400 (OH), 1735 (aldehyde) and 1705 (ketone) cm^{-1}.

Iodolactonization of the acids (III *and* IV, R = H)

(a) A solution of the *endo*-acid (III, R = H, 48 mg) in 0·5N $NaHCO_3$ (1·5 ml) containing a few drops of MeOH, and a solution of I_2 (199 mg) and KI (232 mg) in water (1·5 ml) were mixed together and shaken in the dark for 30 hr at room temp. $CHCl_3$, followed by $Na_2S_2O_3$ aq were added, and the mixture shaken until two colourless phases were obtained. The aqueous phase was further extracted with $CHCl_3$, and the combined extracts washed with dil. $NaHCO_3$. Evaporation yielded a crude iodolactone (50 mg) which recrystallized from light pet. as yellowish needles; m.p. 94–98° (dec.); ν_{max} (C_6H_{12}) 1805 cm^{-1}. The NMR spectrum showed a signal at δ 3·29 ppm (OMe). (Found: C, 46·6; H, 5·2. $C_{14}H_{19}O_5I$ requires: C, 46·4; H, 5·2%.)

On evaporation, the mother liquors from the recrystallization had ν_{max} (C_6H_{12}) 1805 (γ-lactone), 1780 (δ-lactone) and 1710 cm^{-1}.

The *exo*-acid (IV, R = H, 116 mg), when treated in the same way, yielded an iodolactone (190 mg), recrystallized from light pet. as yellowish needles; m.p. 85–90° (dec.); ν_{max} (C_6H_{12}) 1805 cm^{-1}. The NMR spectrum showed a signal at δ 3·29 ppm. (Found: C, 46·9; H, 5·1. $C_{14}H_{19}O_5I$ requires: C, 46·4; H, 5·2%.)

Hydrogenation of the endo*-acid* (III, R = H)

The acid (1 g) was hydrogenated at room temp, and under atm press, in solution in MEOH (30 ml) and over Adam's catalyst (40 mg). When the H_2 uptake had ceased, the catalyst was filtered off and the MeOH removed to yield a solid (1 g). Recrystallization from a mixture of ether and light pet. gave the product, *2-methoxy-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid* (VI, R = H); m.p. 130–131°; ν_{max} (nujol) 1700 (CO_2H) and 1100 (OMe) cm^{-1}. (Found: C, 70·31; H, 9·03. $C_{14}H_{22}O_5$ requires: C, 70·55; H, 9·31%.)

The methyl ester of this acid showed a single peak on GLC. After equilibration with t-BuOK in t-BuOH, the product revealed the presence of both VI and VII (R = Me), the latter predominating

Hydrogenation of the exo*-acid* (IV, R = H)

The acid (0·5 g) was hydrogenated as before, but using 1,2-dimethoxyethane as solvent. The product (0·41) was a waxy solid melting over a wide range. The methylated product showed two peaks due to the esters VII (60%) and VIII (40%) (R = Me), on GLC.

Demethylation of the saturated methoxy acid (VI, R = H)

(a) The acid (1·8 g) was dissolved in an excess of glacial AcOH, HI (16 g) added, and the mixture heated to reflux under N_2 for 3 hr. The volatile materials were removed *in vacuo*, brine added and the product extracted with ether. The crude acidic product was esterified with diazomethane and the mixed esters adsorbed onto a silica gel column. Elution with light pet.–ether (20:1) yielded the *iodoester* (XVI, R = I, R′ = Me), hydrolysis of which gave *2-iodo-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid* (XVI, R = I, R′ = H, 570 mg); m.p. 200°. (Found: C, 46·4; H, 5·6. $C_{13}H_{19}O_5I$ requires: C, 46·7; H, 5·7%.)

Further elution with light pet.–ether (7:3) yielded the *hydroxyester* (XVI, R = OH, R′ = Me) as an oil (800 mg); ν_{max} 3400 (OH), and 1730 (CO_2Me) cm^{-1}. In 0·005 M solution in CCl_4, the ester showed ν_{max} 3593 (OH unbonded) (m), and 3532 (OH bonded, s) cm^{-1}. The NMR spectrum (CCl_4) revealed signals at δ 4·12 (CO_2Me unbonded) and 4·16 (CO_2Me bonded) ppm. Hydrolysis gave *2-hydroxy-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid* (XVI, R = OH, R′ = H) as a waxy solid, recrystallized from hexane–ether, m.p. 124–125°. (Found: C, 69·4; H, 9·3. $C_{13}H_{20}O_5$ requires: C, 69·5; H, 8·9%.)

