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# DIHYDROAROMATIC COMPOUNDS IN THE DIELS–ALDER REACTION—II

## A MODEL FOR VEATCHINE SYNTHESIS

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**Abstract**—The conjugated ketone V has been obtained via the *in situ* isomerization and Diels–Alder reaction with α-acetoxyacrylonitrile, of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene, followed by hydrolysis of the adducts and acid-catalysed rearrangement. Transformations leading to 10-methylene-2(α), 8a(α)-ethano-4a(α)-decahydronaphthalene (XXVII), a model for rings B, C and D of the veatchine alkaloids, are described.

THE USE of the Birch reduction products of aromatic substrates as starting materials for the Diels–Alder synthesis has recently been investigated.[1] The present paper describes one of a series of such applications, the synthetic objective in this instance being the tricyclic olefine (XXVII), a model for rings B, C and D of the veatchine group of diterpene alkaloids.

A tentative approach to the epimeric olefine (XXVIII) was made via the hydroxyester I (R = H), the synthesis of which has been described elsewhere.[1a] This was readily converted into the hypochlorite I (R = Cl), which on refluxing in carbon tetrachloride produced the bicyclic chloroester (II).[cf. 2] Attempts to cyclize this compound to a product with the carbon skeleton of XXVIII were unsuccessful.

The use of α-acetoxyacrylonitrile as a dienophile in the Diels–Alder reaction[cf. 3] with 6-methoxy-1,2,3,4,7,8-hexahydronaphthalene, proved more promising. This gave, in modest yield, a mixture of two epimeric acetoxynitriles. The yield of these products was much improved by employing the *in situ* isomerization of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene.[cf. 1a]

Mild alkaline hydrolysis of either adduct yielded the unsaturated ketone (IV). As expected,[cf. 4] treatment with mineral acid resulted in a smooth rearrangement to the conjugated hydroxyketone (V). Reduction with lithium in liquid ammonia yielded a single glycol to which structure (VI) was assigned as representing the most stable configuration (*trans*-ring fusion; equatorial substituent).[5] Further, the anion-radical, intermediate in the reduction of V is constrained in the conformation considered most likely to lead to a *trans*-ring fusion in the product.[6]

The carbon skeleton required for elaboration to the desired product (XXVII) was obtained in the following manner.

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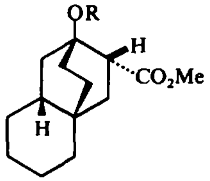

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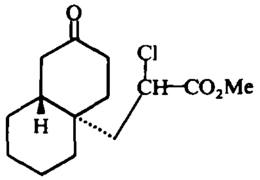

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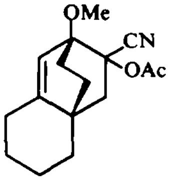

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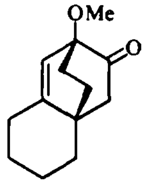

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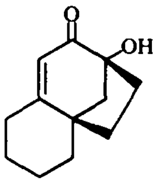

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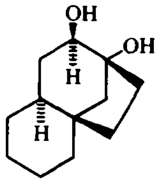

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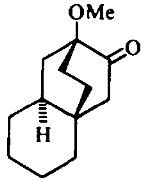
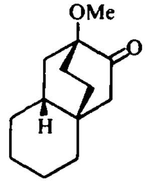


VII



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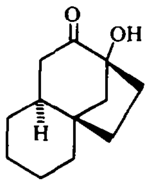

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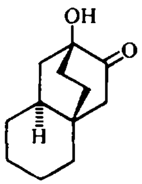
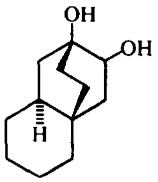
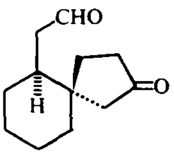


X



XI

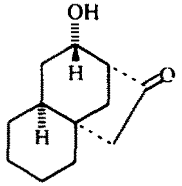


XII

Periodate oxidation to the spirodecanone (XII) followed by cyclization with potassium hydroxide in methanol yielded the hydroxyketone (XIII). The α (equatorial) configuration was assigned to the hydroxy group on the basis of the presumed thermodynamic control of the cyclization reaction. The presence of the bicyclo [3.2.1] octane skeleton in this product was demonstrated in two ways:

(a) oxidation with chromium trioxide in pyridine gave rise to a diketone (XIV) which in the IR region exhibited absorption typical of both 5- and 6-membered ring ketones.

