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SYNTHESIS OF COMPOUNDS WITH JUVENILE HORMONE ACTIVITY—I

(±)-JUVABIONE (METHYL (±)-TODOMATUATE)

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Abstract A total synthesis of (±)-juvabione, a sesquiterpene ester with high juvenile hormone activity, is described.

IN VIEW of its theoretical and practical interest, considerable attention has been directed to the chemistry of juvenile hormone, which regulates larval development or reproduction in insects.[1-3] Quite recently, some natural products with extraordinary high juvenile hormone activity were found. The first of these was juvabione (Ib) isolated from balsam fir (*Abies balsamea* (L.) Miller) by Bowers *et al.*[4] and Černý *et al.*[5] The second material was dehydrojuvabione (II) isolated from the same tree by Černý *et al.*[5] The third was the purified extract of *cecropia* moth, which was shown to be methyl 10-epoxy-3,11-dimethyl-7-ethyl-trideca-2,6-dienoate.[6]

Bowers *et al.*[4] have shown that juvabione is the methyl ester of todomatuic acid (Ia) isolated in 1940 from bisulphite-treated pulp oil of *Abies sachalinensis* (Schmidt) (Japanese name: todomatsu) by Tutihasi and Hanazawa.[7] The structure depicted in the formula was proposed by Momose[8] in 1941. Later Nakazaki and Isoe[9] confirmed the structure by the synthesis of the stable isomer of (±)-desoxodihydrotodomatuic acid (III). At the same time they elucidated the stereochemistry of the sesquiterpene acid. In continuation of this work carried out by the Japanese chemists, we wish to describe the synthesis of (±)-todomatuic acid (Ib) and (±)-juvabione (Ia) which has been briefly reported in a preliminary form.[10]

The synthetic scheme was based on the following principle. Firstly an aldehyde (VII) was prepared from anisole and the isobutyl side chain was attached to it to yield an alcohol (VIII). This was reduced and modified to a ketol acetate (XIb) in which the potential CO group on the side chain was in the form of an acetoxyl group. Finally the carboxyl group was attached to the ring.

Ethyl β-(*p*-methoxyphenyl)crotonate (V)[11], prepared from *p*-methoxyacetophenone (IV) by the Reformatsky reaction, was hydrogenated over Raney nickel W-7 to give ethyl (±)-β-(*p*-methoxyphenyl)butyrate (VIa). The corresponding acid (VIb) was treated with thionyl chloride to give an acyl chloride (VIc). This was poured into aqueous dimethylamine to afford an N,N-dimethylamide (VId). Its reduction by lithium triethoxyaluminohydride[12] gave (±)-β-(*p*-methoxyphenyl)butyraldehyde (VII). Addition of isobutyl magnesium bromide to the aldehyde (VII) afforded 2-(*p*-methoxyphenyl)6-methylheptan-4-ol (VIII).

The modified Birch reduction[13] of this alcohol gave a diene (IX). This was converted to a β,γ-unsaturated ketone (X) by treatment with oxalic acid in methanol-

water. Hydrogenation of the unsaturated ketone over Pd–C gave 2-(4'-oxocyclohexyl)6-methylheptan-4-ol (XIa). The corresonding acetate (XIb) was obtained from the alcohol by the action of acetyl chloride-pyridine. Addition of hydrogen cyanide to the CO group gave a cyanohydrin (XII) which was dehydrated with phosphorus oxychloride and pyridine to give 2-(4'-cyanocyclohex-3'-enyl)4-acetoxy-6-methylheptane (XIII). Hydrolysis of the nitrile with concomitant removal of the acetyl group was effected by heating the nitrile (XIII) with potassium hydroxide in diethylene glycol-water to afford a hydroxy acid (XIV) somewhat contaminated with a β,γ-unsaturated acid. The crude acid was treated with sodium ethoxide in ethanol to give a pure hydroxy acid (XIV). This, upon Jones oxidation, yielded a mixture of the racemates of todomatuic acid (Ia) and its stereoisomer (XVa) as a viscous oil. The amount of oil obtained was 11·4 g starting from 100 g of *p*-methoxyacetophenone. The over-all yield of this 15-step synthesis was 6·8%, which means an average yield of 83·6% for each step.

