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# STEREOSPECIFIC REDUCTIONS OF 1α-ETHYNYL-1β-HYDROXY-5-OXO-7a-METHYL-2,3,5,6,7,7a-HEXAHYDROINDENE AND SOME DIELS ALDER CONDENSATIONS WITH CIS-3-VINYL-6-OXO-3a-METHYL-3a,4,5,6,7,7a-HEXAHYDROINDENE

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**Abstract**—The ethynyl compound (I) named in the title and some of its derivatives have been catalytically reduced with lithium-ammonia and with sodium borohydride. A high degree of stereospecificity is observed in these reductions. The vinyl alcohol (V) was dehydrated to the diene (XV) which condensed readily with *p*-benzoquinone and maleic anhydride.

The stereochemical course of reductions of 9-methyl-$\Delta^{5(10)}$-octalin-1,6-dione, 5,9-dimethyl-$\Delta^{5(10)}$-octalin-1,6-dione and their derivatives with unsaturated functions at $C_1$ to derivatives of decalin have previously been studied.[1–3] Similar reductions (Chart I) in the perhydroindene system carried out with the title compound (I) and its derivatives are the subject of this paper.*

Compound I was previously obtained[4] as the sole product of ethynylation of 1,5-dioxo-7a-methyl-2,3,5,6,7,7a-hexa-hydroindene[5] (XIV) and reduced selectively to the vinyl ketone alcohol (II). Hydrogenation of I in the presence of Pd-$CaCO_3$ in ethanol until 2 moles of hydrogen were absorbed gave the ethylketone alcohol (III) also obtained by controlled hydrogenation of II. The IR and UV absorption data confirm the presence of conjugated carbonyl groups in II and III. Further reduction of III either catalytically or with Li–$NH_3$ gave a single compound (IV) in excellent yield with no evidence of epimer formation. Compound IV must undoubtedly have a *cis* fusion of the rings, since the anion involved in the Birch reduction should be more stable in the *cis* than in the *trans* form.[6] Reductions of I and II with Li–$NH_3$ gave the *cis* perhydroindene derivatives (VI and V) formulated on the basis of their light absorptions and their conversions on catalytic reduction to IV. As far as the orientation of the —OH in compounds II to VI is concerned, it is probably *cis* to the angular methyl as in I. The *cis* orientation of—OH in I is in agreement with the course of ethynylation of 17-keto steroids. The NMR spectrum of I shows signals

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* All formulae represent racemates.

[1] I. N. Nazarov and I. A. Gurvich, *Zh. Obshch. Khim.* **25**, 956 (1955); *Chem. Abstr.* **50**, 3351-b (1956); *Zh. Obshch. Khim.* **29**, 468 (1959); *Chem. Abstr.* **53**, 21823 e (1959).

[2] V. F. Kucherov and I. A. Gurvich, *Zh. Obshch. Khim.* **31**, 796, 804 (1961); *Chim. Abstr.* **55**, 25868 f (1961).