(b) conversion to the dithioketal (XVII) followed by oxidation gave a 6-membered ring ketone (XVIII). These observations eliminate the alternative structure (XX) for the hydroxyketone.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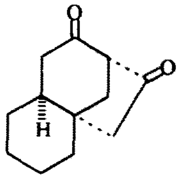
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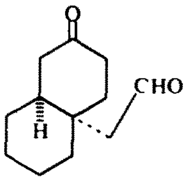
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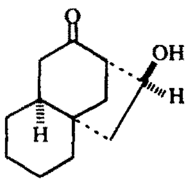
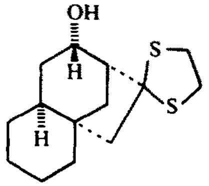

XVI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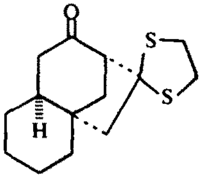
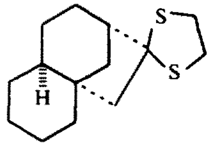

XVIII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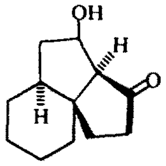
XX

At this stage it was felt desirable to place the *trans*-decalin structure of the glycol (VI) on a firmer footing. This was achieved in the following way. Hydrogenation of the unsaturated ketone (IV), using a Pd catalyst, in methanolic solution, resulted in the formation of a major product (>95%) to which the 8a (α)-configuration (VII) was assigned on the basis of anticipated greater ease of approach to the catalyst surface on the α-face of the molecule.[cf. 1a] The minor product (<5%) was assumed to be the 8a-epimeric ketone (VIII).*

It was initially anticipated that acid-catalysed rearrangement of the methoxyketone (VII) would lead to the hydroxyketone (IX), metal-in-ammonia reduction of which would produce the glycol (VI). In the event, this sequence of reactions led to a crude product, a TLC analysis of which revealed the presence of VI as a minor product, and one, or possibly two, less polar compounds which predominated. Crystallization

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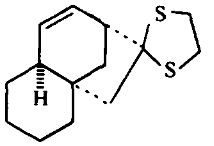
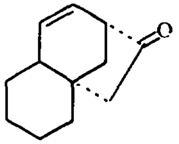
* The possibility that accumulation of polar molecules around the carbonyl group of V might lead to greater ease of catalyst approach to the β-face of the molecule was discounted as a result of hydrogenation in hexane. The product composition in this experiment was nearly identical with that formed in the more polar, hydrogen-bonding solvent.

produced a single glycol, not identical with VI, to which the structure XI* was assigned on the following evidence.

Periodate oxidation (presumably to the *cis*-decalone (XV)), followed by base-catalysed cyclization led to a single hydroxyketone, distinct from XIII, which was assigned structure (XVI) on the basis of its IR spectrum and presumed thermodynamic



XXI



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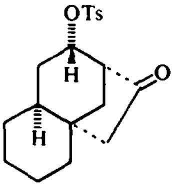

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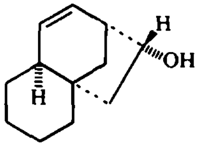

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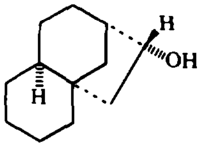
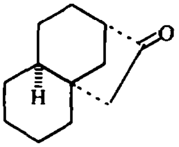
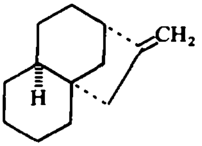