Separation of the two racemates was successfully carried out when it was found that one isomer gave a highly crystalline semicarbazone (XVI). This was hydrolyzed by heating with dilute sulphuric acid to give back the parent acid as pure crystals melting at 66–67°. The fact that the natural acid (Ia, m.p. 58–58·5°)[7] and its semicarbazone (XVI)[7] were crystalline suggested that this crystalline racemate was the desired isomer (Ia).* Comparison of its spectral properties with those of an authentic sample of the natural product (Ia) proved that the crystalline isomer was indeed (±)-todomatuic acid (Ia). The IR (CS_2) and NMR (CCl_4) spectra of the natural and synthetic acids were identical in every detail. The racemic acid was methylated with diazomethane to give (±)-juvabione (Ib). This racemate was indistinguishable from the natural product (Ib) by the comparison of IR (CS_2) and NMR ($CDCl_3$) spectra. The identity was also supported by gas chromatography.

An oily semicarbazone (XVII) remaining in the mother liquor after the removal of the crystalline isomer was hydrolyzed with dilute sulphuric acid to give (±)-epitodomatuic acid (XVa) as an oil. The IR and NMR spectra of these isomeric acids (Ia and XVa) differed only very slightly and were almost superimposable. The oily epimer (XVa) was treated with diazomethane to afford methyl (±)-epitodomatuate (XVb). The spectral properties of the two epimeric esters (Ib and XVb) were also almost identical. Moreover, they could not be separated by gas chromatography.

The juvenile hormone activity of the two epimeric esters (Ib and XVb) was tested on newly molted last instar nymphs of *Pyrrhocoris apterus* L. by the courtesy of Dr. W. S. Bowers of USDA Agricultural Research Service. Supernumerary molting to giant nymphs signaled high activity, while nymphal-adult intermediates were obtained with less active samples. The results are shown in Table 1. From these results, it can be said that (±)-juvabione (Ib) is about a half as active as the natural product. With the latter, 5 μg were sufficient to produce supernumerary nymph in 80% of the test insects. A sample of the epimeric ester (XVb) was less active than the desired isomer (Ib). Since it was probable that the sample of the epimer (XVb) contained a small amount of the correct epimer (Ib), it could not be concluded that the epimer (XVb) was really active. This point awaits further clarification.

* Although the formulae depicted represented only one enantiomer, they are taken to mean a racemate in the case of synthetic products.

Prior to the successful separation of the two epimeric acids, it was thought to be necessary to correlate a synthetic product with a derivative of natural todomatuic acid. Therefore the anilide (XX) of the stable isomer of (±)-desoxodihydrotodomatuic acid (III) was prepared by the following sequence of reactions. A mixture of (±)-todomatuic acid (Ia) and its stereoisomer (XVa) was reduced by the Huang–Minlon procedure to give a mixture of (±)-desoxotodomatuic acid (XVIII) and its stereoisomer. The IR spectrum of this compound was almost identical with that of the

TABLE 1. JUVENILE HORMONE ACTIVITY OF THE SYNTHETIC PRODUCTS

	(±)-juvabione (Ib)	The stereoisomer (XVb)
10 μg	Supernumerary nymph	Nymphal-adult
5 μg	Nymphal-adult	Slightly shortened wings
1 μg	Normal but with short wings	Normal

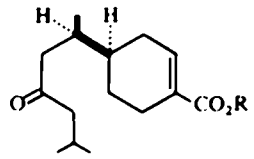
Six insects/test

optically active desoxotodomatuic acid (XVIII). The acid (XVIII) was hydrogenated to give a stereoisomeric mixture of desoxodihydrotodomatuic acid (XIXa). This was esterified with diazomethane, equilibrated by treatment with sodium methoxide in methanol and hydrolysed to give the more stable epimer of (±)-desoxodihydrotodomatuic acid (III) with two equatorial substituents on the cyclohexane ring. The corresponding anilide (XX) was obtained as crystals. After the successful separation of the acids (Ia + XVa), it became unnecessary to compare the synthetic anilide (XX) with the corresponding compound derived from natural todomatuic acid (Ib). Therefore no further effort was made to prepare the anilide (XX) from the natural product and to compare its properties with those of the synthetic product.

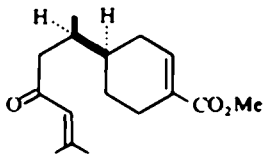
Finally an attempted alternate approach to (±)-juvabione should be mentioned briefly. The scheme was based upon the assumption that the addition of isobutyl magnesium bromide to a racemic aldo ester (XXI) would give a hydroxy ester corresponding to the hydroxy acid (XIV). It was also assumed that the use of isobutenyl magnesium bromide instead of isobutyl magnesium bromide and subsequent oxidation would give (±)-dehydrojuvabione (II).*