By using a larger excess of HI, and a catalytic quantity of red P, the iodoacid (XVI, R = I, R′ = H) could be obtained as the sole product of this reaction.

(b) The acid (VI, R = H, 417 mg) was dissolved in the minimum quantity of glacial AcOH. Redistilled HBr (48%, 11 g) was added, and the mixture heated to 135° for 3 hr. Isolation of the acidic product, followed by chromatography on silica gel afforded on elution with light pet.–ether (4:1), unchanged starting material (120 mg) and on further elution with light pet.–ether (1:1), the hydroxyacid (XVI, R = OH, R′ = H, 204 mg).

By continuing the reflux for 24 hr, followed by separation of the acidic products by chromatography of their methyl esters and subsequent hydrolysis, the major product was *2-bromo-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid* (XVI, R = Br, R′ = H); m.p. 155–156°. (Found: C, 54·3; H, 6·7; Br, 27·5. $C_{13}H_{19}O_2Br$ requires: C, 54·3; H, 6·6; Br, 27·8%.) This product was accompanied by 30% of the hydroxyacid (XVI, R = OH, R′ = H).

(c) The acid (206 mg) in dry ether (4 ml) was added to a solution of BF_3-etherate (3 ml) in Ac_2O (8 ml), and the mixture maintained at 0° for 20 hr, and then at room temp for 30 min, cautious addition of MeOH, and then of water at 0° was followed by removal of solvents *in vacuo*, and extraction to give a mixture of the acids (XVI, R = OH, R′ = H and R = OAc, R′ = H) and their methyl esters. Mild alkaline hydrolysis of the mixture yielded the hydroxyacid (XVI, R = OH, R′ = H; 106 mg).

(d) The acid (6 g) was dissolved in CH_2Cl_2 (35 ml), and BCl_3 (25 ml) added at −60°. The vessel was sealed and shaken at room temp for 20 hr. The container was then opened, and the excess BCl_3 allowed to evaporate. MeOH (8 ml) was added cautiously with swirling. On removal of all volatile materials *in vacuo*, a thick syrupy product (5·5 g) was obtained. Esterification with diazomethanane gave a mixture of the esters (XVI, R = OH, R′ = Me and R = Cl, R′ = Me) which could be separated into its components on column chromatography, but was normally used further, without additional purification.

The chloro acid (XVI, R = Cl, R′ = H)

A solution of the hydroxy ester (XVI, R = OH, R′ = Me), or of the mixed esters described in (d) above (5 g) in dry ether, was added to a suspension of PCl_5 (25 g) in CCl_4 (100 ml) and the mixture stirred at room temp for 3 days, with rigorous exclusion of moisture. The mixture was then cooled in ice, and ice-water cautiously added. Extraction with ether yielded the *chloro ester* (XVI, R = Cl, R′ = Me; 5·4 g), which on mild alkaline hydrolysis yielded *2-chloro-2(β),4a(β)-ethano-8a(β)-decahydronaphthalene-3(α)-carboxylic acid* (XVI, R = Cl, R′ = H), recrystallized from light pet.; m.p. 155–156° (4·4 g). (Found: C, 64·55; H, 7·89; Cl, 14·77. $C_{13}H_{19}O_2Cl$ requires: C, 64·33; H, 7·83; Cl, 14·63%.)

Hydrolysis of the halogeno acids (XVI, R = Cl *and* Br, R′ = H)

The acid (150 mg) in EtOH (0·5 ml) was added to a 1% NaOH solution in 50% EtOH (10 ml) and the mixture heated under reflux for 24 hr. Extraction of the organic acid and recrystallization from n-hexane–ether gave the hydroxy acid (XVI, R = OH, R′ = H), m.p. 124–125° alone, and in admixture with an authentic sample.