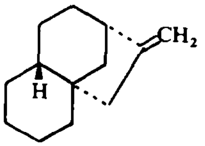
XXV



XXVI



XXVII



XXVIII

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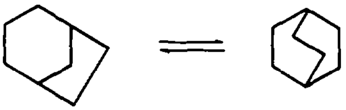
* The production of this glycol on reduction of ketonic precursor implies that for the equilibrium IX ⇌ X, the equilibrium constant has a value considerably in excess of unity. The result may be contrasted with that for the parent hydrocarbon system



in which the equilibrium favours the bicyclo(3,2,1) octane structure.[8] These results may be reconciled with each other and with that for the system

where the equilibrium strongly favours the bicyclo[2.2.2] octenone side,[9] in terms of the contrasting effect of converting a tetrahedral to a trigonal carbon atom in the two systems. This will, inter alia, increase the angle strain in the bicyclo [3.2.1] octane, and reduce non-bonded interactions in the bicyclo [2.2.2] octane system.

control in the cyclization step. Oxidation led to the diketone XIV, previously obtained by oxidation of XIII.

Further synthetic work was concentrated on production of the ketone XXVI. This was obtained in a number of ways:

(a) Wolff–Kishner reduction of the dithioketal XVIII, followed by hydrolysis of the product (XIX) in presence of mercuric acetate.

(b) All attempts to dehydrate the hydroxyketone (XIII) were unsuccessful, but dehydration of the dithioketal (XVI) followed by hydrolysis of the product (XXI) gave the unsaturated ketone (XXII) in very poor yield. Hydrogenation led to the desired product.

(c) The only practicable route discovered lay through the *p*-toluene sulphonate (XXIII). LAH reduction gave the alcohol (XXV) together with a small quantity of the unsaturated compound (XXIV). The *endo*-configuration was assigned to these alcohols on the basis of the known tendency of LAH reduction to produce the epimer arising from approach of the reagent to the less hindered face of the CO group.[10]

Hydrogenation of the unsaturated components of the product, followed by chromic acid oxidation, produced the desired ketone (XXVI) in reasonable yield. Wittig reaction with methylene triphenyl phosphorane gave the desired olefine (XXVII) as an oil, homogeneous to gas–liquid chromatography.

## 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°.

### 2-*Methoxy*-2,4a-*ethano*-$\Delta^{1,8a}$-*octahydronaphthalene*-3-*one* (IV)

A mixture of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (15 g), α-acetoxyacrylonitrile (20 ml) and hydroquinone (0·25 g) was heated under $N_2$, in a sealed tube at 150° for 36 hr. Volatile materials were removed from the black viscous product on a steam-bath, under vacuum. Repeated extraction with ether, followed by evaporation gave a crude adduct (33 g). Adsorption on silica gel and elution with light pet–ether (3:1) gave the *adduct* III as a white, crystalline solid (24 g).

More careful chromatography enabled the two isomers to be separated. They were present in a ratio of about 3:2 and had the following properties.

*Isomer* A. m.p. 102–103°; $\nu_{max}$ 2260, 1760 and 1660 cm$^{-1}$; The NMR spectrum showed signals at $\delta$ 5·72 (vinyl proton), 3·44 (OMe) and 2·03 (OAc) ppm. (Found: C, 69·8; H, 7·4; N, 5·4. $C_{16}H_{21}O_3N$ requires: C, 69·8; H, 7·7; N, 5·1%).

*Isomer* B. m.p. 98–100°; $\nu_{max}$ 2260, 1760 and 1660 cm$^{-1}$; The NMR spectrum showed signals at $\delta$ 5·83 (vinyl proton), 3·42 (OMe) and 2·1 (OAc) ppm. (Found: C, 69·9; H, 7·9; N, 4·8. $C_{16}H_{21}O_3N$ requires: C, 69·8; H, 7·7; N, 5·1%).