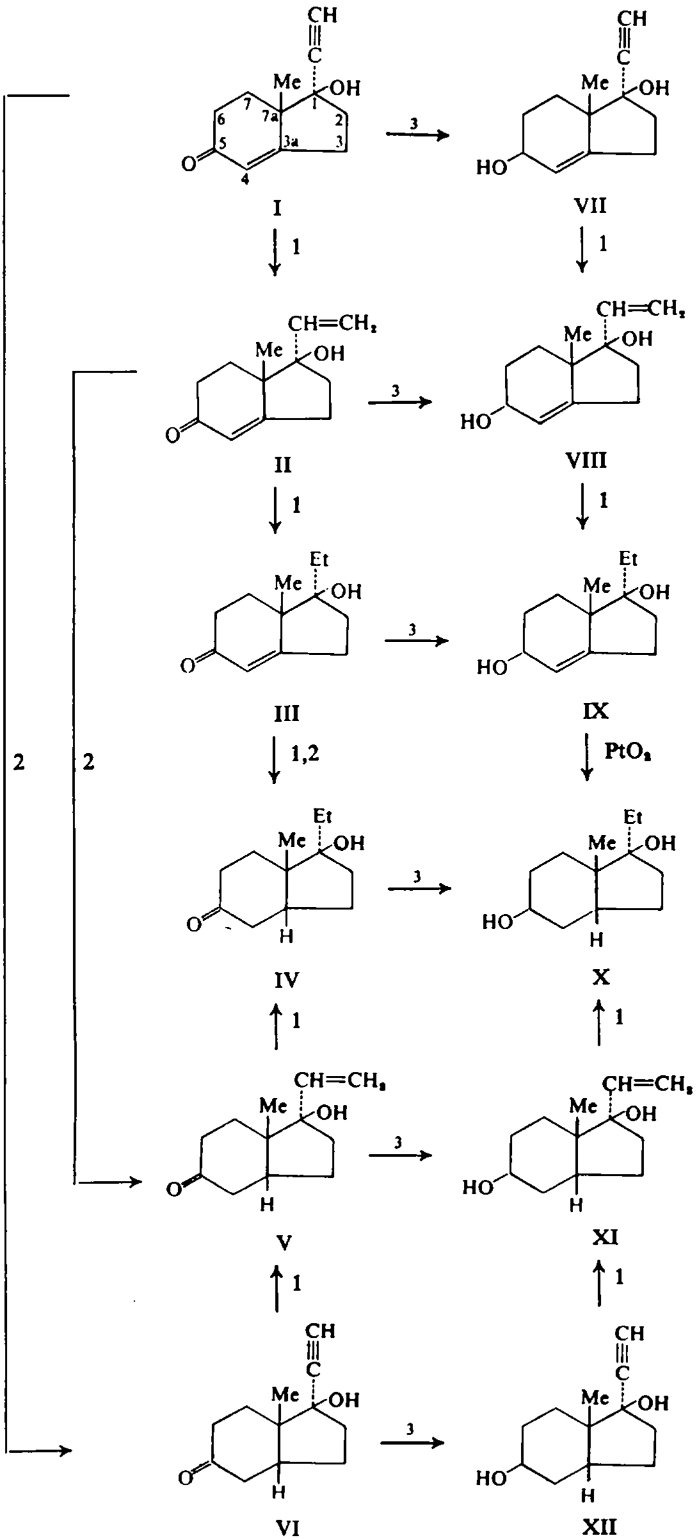
[3] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.* 2680 (1960).

[4] S. Swaminathan, J. P. John, P. S. Venkataramani and K. Viswanathan, *Proc. Ind. Acad. Sci.* LVIIA, 44 (1963).

[5] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.* 2022 (1959).

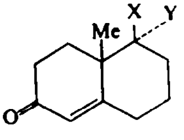
[6] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.* 4547 (1960).

Chart I.



1—$H_2$-Pd ($CaCO_3$)
2—Li-$NH_3$
3—$NaBH_4$

at τ 4·13–4·2 (triplet, O=C—C*H*=C—), τ 6·8 (—O*H*, singlet), τ 7·38 (singlet, —C≡C—*H*) and at τ 8·73 (singlet, —C—C$H_3$). A comparison with the —OH absorptions of the epimers XIIIA and XIIIB which appear[7] at τ 7·44 and τ 7·55 respectively seems to suggest that the —OH is probably less hindered and hence equatorial and *cis* to the —$CH_3$ as indicated in I. A more appropriate comparison will however be with the $C_1$ epimer of I which unlike[8] XIIIA, has resisted all attempts at epimerization.