Etherification of the hydroxy ester (XVI, R = OH, R′ = Me)

The hydroxy ester (151 mg) in dry ether (5 ml) was added to a suspension of NaH (3000 mg) in dry ether (10 ml), and the mixture heated under reflux, under N_2 for 48 hr. MeI (8 ml) was added, and the heating continued for 16 hr. More MeI (2 ml) was added, and the heating continued for a further 4 hr. The excess NaH was then decomposed by the addition of AcOH at 0°C, and the crude product esterified with diazomehtane to yield a mixture of hydroxy and methoxy esters (138 mg), which was separated into its components by column chromatography. GLC revealed that the methoxy ester was a mixture of VI and VII (R = Me), in which the latter predominated.

Reduction of the halogeno acids (XVI, R = X, R′ = H)

A solution of the chloro acid (XVI, R = Cl, R′ = H; 4 g) in tetrahydrofuran (20 ml) and dry t-BuOH (100 ml) was heated to reflux under N_2. Li (10 g) was added in small pieces over a period of 30 min, followed by more t-OH (5 ml), and the refluxing continued for 3 hr. MeOH was added to destroy the excess Li, the mixture acidified with 2N HCl and the product extracted to yield a solid

melting over a wide range (3·4 g). GLC of the methyl ester revealed the presence of two components. By analogy with the methoxy-esters (VI and VII, R = Me), the component of lower retention time was assigned the *endo*-configuration (XVI, R = H, R′ = Me), the other component (XVII, R = H, R′ = Me) being present to the smaller extent. This material, after recrystallization from n-hexane, was used without further purification in all subsequent stages; m.p. 114–120°. (Found: C, 75·0; H, 9·7. $C_{13}H_{20}O_2$ requires: C, 75·0; H, 7·9%.)

Adsorption of the mixed acids (340 mg) onto a silica gel column followed by elution with light pet.–ether (19:1) gave a large fraction (270 mg) melting at 107–114°. Recrystallization from n-hexane gave white crystals, m.p. 110–113°. GLC of the methyl esters revealed that the major component of the acid was 2(β),4a(β)-*ethano*-8a(β)-*decahydronaphthalene*-3(α)-*carboxylic acid* (XVII, R = R′ = H; 82%) accompanied by the 3(β)-isomer (18%). Further elution with light pet.–ether (9:1) gave a second fraction (32 mg), m.p. 114–120°. GLC of the methyl esters revealed that the main component of this acid was 2(β),4a(β)-*ethano*-8a(β)-*decahydronaphthalene*-3(β)-*carboxylic acid* (XVII, R = H, R′ = H; 83%) accompanied by the 3(α)-isomer (17%).

The 2-bromo and 2-iodo acids behaved similarly on reduction.

3-*Methylene*-2(β),4a(β)-*ethano*-8a(β)-*decahydronaphthalene* (XXIII)

(a) The mixed acids (XVI and XVII, R = R′ = H; 500 mg) were reduced with LAH to the *alcohols* (XVIII, R = OH; 490 mg). The oily product was stirred with trifluoroacetic anhydride (5 ml) for 2 hr at room temp. The volatile materials were removed under red. press., and dry CCl_4 (2 ml) added, and then distilled off. This process was repeated three times, and then the product dissolved in CCl_4 and shaken with anhdrous $NaHCO_3$, the solution filtered and evaporated to yield the *trifluoroacetates* (XVIII, R = O·CO·CF_3; 570 mg); ν_{max} 1790 cm^{-1}.

The oily esters were dissolved in pyridene (2 ml) and passed down a pyrolysis tube at 400° in a stream of dry N_2, the product (300 mg) being collected in a trap cooled by an acetone–Drikold bath. Chromatography on an alumina column gave, on elution with pentane, the *exo*-cyclic methylene compound (XXIII; 84 mg); ν_{max} 1730 (w), 1680 (w) and 880 and 885 (s) cm^{-1}. GLC showed the product to be 95% pure.

(b) The mixed acids (XVI and XVII, R = R′ = H; 2 g) were refluxed in thionyl chloride for 3 hr. The excess thionyl chloride was removed *in vacuo*, and the crude acid chlorides (ν_{max} 1800 cm^{-1}) dissolved in dry ether (5 ml), cooled to 0°, added slowly to dimethylamine (5 ml) cooled to −30°, and allowed to stand at 0° for 4 hr. On evaporation of the volatile materials, and washing with brine, the crude amides (1·9 g), ν_{max} 1655 cm^{-1}, were obtained. Reduction with an excess of LAH (3 hr at room temp) gave the amines (XVIII, R = NMe_2; 1·7 g).