A comparison of the vinyl proton and acetate resonances suggests that *isomer* A has the *endo*-acetoxy-*exo*-nitrile configuration and *isomer* B the *exo*-acetoxy-*endo*-nitrile configuration.

To a soln of the mixed adducts (18 g) in THF (200 ml) was added 14% KOHaq (100 ml) and MeOH (40 ml). The mixture was heated to 40° for 3 hr and MeOH and THF removed on a rotary evaporator. Water was added and the mixture extracted with ether to give crude IV (12·4 g), which was purified by distillation, b.p. 120°/0·07 mm. The product, a colourless liquid, gave a single peak on GLC, and had $\lambda_{max}$ 296 mμ ($\varepsilon_{max}$ 260), characteristic of an unconjugated ketone with a double bond suitably placed for n–π* enhancement;[cf. 11] $\nu_{max}$ 1725 and 1105 cm$^{-1}$. (Found: C, 75·8; H, 9·0. $C_{13}H_{18}O_2$ requires: C, 75·7; H, 8·8%).

### 3-*Hydroxy*-3,4a-*ethano*-$\Delta^{1,8a}$-*octahydronaphthalene*-2-*one* (V)

The methoxyketone IV (30 g) was heated on the steam bath for 3·5 hr with a mixture of glacial AcOH (15 ml) and conc HCl (30 ml). After dilution with water (500 ml), the product was extracted with ether, washed with $Na_2CO_3$aq, dried and evaporated. The product was recrystallized from ether–light pet. to give V as white crystals (27·9 g); m.p. 90–91°; $\nu_{max}$ (Nujol) 3480, 1675 and 1600 $cm^{-1}$. (Found: C, 75·1; H, 8·2. $C_{12}H_{16}O_2$ requires: C, 75·0; H, 8·4%).

2(β),3-*Dihydroxy*-3(β), 4a(β)-*ethano*-8a(α)-*decahydronaphthalene* (VI)

(a) To a soln of V (5·05 g) in dry ether (50 ml) was added abs EtOH (75 ml) and liquid ammonia (300 ml). To the stirred soln was added Li metal (5 g) in small pieces over 20 min. Stirring was continued for a further 30 min when brine was cautiously added. Extraction with ether yielded a crude product (4·68 g), elution of which from a short silica gel column with light pet./ether gave the *glycol* VI (3·72 g) as a white solid; m.p. 196–197°; $\nu_{max}$ (Nujol) 3480 $cm^{-1}$. (Found: C, 73·3; H, 10·3. $C_{12}H_{20}O_2$ requires: C, 73·4; H, 10·3%).

(b) The ketone V (0·8 g) was hydrogenated in MeOH, at room temp and under atm press, over a Pd–C catalyst. The product (0·74 g), assumed to be IX, was a viscous oil; $\lambda_{max}$ 287 mμ ($\varepsilon_{max}$ 46); $\nu_{max}$ 3480, and 1710 $cm^{-1}$. On GLC analysis it exhibited a single peak.

Reduction with lithium in liquid ammonia as above, gave the glycol (VI), identical with a sample prepared as above.

3(α)-*Hydroxy*-2(α), 8a(α)-*ethano*-4a(α)-*decahydronaphthalene*-10-*one* (XIII)

To a soln of the glycol (5 g) in MeOH (60 ml) was added sodium metaperiodate (10 g), and the mixture stirred vigorously for 16 hr. Removal of MeOH followed by extraction with ether gave a semicrystalline product, containing both the spirodecanone XII and the hydroxyketone XIII; $\nu_{max}$ 2725, 1740, and 1725 $cm^{-1}$.

The crude product (2·8 g) in MeOH (50 ml) was added to a soln of KOH (0·8 g) in water (50 ml) and the mixture allowed to stand at room temp for 4 hr. MeOH was removed at 30° on a rotary evaporator, water added and the product extracted into ether. Recrystallization from light pet–ether (4:1) gave the *hydroxyketone* XIII (2·3 g) as white needles; m.p. 120–121°; $\nu_{max}$ ($CCl_4$) 3480 and 1738 $cm^{-1}$; $\lambda_{max}$ (EtOH) 295 mμ ($\varepsilon_{max}$ 35). (Found: C, 74·1; H, 9·1. $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·3%).