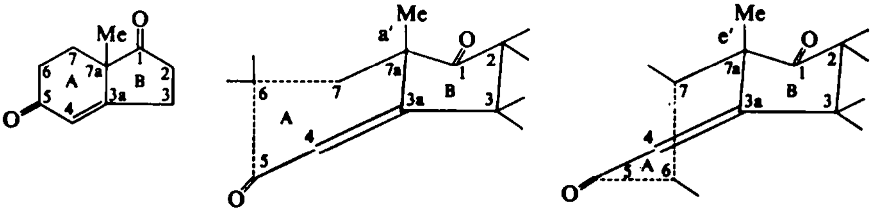


XIII A, X = —OH, Y = —C≡CH
XIII B, X = —C≡CH, Y = —OH

Since one of the objects of the present study was to set up a *trans* ring fusion, if possible and since it has been reported[8] in the octalin series that the course of hydrogenation depends on the nature of the oxygenated function at $C_6$, compound III was first reduced with sodium borohydride to IX and then hydrogenated ($PtO_2$). However the diol (X) obtained was the same as the product of reduction of IV directly with sodium borohydride. Reductions of the keto alcohols I, II, V and VI similarly with sodium borohydride gave the diols VII, VIII, XI and XII respectively, in excellent yields, with no evidence of epimers formation. The diols VII to XII must have the same orientation of the substituents since these could be hydrogenated, as indicated, to the same saturated diol (X).

Models show that two conformations (XIVa and XIVb) are possible for the parent diketone (XIV) from which I is obtained. The two half-chair conformations of ring A represented below are interconvertible by rotation of C—C bonds at positions 5,6 and 7. Conformation XIVb seems energetically favourable since the axial $CH_3$:H interaction present in ring A of XIVa may be expected[9] to be more severe than the axial interaction between a hydrogen and the trigonal carbonyl carbon of ring B in XIVb. However, when this carbonyl carbon becomes tetrahedral as in the hydroxy ketone (I), this conformational preference may be expected to be reversed due now to the greater axial interaction between the substituted $C_1$ and a hydrogen as compared

Chart II.



XIV XIVa XIVb

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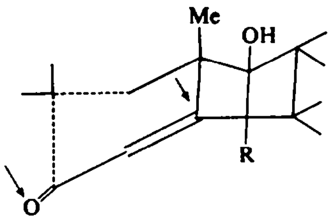
[7] S. Swaminathan, S. Ramachandran and S. K. Sankarappa, *Tetrahedron* **20**, 1119 (1964).

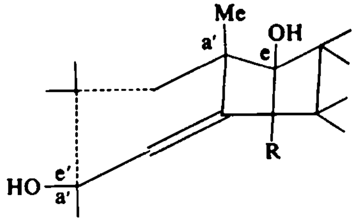
[8] M. S. Newman, S. Ramachandran, S. K. Sankarappa, and S. Swaminathan, *J. Org. Chem.* **26**, 727 (1961).

[9] A. S. Dreiding, *Chem. & Ind.* 1419 (1954).

to the $CH_3$:H interaction referred to. Since the —OH in I has probably the $\beta$-configuration as already pointed out, the conformations of I and its hydrogenated products II and III may be represented as below:



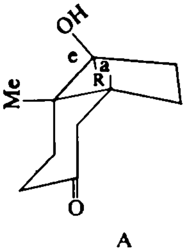
I, II, III



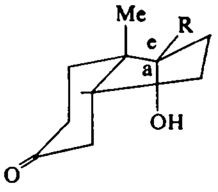
VII, VIII, IX

I, VII R = $-C{\equiv}CH$
II, VIII R = $-CH{=}CH_2$
III, IX R = $-CH_2CH_3$

Consistent with the usual course of reduction of unhindered ketones of the cholestenone type with metal hydrides to the more stable equatorial hydroxy compounds, the allylic alcohols VII to IX must be assigned the conformations shown where the 5-OH is oriented quasi-equatorially. This assignment is in accord with the finding that the diol (IX) is oxidized readily to the diketone (III) at room temperature with manganese dioxide—a reagent that has been shown[10] to be specific for oxidation of equatorial —OH groups. Since both catalytic reduction and Li–$NH_3$ reduction of III gave compound IV having *cis* ring fusion, the addition of hydrogen must occur as indicated by arrows on the side of the methyl group. The catalytic reduction of IX to X which is also obtained by sodium borohydride reduction of IV indicates that the hydrogenation of IX proceeds likewise from the $\beta$ side and furthermore that the secondary —OH in X (also XI and XII) has the same $\beta$ orientation as in VII to IX. This result is rather unexpected since coprastanone type steroids are usually reduced to 3$\alpha$-hydroxy compounds in hydride reductions, and must mean that the ketones IV to VI react preferentially in conformation A rather than in B. The diols X, XI, and XII may have either of the two conformations A or B with a 5-equatorial —OH but no work has been done to determine the actual preference, if any.