The aldo ester (XXI) was prepared in the following manner. Ethyl (±)-β-(*p*-methoxyphenyl)butyrate (VIa) was reduced with LAH to give an alcohol (XXII). The same sequence of reactions as used for the transformation of the alcohol (VIII) to the hydroxy acid (XIV) was then applied to this alcohol (XXII). Its reduction by lithium–ammonia[13] gave a diene (XXIII), which was treated with acid to afford an unsaturated ketone (XXIV). This was hydrogenated to give a ketol (XXVa). After the protection of the OH group, hydrogen cyanide was added to the ketone to generate a cyanohydrin (XXVI). Dehydration of this by phosphorus oxychloride-pyridine gave an unsaturated nitrile (XXVII). This was hydrolysed with potassium hydroxide in diethylene glycol–water to give a crystalline hydroxy acid (probably XXVIIIa) and an oily epimer (XXIXa). The corresponding methyl esters, (XXVIIIb and XXIXb),

* Although this approach failed, a successful synthesis of a mixture of (±)-dehydrojuvabione (II) and its stereoisomer has been accomplished.



Ia: R = H
b: R = Me



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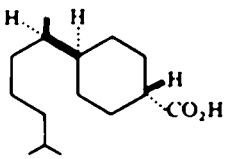
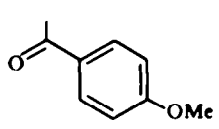


III



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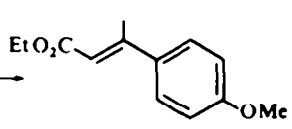
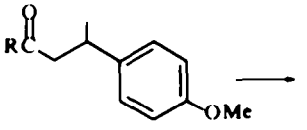
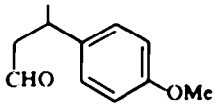


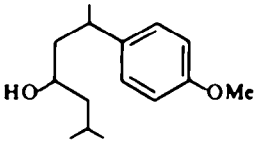
V



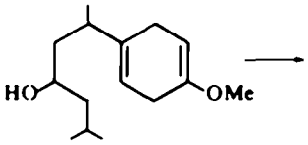
VIa: R = OEt; b: R = OH
c: R = Cl; d: R = NMe_2



VII



VIII



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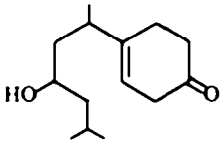
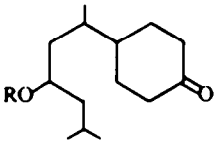
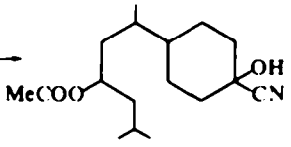