The mixed amines (704 mg) were dissolved in MeOH (10 ml), H_2O_2 (100 vol., 6 ml) added dropwise, and the reaction mixture kept at room temp for 24 hr. Moistened Pt black (300 mg) was added at 0°, and the mixture stirred at for 16 hr at room temp. Filtration of the catalyst followed by evaporation of the solvents yielded the *hydrated amine oxide* (XVIII, R = NMe_2^+ O·H_2O) as a thick syrup. This product was heated slowly to 160–190°, under partial vacuum, while a stream of N_2 was passed through the system. Volatile materials were collected in an acetone–Drikold cooled trap. After 2 hr, the distilled material (240 mg) was collected, and chromatographed on alumina to yield the hydrocarbon (XXIII, 22 mg). The spectroscopic and GLC behaviour were identical with those of the product of the previous experiment.

(c) The mixed acids (700 mg) were added to freshly distilled thionyl chloride (30 ml) and the mixture refluxed for 1 hr. Br_2 (4 ml) was then added slowly and the heating continued for a further 4 hr. The volatile materials were evaporated, yielding the crude α-*bromo acid chloride* (XIX). A solution of NaOH (5 g) in water (25 ml) and 1,2-dimethoxyethane (25 ml) was added, and the mixture heated under reflux for 3·5 hr. Acidification and extraction gave the crude α-*hydroxy acid* (XX) as a viscous oil (600 mg). Esterification of a small portion with diazomethane yielded the hydroxy ester; ν_{max} 3400 (OH) and 1740 (CO_2Me) cm^{-1}.

The crude hydroxy acid was dissolved in dry ether (10 ml), added to a suspension of LAH (500 mg) in dry ether (20 ml) and refluxed for 4 hr. The excess hydride was decomposed carefully with water, and the product isolated by extraction with ether. The crude *glycol* (XXI; 400 mg) was obtained as viscous oil; ν_{max} 3400 cm^{-1}.

The crude glycol (5·03 g), in MeOH (30 ml), was added to a solution of $NaIO_4$ (12·5 g) in MeOH (445 ml) and water (25 ml). The mixture was stirred at room temp for 40 hr, and then the MeOH

evaporated *in vacuo* and the crude product isolated as an oil (4·3 g). Adsorption onto a silica gc column, and elution with light pet.–ether (19:1) gave *2(β),4a(β)-decahydronaphthalene-3-one* (XXII; 1·7 g) as a colourless oil. The product showed a single peak on GLC; ν_{max} 1710 cm^{-1}. The *2,4-dinitrophenylhydrazone* had m.p. 175–176°. (Found: C, 60·33; H, 6·37; N, 15·50. $C_{18}H_{22}O_4N_4$ requires: C, 60·32; H, 6·19; N, 15·63%.) Further elution with light pet.–ether (3:1) gave a mixture of the ketone (XXII) and the glycol (XXI).

Into a solution of the ketone (800 mg) in dry ether (10 ml) was filtered through glass wool, a solution of methylene triphenyl phospharane (from triphenylmethylphosphonium bromide, 20 g)[36] in dry ether (150 ml), under N_2. The mixture was stirred for 12 hr at room temp, and then dry tetrahydrofuran added while the ether was being removed by distillation. When the distillation temp rose to 65° the addition was stopped, and the mixture refluxed for a further 6 hr. The volatile materials were removed and the product (1·25 g) extracted into n-pentane, washed with water, dried and evaporated.

Adsorption onto an alumina column, and elution with n-pentane gave the product, *3-methylene-2(β),4a(β)-ethano-8a(β)-decahydronapthhalene* (XXIII; 200 mg) as a colourless oil. GLC revealed a single peak; ν_{max} 3050 (m) (=CH_2 stretch), 1670 (m) (C=C stretch) and 880 and 885 (s) (=CH_2 out of plane bending) cm^{-1}. The NMR spectrum showed a complex multiplet with peaks at δ 4·58 and 4·70 ppm, integrating correctly for two vinyl protons. (Found: C, 88·77; H, 11·30. $C_{15}H_{26}$ requires: C, 88·57; 11·43%.)