A



B

In related studies aimed at the synthesis of the steroidal system containing a five membered ring B, we have dehydrated the vinyl alcohol (V) with potassium bisulphate to the *cis* diene (XV) in 56·5% yield. Condensation[11] with *p*-benzoquinone at room temperature furnished two pale yellow adducts in a ratio of 7:4 while from the condensation with maleic anhydride only a single colourless adduct was isolated.

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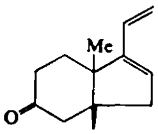
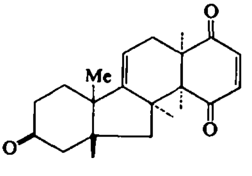
[10] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 1226 (1954).

[11] For similar condensations with bicyclic dienones of the type XV but containing a six membered ring B, see I. N. Nazarov, G. P. Verkholerova and I. V. Torgov, *Bull. Acad. Sci., Div. Chem. Sci.* 283 (1959); *Chem. Abstr.* **53**, 22082 (1959); I. N. Nazarov and I. A. Gurvich, *Bull. Acad. Sci. Div. Chem. Sci.* 293 (1959); *Chem. Abstr.* **53**, 22082 (1959) and Refs cited therein.

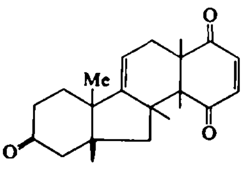
These adducts are tentatively formulated as XVI, XVII and XVIII respectively. The diene XV can adopt either conformation XVa or XVb; an examination of models shows that endo addition of the dienophile from the methyl side should be favoured leading predominantly to the stereochemistry represented in XVI and XVIII irrespective of which conformation XV adopts. Such an addition seems particularly favoured in conformation XVa due to hindrance from the axial hydrogen atoms at $C_4$ and $C_6$ to condensation on the α side and only less so in the case of XVb where only the axial hydrogen at $C_7$ interferes with the attack on the α-side. The less abundant adduct obtained with *p*-quinone is accordingly represented by XVII. The more abundant adduct XVI on exposure to light and also on repeated crystallization isomerized to a higher melting colourless solid formulated as XIX on the basis of its spectral properties.



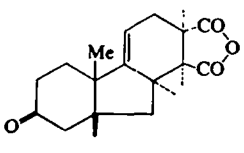
XV



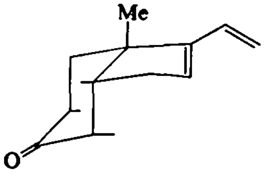
XVI
(major)



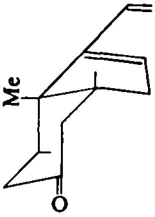
XVII
(minor)



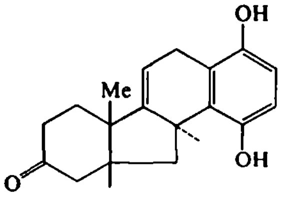
XVIII



XVa



XVb

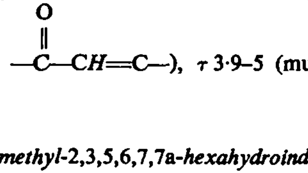


XIX

Work on transformation of the D rings in XVI and XVII to steroidal type five membered rings is in progress.