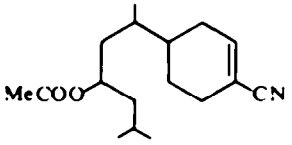
X



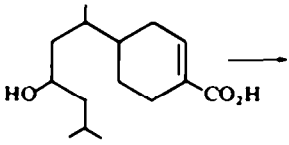
XIa: R = H
b: R = COMe



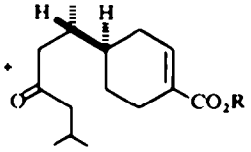
XII



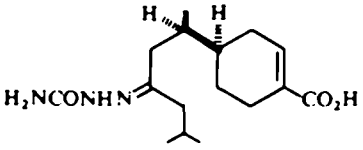
XIII



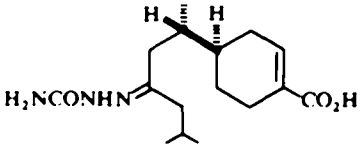
XIV



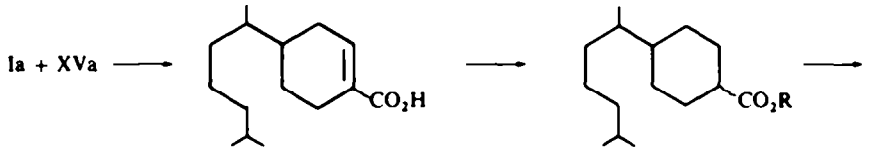
XVa: R = H
b: R = Me



XVI

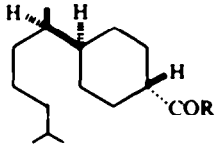


XVII

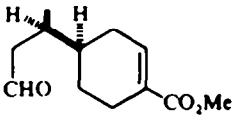


XVIII

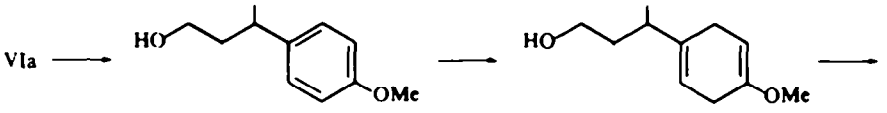
XIXa: R = H
b: R = Me



XX: III: R = OH
XX: R = NHPh

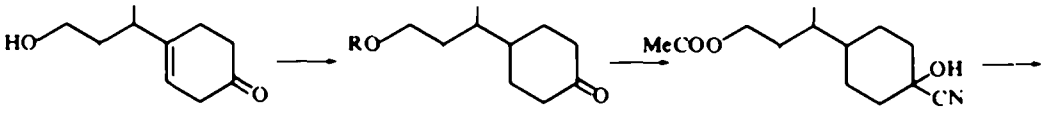


XXI



XXII

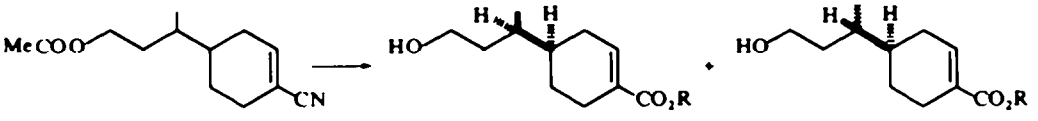
XXIII



XXIV

XXVa: R = H
b: R = COMe

XXVI



XXVII

XXVIIIa: R = H
b: R = Me

XXIXa: R = H
b: R = Me

were prepared by treatment with diazomethane. Oxidation of the hydroxy ester (XXVIIIb) to the desired aldo ester (XXI) was found to be difficult. Both chromic acid[15] and lead tetraacetate-pyridine[16] failed to give the desired product in appreciable yields. t-Butyl chromate[17] oxidized the alcohol (XXVIIIb) to the aldehyde (XXI), characterized as crystalline 2,4-dinitrophenylhydrazone, in 13% yield. In view of the disappointing yield, further work along this line was abandoned.*

EXPERIMENTAL

All m.ps and b.ps were uncorrected.

Ethyl β-(p-*methoxyphenyl*)*crotonate* (V)

About 20 ml of a soln of IV (100 g) and ethyl bromoacetate (132 g) in benzene (300 ml) was added to Zn turnings (60 g). A vigorous reaction took place when the mixture was heated after the addition of a small amount of I_2. The rest of the soln was added to the stirred soln during 40 min at reflux temp. After the addition, the reaction mixture was stirred and heated under reflux for an additional hr. After cooling, the mixture was washed with dil H_2SO_4 and sat brine, dried ($MgSO_4$) and distilled to give 124 g (79%) of the product, b.p. 150–170°/7 mm. An analytical sample boiled at 156–158°/3 mm; n_D^{19} 1·5632; ν_{max} (film) 1700, 1660, 1620, 1600, 1510, 1250, 1160, 1030, 825 cm^{-1} (Found: C, 71·21; H, 7·42. $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32%).

Ethyl (±)-β-(p-*methoxyphenyl*)*butyrate* (VIa)

The ester V (120 g) dissolved in 95% EtOH (250 ml) was hydrogenated over Raney Ni W-7 (30 g) at an initial press of 70 kg/cm^2 and 40° for 4 hr. The catalyst was filtered off and the filtrate was distilled to give 111 g (93%), b.p. 130–150°/7 mm. An analytical sample boiled at 129–132°/3 mm; n_D^{20} 1·4998; ν_{max} (film) 1720, 1600, 1510, 1240, 1170, 1030, 825 cm^{-1}. (Found: C, 70·61; H, 8·33. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%).

(±)-β-(p-*Methoxyphenyl*)*butyric acid* (VIb)

To a soln of VIa (123 g) in 95% EtOH (350 ml), 50% KOH aq (60 ml) was added. The soln was heated under reflux for 3 hr. EtOH was removed *in vacuo* and the residue was diluted with water. The aqueous soln was extracted with ether to remove neutral impurities. The aqueous layer was acidified with conc HCl and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated to give a crystalline product (100 g, 93%). Recrystallization from EtOAc–petrol gave prisms, m.p. 66–67°; ν_{max} (Nujol) ~2600, 1700 (1690 sh.), 1610, 1510, 1236, 1220, ~930, 830 cm^{-1}. (Found: C, 68·48; H, 7·72. $C_{11}H_{14}O_3$ requires: C, 68·02; H, 7·27%).