*Oxidation of the hydroxy-ketone* (XIII)

$CrO_3$ (100 mg) was added to pyridine (1 ml) and then XIII (100 mg) in pyridine (0·5 mg) added with stirring. Stirring was continued for 20 hr, and then water added and the product extracted with ether. The resulting diketone XIV (60 mg) was obtained as an oil; $\nu_{max}$ 1702 and 1735 $cm^{-1}$.

*The hydroxydithioketal* (XVII)

The hydroxyketone XIII (1 g) was dissolved in ethane dithiol (6 ml) and $BF_3$–$Et_2O$ (3 ml) added. The mixture was allowed to stand at room temp for 18 hr and then brine added and the product extracted with benzene. Washing with N KOH was followed by washing with water, drying and evaporation to give a white solid. Recrystallization from benzene–n-hexane (1:4) gave XVII (1·3 g) as white crystals; m.p. 111–113°; $\nu_{max}$ (Nujol), 3480 and 1050 $cm^{-1}$. (Found: C, 62·1; H, 8·3; S, 23·6. $C_{14}H_{22}OS_2$ requires: C, 62·2; H, 8·2; S, 23·7%).

*Oxidation of the hydroxydithioketal* (XVII)

Compound XVII (150 mg) was oxidized using $CrO_3$ (15 mg) in pyridine (3 ml). The product was the *ketodithioketal* XVIII (140 mg), having a peak in the IR region at 1702 $cm^{-1}$.

*Hydrogenation of the unsaturated methoxyketone* (IX)

(a) The ketone IV (1 g) in MeOH (20 ml) was hydrogenated at room temp and under atm press using 5% Pd–C (40 mg) as catalyst. Filtration from the catalyst followed by evaporation gave the product as a colourless oil; $\nu_{max}$ 1720 $cm^{-1}$; $\lambda_{max}$ (EtOH) 292 mμ ($\varepsilon_{max}$ 60). GLC analysis revealed one peak with a small shoulder (<5%). The major component was assumed to be VII. (Found: C, 75·2; H, 10·0. $C_{13}H_{20}O_2$ requires: C, 75·0; H, 9·7%).

(b) The unsaturated ketone (100 mg) was hydrogenated as above, but in n-hexane. The product gave a virtually identical GLC analysis.

*Acid-catalysed rearrangement of the saturated methoxyketone* (VII)

The ketone VII (1·2 g) was dissolved in glacial AcOH (2 ml), conc HCl (4 ml) added, and the mixture heated on a steam-bath for 4 hr. After dilution with water, extraction with ether gave an oily product (1·1 g), $\nu_{max}$ 3500, and 1720 (with a shoulder at 1733 cm$^{-1}$; $\lambda_{max}$ (EtOH) 28·5 mμ ($\varepsilon_{max}$ 50).

### 10-β-*Hydroxy*-2(α),8a(α)-*ethano*-4a(α)-*decahydronaphthalene*-3-*one* (XVI)

The product of the above rearrangement in ether (10 ml) was reduced with Li (0·8 g) in liquid ammonia (60 ml) and EtOH (12 ml). The crude solid product was recrystallized from light pet./ether (4:1) to give the *glycol* XI (800 mg) m.p. 244–245°.

To the glycol XI (380 mg) was added glacial AcOH (2 ml) and lead tetracetate (600 mg) and the mixture stirred at room temp for 40 hr. Dilution followed by extraction gave a crude product; $\nu_{max}$ 2725, 1725 and 1710 cm$^{-1}$. This was dissolved in MeOH (25 ml) and allowed to stand at room temp for 4 hr. Removal of MeOH on a rotary evaporator followed by dilution and extraction with ether gave XVI (270 mg); m.p. 155–160°; $\nu_{max}$ 1705 cm$^{-1}$.