## EXPERIMENTAL

1α-*Ethynyl*-1β-*hydroxy*-5-*oxo*-7a-*methyl*-2,3,5,6,7,7a-*hexahydroindene* (I) was obtained as described previously.[4] The yield of material m.p. 129·5–130·5° was 20 g from 35 g of XIV. Hydrogenation of I in the presence of Pd–$CaCo_3$ in pyridine solution furnished II m.p. 108–109° in quantitative yield.[4]



NMR[11] ($CDCl_3$) τ 4·18 (Triplet, $-\overset{\overset{O}{\|}}{C}-CH{=}C-$), τ 3·9–5 (multiplets for $-CH{=}CH_2$), τ 7·15 ($-OH$) and τ 8·19 ($-\underset{|}{\overset{|}{C}}-CH_3$).

1α-*Ethyl*-1β-*hydroxy*-5-*oxo*-7a-*methyl*-2,3,5,6,7,7a-*hexahydroindene* (III). The vinyl alcohol (II 1·92 g) was hydrogenated in EtOH (20 ml) in the presence of Pd–$CaCO_3$ until 1 mole $H_2$ was absorbed. The catalyst was removed and solvent distilled off. Trituration of the residual viscous liquid with

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[11] N.M.R. Spectra were obtained in the solvents specified with a Varian Model A.60 Spectrometer using tetramethylsilane as an internal standard.

ether and cooling furnished 1·4 g material which was crystallized from ether–petroleum (40–60°), m.p. 67–68°. (Found: C, 73·8, H, 9·4. $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·2%), $\lambda_{\max}^{\mathrm{EtOH}}$ 245 m$\mu$ ($\log_{10} \varepsilon$, 4·14) $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75, 6·03 $\mu$. Direct hydrogenation of I under similar conditions until no more than 2 moles $H_2$ were absorbed also gave III.

cis-1α-*Ethyl-1β-hydroxy-5-oxo-7*a-*methyloctahydroindene* (IV). To a solution of Li (0·4 g) in liquid ammonia (100 ml) well cooled in a dry ice–acetone bath was added a solution of III (5 g) in ether (30 ml). The mixture was stirred for 2 hr, decomposed with solid $NH_4Cl$ and $NH_3$ removed. Extraction of the residue with ether gave crude IV which was recrystallized from ether–petroleum (40–60°) m.p. 71·5–72·5°. (Found: C, 73·8, H, 10·6, $C_{12}H_{20}O_2$ requires: C, 73·4; H, 10·3%), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75, 5·86 $\mu$.

The same product (no depression of m.p.) was obtained by catalytic (Pd–$CaCO_3$) hydrogenation of III or V in EtOH solution.

cis-1α-*Vinyl-1β-hydroxy-5-oxo-7*a-*methyloctahydroindene* (V). Reduction of II (6 g) with Li (0·4 g) in liquid ammonia as described for IV furnished 4 g of V; m.p. 105–106° from ether–pet. ether. (Found: C, 74·5; H, 9·5; $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·3%), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75, 5·86 $\mu$. No strong absorption of UV in the range 220–300 m$\mu$. The same product could be obtained by hydrogenation of VI with Pd–$CaCo_3$ in pyridine.

cis-1α-*Ethynyl-1β-hydroxy-5-oxo-7*a-*methyloctahydroindene* (VI). Reduction as above with Li–$NH_3$ of I (4 g) furnished 2·1 g of VI; m.p. 138–138·5° from AcOEt. (Found: C, 75·3, H, 8·6; $C_{12}H_{16}O_2$ requires: C, 75·0; H, 8·3%), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75, 3·0, 5·85 $\mu$. No intense absorption in the UV region.

*Reductions with sodium borohydride:* 1α-*ethynyl-1β,5β-dihydroxy-7*a-*methyl*-2,3,5,6,7,7a-*hexahydroindene* (VII). To an ice cooled and stirred solution of I (1 g) in EtOH (15 ml) and dioxan (5 ml) $NaBH_4$ (100 mg) was added. Stirring was continued for 4 hr and the mixture kept overnight. A few drops of AcOH were then added to decompose the complex and the solvent removed. The residue was mixed with water and extracted with $CHCl_3$. This extract furnished solid (1 g) which was crystallized from ether, m.p. 149–150°. (Found: C, 75·1, H, 8·6. $C_{12}H_{16}O_2$ requires: C, 75·0, H, 8·3%), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·775 $\mu$ (—OH) and 3·025 $\mu$ (—C≡CH). No—C=O absorption.