(±)-β-(p-*Methoxyphenyl*)*butyryl chloride* (VIc)

To a soln of VIb (100 g) in benzene (300 ml) $SOCl_2$ (120 ml) was added and the mixture heated under reflux for 2·5 hr. After concentration *in vacuo*, the remaining oil was employed for the next step without further purification. A small amount of the oil was distilled *in vacuo* to obtain an analytical sample, b.p. 145°/8 mm; n_D^{20} 1·5282, ν_{max} (film) 1800, 1610, 1590, 1510, 1250, 1040, 970, 830 cm^{-1}. (Found: C, 61·89; H, 6·26. $C_{11}H_{13}O_2Cl$ requires: C, 62·12; H, 6·16%).

N,N-*Dimethylamide of* (±)-β-(p-*methoxyphenyl*)*butyric acid* (VId)

A soln of crude VIc (from 100 g VIb) in dry benzene (200 ml) was added dropwise to an ice-cooled soln of Me_2NH (400 ml 30% Me_2NH and 150 ml water) at 10–15° with stirring. After the addition, the mixture was stirred for 1 hr. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic soln was washed with water and brine, dried ($MgSO_4$) and distilled to give 106 g (93%) of the product, b.p. 160–165°/3 mm. An analytical sample boiled at 162–163°/3 mm; n_D^{21} 1·5290; ν_{max} (film) 1630 (1610 sh), 1590, 1510, 1240, 1030, 830 cm^{-1}. (Found: C, 69·92; H, 8·39; N, 6·33. $C_{13}H_{19}O_2N$ requires: C, 70·55; H, 8·65; N, 6·33%).

* Unfortunately we could not study the oxidation with DMSO owing to the shortage of the starting material.[18]

(±)-β-(p-*Methoxyphenyl*)*butyraldehyde* (VII)

A suspension of lithium triethoxyaluminohydride in ether was prepared by adding EtOAc (67 g) to a soln of LAH (20·4 g) in ether (500 ml) at 5–20° during 1·5 hr. The mixture was stirred for 30 min after the addition. To the stirred mixture VId (106 g) was added at 5–10°. The stirring was continued for an additional hr at 0°. Then the mixture was left overnight at room temp. The content of the flask was poured into ice and H_2SO_4 (100 ml). The aqueous layer was extracted with ether. The ether soln was washed with water, transferred to a 1 l.-round-bottomed flask and shaken with sat $NaHSO_3$ aq. The precipitated bisulphite adduct of the aldehyde was collected on a filter and washed with ether. From this ether soln, 22 g of the N,N-dimethylamide was recovered. The crystalline bisulphite adduct was dissolved in a minimum amount of hot water and decomposed by the addition of powdered Na_2CO_3. The separated oily aldehyde was extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and distilled to give 28 g (42% from consumed amide) of the aldehyde. An analytical sample boiled at 130–132°/7 mm; n_D^{19} 1·5218; ν_{max} (film) 2750, 1720, 1610, 1585, 1510, 1240, 1170, 1025, 820 cm^{-1}. (Found: C, 73·59; H, 7·91. $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92%). The *2,4-dinitrophenylhydrazone*: orange needles from EtOAc, m.p. 126–127°; ν_{max} (Nujol) 3250, 1615 (1600 sh), 1510, 1330 cm^{-1}. (Found: C, 57·21; H, 5·43; N, 15·67. $C_{17}H_{18}O_5N_4$ requires: C, 56·98; H, 5·06; N, 15·64%).

2-(p-*Methoxyphenyl*)*6-methylheptan-4-ol* (VIII)

A Grignard reagent was prepared from freshly distilled i-BuBr (35 g) and Mg (6·5 g) in dry ether (120 ml) and a soln of VII (27·5 g) in ether (100 ml) added with stirring at 0°. After the addition the mixture was stirred for 30 min at 0° and then for 30 min under reflux. After cooling, ice and sat NH_4Cl aq was added and the ether layer separated. The ether extract was washed with sat NH_4Cl aq and $NaHCO_3$ aq, dried ($MgSO_4$) and distilled to give 34·1 g (95%) of the product, b.p. 118–120°/0·4 mm; n_D^{17} 1·5062; ν_{max} (film) 3350, 1610, 1585, 1510, 1235, 1165, 1030, 820 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln.) 0·76 (3H, d, J ~ 6 c/s), 0·86 (3H, d, J ~ 6); 1·16 (3H, d, J ~ 6), 2·55–3·00 (1H, m, $CH_3C\underline{H}$), 3·1–3·6 (1H, m, $C\underline{H}OH$), 3·64 (3H, s, $OC\underline{H}_3$), 6·63, 6·72, 6·45, 7·04 (4H, arom.). (Found: C, 75·93; H, 9·36. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