Oxidation of this hydroxyketone, using $CrO_3$ in pyridine gave XIV, identical with a sample prepared by oxidation of XIII.

### 2(α),8a(α)-*Ethano*-4a(α)-*decahydronaphthalene*-10-*one* (XXVI)

(a) A mixture of XVIII (150 mg), hydrazine hydrate (0·125 ml), triethylene glycol (1·25 ml) and KOH (150 mg) was heated at 130° for 6 hr. Dilution followed by extraction gave crude oily XIX (61 mg), which showed no CO absorption in the IR region.

To a soln of this dithioketal (60 mg) in acetone (3 ml) was added mercuric acetate (120 mg) in water (1 ml) and the mixture stirred at room temp for 2 hr. Filtration into water and extraction with ether gave XXVI (26 mg) as an oil; $\nu_{max}$ ($CCl_4$) 1740 cm$^{-1}$.

(b) To a chilled soln of XVII (147 mg) in dry pyridine (0·5 ml) was added $POCl_3$ (0·2 ml) and the mixture allowed to stand at room temp for 30 min refluxed for 45 min and poured on to crushed ice. Extraction with benzene gave a viscous product (130 mg) which exhibited no OH peak in the IR region. NMR analysis showed a vinyl proton multiplet centred at $\delta$ 5·7 ppm. Integration revealed that the desired compound XXI was not the major product.

(c) To a soln of XVII (0·8 g) in dry pyridine was added *p*-toluenesulphonyl chloride (0·9 g) in dry pyridine (2 ml) and the mixture allowed to stand at room temp for 48 hr. Soln in ether was followed by washing with 4% $Na_2CO_3$aq followed by chilled 5% HCl and finally water. Drying and evaporation followed by recrystallization from ether yielded the *dithioketal* of the *tosyloxyketone* XXIII (1·44 g); m.p. 131–133°. (Found: C, 59·2; H, 6·5; S, 22·5. $C_{21}H_{28}O_3S_3$ requires: C, 59·4; H, 6·7; S, 22·6%).

To this product (1·32 g) was added dry, distilled collidine (15 ml) and the mixture refluxed for 5 hr.[12] The mixture was taken up into ether and washed thoroughly with distilled 10% HCl, followed by water. Drying and evaporation of solvent yielded a pale, viscous product (0·48 g) assumed to be XXI. NMR analysis revealed a vinyl proton multiplet centred at $\delta$ 5·6 ppm, integration of which suggested that some 80% of the desired product was present.

Hydrolysis with mercuric acetate in aqueous acetone gave the impure ketone XXII as an oil; $\nu_{max}$ 1740 cm$^{-1}$. GLC analysis revealed that the product was ca. 95% pure.

Hydrogenation over a Pd catalyst, to the saturated ketone XXVI was only partially successful, possibly due to the presence of sulphur containing impurities.

(d) To a soln of XIII (2 g) in dry pyridine (8 ml) was added a soln of *p*-toluenesulphonyl chloride (2·4 g) in dry pyridine (8 ml) and the mixture allowed to stand at room temp for 48 hr. On work-up, the *keto-tosylate* (XXIII) was obtained as a solid (3·44 g) recrystallized from n-hexane–ether (3:2); m.p. 106–109°; $\nu_{max}$ (Nujol) 1738 cm$^{-1}$. The NMR spectrum was consistent with the structure assigned. (Found: C, 65·3; H, 6·9; S, 9·4. $C_{19}H_{24}O_4S$ requires: C, 65·6; H, 6·9; S, 9·2%).