Similarly the keto alcohol II (1 g) furnished 1 g of 1α-*vinyl-1β,5β-dihydroxy-7*a-*methyl*-2,3,5,6,7,7a-*hexahydroindene* (VIII), m.p. 121·6–122·6° from ether–pet. ether, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75 $\mu$ no carbonyl. (Found: C, 74·2, H, 9·3, $C_{12}H_{18}O_2$ requires: C, 73·9, H, 9·1%.)

From the keto alcohol III (1 g), 1α-*ethyl-1β,5β-dihydroxy-7*a-*methyl*-2,3,5,6,7,7a-*hexahydroindene* (IX), m.p. 143–144° from AcOEt was obtained. (Found: C, 73·5; H, 10·4; $C_{12}H_{20}O_2$ requires: C, 73·4; H, 10·3%.)

Reduction of IV (1 g) furnished 1 g of cis 1α-*ethyl-1β,5β-dihydroxy-7*a-*methyloctahydroindene* (X), m.p. 143–145° from AcOEt. (Found: C, 72·8; H, 11·4; $C_{12}H_{22}O_2$ requires: C, 72·7, H, 11·2%.)

Catalytic hydrogenation of IX (250 mg) with $PtO_2$ in EtOH also furnished material m.p. 142–143° undepressed by authentic X but showing depression with starting material.

From V (1 g) 1 g of cis-1α-*vinyl-1β,5β-dihydroxy-7*a-*methyloctahydroindene* (XI), m.p. 107–108° from ether–pet. ether was obtained. (Found: C, 73·7; H, 10·4; $C_{12}H_{20}O_2$ requires: C, 73·5, H, 10·2%), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75 $\mu$, no carbonyl.

From VI (700 mg), 700 mg of cis-1α-*ethynyl-1β,5β-dihydroxy-7*a-*methyloctahydroindene* (XII), m.p. 133–135° from ether–pet. ether, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·75, 3·0 $\mu$ was obtained. (Found: 73·8, H, 9·6; $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·3%), compounds VII and XII could be converted to VIII and XI respectively by hydrogenation in pyridine (Pd–$CaCo_3$) and then into IX and X respectively by hydrogenation in EtOH solution.

*Manganese dioxide oxidation of* IX. A solution of IX (250 mg) in $CHCl_3$ (25 ml) was stirred with freshly prepared $MnO_2$ (4 g) for 15 hr at room temp. The $MnO_2$ was removed and the solvent distilled off. The product (100 mg) was III by mixed m.p. determination and comparison of IR spectra.

cis-3-*Vinyl-6-oxo-3*a-*methyl*-3a,4,5,6,7,7a-*hexahydroindene* (XV). An intimately ground mixture of V (8 g) $KHSO_4$ (4 g) and pyrogallol (0·2 g) was heated at 120–125° *in vacuo* (30 mm) for ½ hr. The reaction was brisk and water condensed on the cooler parts of the flask. The mixture was then allowed to come to room temp and extracted with ether. The extract was washed with $NaHCO_3$aq and then water, dried and then freed of solvent. The residual liquid was distilled *in vacuo* to give the colourless pleasant smelling diene XV (4·1 g); b.p. 86–87°/0·5 mm. (Found: C, 82·1; H, 8·9;

$C_{12}H_{16}O$ requires: C, 81·8; H, 9·2%), $\lambda_{max}^{CHCl_3}$ 5·85 μ; NO—OH absorption, $\lambda_{max}^{EtOH}$ 234 mμ ($\log_{10} \varepsilon$, 4·12). The diene could be stored for a week without any apparent changes taking place.