2-(4′-*methoxycyclohexa*-1′,4′-*dienyl*)-6-*methylheptan*-4-*ol* (IX)

A soln of VIII (17 g) in THF (150 ml) and t-BuOH (150 ml) was added to liquid NH_3 (350 ml) cooled in a dry ice-acetone bath. Li (7 g) was added portionwise during 1 hr to the stirred soln. After the addition, the mixture was stirred for 4 hr at dry ice–acetone temp. Then the excess Li was destroyed by the addition of EtOH (50 ml). The mixture was left at room temp to evaporate NH_3. Water (200 ml) was added to the residue with stirring. The mixture was then concentrated *in vacuo* to remove THF, t-BuOH and EtOH. The remaining aqueous soln was extracted with ether. The ether extract was washed with water and sat brine, dried ($MgSO_4$) and distilled to give 15·8 g (93%) of an oil, b.p. 148–150°/0·8 mm; n_D^{17} 1·4886; ν_{max} (film) ~ 3400, 1694, 1662, 1610, 1218, 1170, 790 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·88 (6H, doubled d, J = 6 c/s), 1·02 (3H, d, J ~ 6 c/s), 2·18 (2H, m, C-6′ $C\underline{H}_2$), 2·64 (2H, s, C-3′ $C\underline{H}_2$), 3·38 (1H, s, OH) 3·45 (3H, s, OCH_3), 4·48 (1H, C-5′ C$\underline{H}$), 5·38 (1H, C-2′ C$\underline{H}$). (Found: C, 75·06; H, 10·75. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

2-(4′-*Oxocyclohex*-1-*enyl*)-6-*methylheptan*-4-*ol* (X)

A soln of IX (31·5 g) in MeOH (200 ml) was mixed with an aqueous soln of oxalic acid (3·5 g in 45 ml). The mixture was heated at 25–40° for 40 min. Then the mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and distilled to give 27·0 g (89%) of the product, b.p. 130–140°/0·4 mm. An analytical sample was distilled at 130–132°/0·3 mm, n_D^{16} 1·4845; ν_{max} (film) ~ 3400, 1715, 1192, 1055, 810 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·88 (3H, d, J = 6 c/s), 0·90 (3H, d, J ~ 6 c/s), 1·03 (3H, d, J = 6 c/s), 3·0 (1H, broad, OH) 3·20–3·70 (1H, m, CHOH) 5·46 (1H, q, C$\underline{H}$=C). (Found: C, 74·57; H, 10·51. $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%).

2-(4′-*Oxocyclohexyl*)*6-methylheptan*-4-*ol* (XIa)

The oily X (26·6 g) dissolved in EtOAc (120 ml) was hydrogenated over 10% Pd-C (5 g) at room temp under atmo press. The H_2 uptake ceased after 5 hr. The catalyst was filtered off and the filtrate was distilled to give 24·9 g (94%) of the product, b.p. 125–140°/0·4 mm. An analytical sample boiled at 132–135°/0·4 mm; n_D^{19} 1·4770; ν_{max} (film) 3360, 1705, 1160, 1050 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·90 (9H, d, J ~ 7 c/s), 2·25 (4H, broad, $CH_2COC\underline{H}_2$), 3·09 (1H, s, O$\underline{H}$), 3·60 (1H, m, C$\underline{H}$OH). (Found: C, 74·03; H, 11·61. $C_{14}H_{26}O_2$ requires: C, 74·28; H, 11·58%).

2-(4'-Oxocyclohexyl)4-acetoxy-6-methylheptane (XIb)

To a soln of XIa (22 g) in ether (80 ml) and pyridine (20 ml) was added portionwise a soln of AcCl (10 g) in ether (40 ml) at 0–5°. The mixture was stirred for 30 min at 0–5° and then stirred and heated under reflux for 30 min. The mixture was diluted with ice-water and extracted with ether. The ether extract was washed successively with dil HCl, water, sat $NaHCO_3$ aq and sat brine, dried ($MgSO_4$) and concentrated to give 25·5 g (97%) of a crude oily acetate. An analytical sample boiled at 125–127°/0·2 mm, n_D^{19} 1·4630; ν_{max} (film) 1735, 1720, 1245 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·90 (9H, d, J = 7), 1·94 (3H, s, CH_3CO), 2·25 (4H, broad, CH_2COCH_2), 4·95 (1H, m, CH_3COOCH). (Found: C, 71·60; H, 10·29. $C_{16}H_{28}O_3$ requires: C, 71·60; H, 10·52%).