This product XXIII (1·9 g) in dry ether (50 ml) was added slowly to a stirred suspension of LAH (2 g) in dry ether (50 ml). The mixture was refluxed for 4 hr and allowed to stand overnight at room temp. Water was added cautiously, and then the mixture acidified with chilled 10% HCl. Extraction with ether gave an oily product (1·09 g); $\nu_{max}$ 3410 cm$^{-1}$. GLC analysis revealed two peaks, corresponding to 85 and 15% of the product. The major product was presumed to be the *saturated alcohol* XXV, the minor component being the *unsaturated alcohol* XXIV. This assignment was supported by NMR analysis which revealed a weak vinyl proton multiplet centred at $\delta$ 5·6 ppm.

Hydrogenation in MeOH, over a Pd catalyst almost completely removed the minor component.

Chromium trioxide (1·5 g) was carefully added to dry, distilled pyridine (15 ml) with stirring, the temp being maintained below 30°. To the resulting slurry was added slowly a soln of XXV (0·7 g) in dry pyridine

(5 ml) and the mixture stirred at room temp for 20 hr. Water was added and the product extracted into ether. Washing with chilled 5% HCl followed by water, drying and evaporation of solvent gave XXVI (0·6 g) as a pale mobile oil with a strong camphor-like odour; $\nu_{max}$ 1740 cm$^{-1}$; $\lambda_{max}$ (EtOH) 285 mμ ($\varepsilon_{max}$ 60). GLC analysis suggested that the ketone was better than 95% pure, the main contaminant being a trace of XXII. The 2,4-dinitrophenyhydrazone had m.p. 144–147°. (Found: C, 60·0; H, 6·3; N, 15·7. $C_{18}H_{24}N_4O_5$ requires: C, 60·3; H, 6·2; N, 15·6%).

*10-Methylene-2-(α),8a(α)-ethano-4a(α)decahydronaphthalene* (XXVII)

Into a soln of XXVI (220 mg) in dry ether (5 ml) under $N_2$ was filtered through glass wool a soln of methylene triphenyl phosphorane (from triphenyl methyl phosphonium bromide, 6 g).[13] The mixture was stirred for 12 hr at room temp and then dry THF 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 then removed and the product (264 mg) extracted into n-pentane, washed with water, dried and evaporated.

Adsorption into an alumina column, and elution with n-pentane gave *10-methylene-2(α)-8a(α)-ethano-4a(α)-decahydronaphthalene* (XXVII, 160 mg) as a colourless oil, homogeneous to GLC analysis; $\nu_{max}$ 3040, 1675, 870 and 865 cm$^{-1}$. The NMR spectrum showed a poorly resolved multiplet at δ 4·72 ppm integrating correctly for two vinyl protons. (Found: C, 88·4; H, 11·8. $C_{13}H_{20}$ requires: C, 88·6; H, 11·5%).

## REFERENCES

[1] [a] Part I of this series: M. A. Qasseem, A. A. Othman and N. A. J. Rogers, *Tetrahedron* **23**, 87 (1967).
[b] A. J. Birch and J. S. Hill, *J. Chem. Soc.* (C), 419 (1966).
[2] F. D. Greene *et al.*, *J. Org. Chem.* **28**, 55 (1963).
[3] P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.* **78**, 2473 (1956).
[4] K. W. Bentley, J. Dominguez and J. P. Ringe, *J. Org. Chem.* **22**, 418 (1957).
[5] cf. H. O. House, *Modern Synthetic Reactions*, p. 54 et seq. Benjamin (1965).
[6] M. J. T. Robinson, *Tetrahedron* **21**, 2476 (1965).
[8] P. von R. Schleyer, K. R. Blanchard and C. D. Woody, *J. Am. Chem. Soc.* **85**, 1358 (1963).
[9] K. L. Rabone and N. A. J. Rogers, *Chem. & Ind.* 1838 (1965).
[10] H. O. House, Ref. 5, p. 29 et seq.
[11] A. I. Scott *Interpretation of Ultraviolet Spectra of Natural Products*. p. 75. Pergamon, Oxford (1964).
[12] R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.* **26**, 2883 (1961).
[13] S. Trippett, *Advances in Organic Chemistry, Methods and Results* Vol. 1; p. 98.