*Condensation of the diene* XV *with* p-*benzoquinone.* A solution of XV (4 g) in dry benzene (10 ml) was mixed with a solution of freshly sublimed *p*-benzoquinone (2·45 g) in benzene (10 ml) and the mixture kept at room temp for a week. The pale yellow crystals that had deposited were collected to give I (3·45 g, m.p. 151–154°). The mother liquor when concentrated and diluted with ether gave a II crop, also pale yellow (2 g, m.p. 143–147°).

The first crop was recrystallized 4 times from MeOH to give an analytical sample of XVI. This analytical sample when heated became a cloudy melt at 152–154, solidified at 160° and remelted at 225–230°, indicating some changes on heating. (Found: C, 75·7, H, 6·8. $C_{18}H_{20}O_3$ requires: C, 76·1, H, 7·0%), $\lambda_{max}^{CHCl_3}$ 5·88, 5·95 μ; $\lambda_{max}^{EtOH}$ 228 mμ ($\log_{10} \varepsilon$, 3·98). Concentration of the recrystallization mother liquors of the first crop gave ca. 200 mg of a solid, m.p. 210–235°, probably impure XIX described later.

Recrystallization of II referred to above from MeOH furnished XVII, m.p. 153–154°. The melt was clear and there was no evidence of any changes of the type observed on heating XVI. (Found: C, 75·8, H, 7·3, $C_{18}H_{20}O_3$ requires: C, 76·1; H, 7·0%), $\lambda_{max}^{CHCl_3}$ 5·88, 5·95 μ, $\lambda_{max}^{EtOH}$ 228 mμ ($\log_{10} \varepsilon$, 3·98); NMR ($CDCl_3$): τ 3·43 (singlet, 2H, ), τ 4·6–4·75 (multiplet, 1H, $-\overset{|}{C}=\overset{|}{C}-H$) and τ 8·68 (singlet, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$).

A mixture of the two adducts melted ca. 140°.

*Photoisomerization of* XVI *to* XIX. The adduct XVI on exposure to light for a few days became colourless, had m.p. 225–230° and was sparingly soluble in the usual solvents. Several crystallizations from MeOH raised the m.p. to 236–239°. (Found: C, 75·8, H, 7·3, $C_{18}H_{20}O_3$ requires: C, 76·1, H, 7·1%), $\lambda_{max}^{Nujol}$ 2·92 (non-bonded-OH), 3·06 (bonded —OH), 5·95 (C=O) and 6·24 μ (ω, aromatic) $\lambda_{max}^{EtOH}$ 292 mμ ($\log_{10} \varepsilon$, 3·54).

The same product was obtained by heating the adduct XVI to 170°. The isomeric adduct (XVII) was relatively stable to light.

*Condensation of* XV *with maleic anhydride.* To a solution of XV (1·45 g) in benzene (4 ml) a solution of maleic anhydride (0·8 g) in benzene (6 ml) was added. The reaction was exothermic and the crystalline adduct XVIII separated within a few min. The mixture was kept overnight and the crude solid (1·47 g) collected and recrystallized from acetone; m.p. 189–190°. (Found: C, 69·9; H, 6·9; $C_{16}H_{18}O_4$ requires: C, 70·1, H, 6·6%), $\lambda_{max}^{CHCl_3}$ 5·41, 5·625 μ ($-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-$); NMR (Dimethyl sulphoxide) τ 4·2–4·4 (multiplet for $-CH=\overset{|}{C}-$) and τ 8·88 (singlet $-\overset{|}{\underset{|}{C}}-CH_3$).

*Hydrolysis of the adduct* XVIII. The adduct (800 mg) was refluxed with a mixture of dioxan (8 ml) and water (2 ml) for 10 hr. The solvent was removed, the residue triturated with some ether and the solid collected. Recrystallization from acetone furnished the diacid corresponding to the anhydride (XVIII), m.p. 180–180·5°. (Found: C, 66·0, H, 7·0. $C_{16}H_{20}O_5$ requires: C, 65·8, H, 6·9%.)

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