2-(4'-Hydroxy-4'-cyanocyclohexyl)4-acetoxy-6-methylheptane (XII)

To a stirred and ice-cooled soln of XIb (25·2 g) in 95% EtOH (160 ml) powdered KCN (36 g) was added followed by AcOH (38 ml). The addition of AcOH required about 10 min. After the addition, the mixture was stirred for 30 min at 0–5° and then for 30 min at 40–50°. The excess HCN was removed *in vacuo* after the addition of 2–3 drops of conc HCl. The mixture was diluted with water and extracted with ether. The ether extract was washed with dil HCl and sat brine, dried ($MgSO_4$) and concentrated to give 27·0 g (98%) of crude cyanohydrin. This was employed for the next reaction without further purification; ν_{max} (film) 3420, 2270, 1730, 1705, 1230 cm^{-1}.

2-(4'-Cyanocyclohex-3'-enyl)4-acetoxy-6-methylheptane (XIII)

To an ice-cooled soln of XII (27·0 g) in pyridine (120 ml) was added $POCl_3$ (31 g). The dark-colored mixture was left overnight at room temp, heated under reflux for 30 min and finally poured into ice-water containing conc HCl (200 ml). The mixture was extracted with ether. The ethereal soln was washed with water, $NaHCO_3$ aq and sat brine, dried ($MgSO_4$) and concentrated to give 21·5 g (85%) of the crude product. An analytical sample boiled at 140–142°/0·4 mm, n_D^{21} 1·4738; ν_{max} (film) 2270, 1740, 1645, 1250, 1026, 950, 928, 840 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·89 (9H, d, J = 7), 1·94 (3H, s, CH_3CO), 4·92 (1H, m, CH_3COOCH), 6·50 (1H, q, CH=C). (Found: C, 73·46; H, 9·53; N, 4·92. $C_{17}H_{27}O_2N$ requires: C, 73·60; H, 9·81; N, 5·05%).

2-(4'-Carboxycyclohex-3-enyl)6-methylheptan-4-ol (XIV)

A soln of the crude XIII (21·0 g) in diethylene glycol (150 ml) was mixed with KOH aq (35 g in 120 ml) and the mixture heated under reflux for 42 hr. After cooling, the mixture was diluted with water and extracted with ether to remove the neutral impurities. The alkaline aqueous layer was acidified with conc HCl (100 ml) and extracted with ether. The ethereal soln was washed with water and brine, dried ($MgSO_4$) and evaporated. Water was removed from the residual oily acid by repeated addition and distillation of dry benzene. The residual oil (ν_{max} (film) ~3400, ~2600, 1705, 1685, 1648, 1280 cm^{-1}) was dissolved in abs EtOH (50 ml). A soln of NaOEt (from 5 g Na) in EtOH (200 ml) was added to the hydroxy acid in EtOH and the mixture was heated under reflux for 3 hr. Water (100 ml) was added to the mixture. Then it was concentrated *in vacuo*, acidified with conc. HCl and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated to give 18 g (93%) of the product. This was employed for the next step without further purification; ν_{max} (film) ~3420–~2600, 1700, 1645, 1280, ~950 cm^{-1}.

2-(4'-Carboxycyclohex-3-enyl)6-methylheptan-2-one = (±)-todomatuic acid and its stereoisomer (Ia + XVa)

To a soln of XIV (18 g) in acetone (300 ml) was added Jones reagent[15] (15 ml) at 0–5°. After 10 min MeOH was added to destroy the excess oxidant. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal soln was washed with water and brine, dried ($MgSO_4$) and concentrated to give 16·5 g of an oily acid. This was distilled *in vacuo* to give 11·4 g (64%) of viscous oil, b.p. 185–190°/0·6 mm. An analytical sample boiled at 182–183°/0·6 mm, n_D^{15} 1·4952. After standing in a refrigerator it partly crystallized; ν_{max} (CS_2) ~3200–~2400, 1716, 1692, 1650 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·85 (3H, d, J = 6 c/s), 0·92 (6H, d, J = 6 c/s), 7·08 (1H, broad) 11·62 (1H, CO_2H). (Found: C, 71·55; H, 9·48. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

A mixture of (±)-juvabione (Ib) *and its stereoisomer* (XVb)

The acid Ia + XVa (2·4 g) in ether was esterified with diazomethane. Subsequent work-up gave 1·9 g (79%) of the ether, b.p. 130–140°/0·4 mm. An analytical sample boiled at 130–133°/0·4 mm, n_D^{18} 1·4812; ν_{max} (film) 1724, 1716, 1654, 1256, 1083, 1032, 920, 802, 745, 715; (CS_2) 1724, 1720, 1654, 1252, 1083, 1030,

920, 802, 745, 715 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·85 (3H, d, J = 6 c/s), 0·89 (6H, d, J = 6 c/s), 1·0–1·85 (ca. 5H), 1·85–2·5 (ca. 8H), 3·65 (3H, s), 6·93 (1H, broad CH=C) (Found: C, 72·65; H, 9·70. $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%).

Semicarbazones of (±)-todomatuic acid and its stereoisomer

To a soln of Ia + XVa (4·3 g) in 95% EtOH (14 ml) a soln of semicarbazide hydrochloride (4·2 g) and KOAc (4·0 g) in water (14 ml) was added. The mixture was heated under reflux for 30 min. The separated crystalline semicarbazone was collected on a filter and washed with ether to give 2·55 g (49%) of fine prisms. The crystalline XVI was recrystallized from EtOH to give fine prisms, m.p. 186–188°; ν_{max} (Nujol) 3470, ~3200, ~2600, 1695, 1660, 1575, 1270, 1080, ~950; ($CHCl_3$) 3520, ~3200, ~2600, 1695, 1655, 1560, 1265, ~1080 cm^{-1}. (Found: C, 61·80; H, 8·79, N, 13·25. $C_{16}H_{27}O_3N_3$ requires: C, 62·11; H, 8·80, N, 13·58%). The mother liquor was extracted with ether. The extract was combined with the ether washings. The ethereal soln was washed with water, dried ($MgSO_4$) and concentrated to give 2·6 g (50%) of the oily semicarbazone (XVII)

(±)-Todomatuic acid (Ia)

A suspension of the crystalline semicarbazone (3·0 g) in 95% EtOH (20 ml) and 20 (v/v)% H_2SO_4 (30 ml) was heated under reflux for 40 min. During this period the mixture became homogeneous. EtOH was removed *in vacuo*. Water and ether were added to the residue. The ethereal soln was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residual oil was triturated with petrol to give 1·5 g (36% from the mixture of Ia and XVa or 72% recovery from XVI) of crystals. Recrystallization from petrol gave rods, m.p. 66–67° (sinter at 59°); natural acid; m.p. 57–59° (Dr. Isoe's sample); mixture m.p. 57–66°; ν_{max} (Nujol) ~3200–~2500, 1714, 1694, (1652 sh), 1648, 1278, 950, 940, 920, 783, 740, 708; (CS_2) ~3200–~2500, 1720, 1694, (1654 sh), 1650, 1275, 935, 920 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln.) 0·83 (3H, d, J = 6 c/s), 0·88 (6H, d, J = 6 c/s), 7·02 (1H) 12·18 (1H, $CO_2\underline{H}$) λ_{max} (EtOH) 215 mμ (ε 10,200). (Found: C, 71·71; H, 9·60 $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

(±)-Epitodomatuic acid (XVa)

A soln of the oily semicarbazone (2·6 g) in 95% EtOH (20 ml) and 20 (v/v)% H_2SO_4 (30 ml) was heated under reflux for 40 min. EtOH was removed *in vacuo*. Water and ether were added to the residue. The ethereal soln was washed with brine, dried ($MgSO_4$) and concentrated to give 2·2 g of crude oily acid. An analytical sample boiled at 160–164°/0·2 mm, n_D^{20} 1·4930; ν_{max} (CS_2) ~3200–~2500, 1720, 1694, (1652 sh), 1650, 1270, 1250 (m), 935, 920 cm^{-1}. The IR spectrum was almost identical with that of the crystalline isomer except a band at 1250 cm^{-1} and intensity ratio of some bands; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·83 (3H, d, J = 6 c/s) 0·91 (6H, d, J = 6 c/s), 7·04 (1H), 9·66 (1H, $CO_2\underline{H}$); λ_{max} (EtOH) 217 mμ (ε 8520). (Found: C, 71·45; H, 9·88. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

(±)-Juvabione (=methyl (±)-todomatuate, Ib)

The crystalline Ia (1·2 g) was esterified with diazomethane and the product was distilled *in vacuo* to give 1·0 g of the ester. An analytical sample boiled at 140–141°/0·1 mm, n_D^{19} 1·4818; ν_{max} (film) 1726, 1718, 1654, 1256, 1084, 1034, 922, 805, 745, 715; (CS_2) (1724 sh), 1718, 1654, 1254, 1076, 1032, 920, 804, 742, 714 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·88 (3H, d, J = 6 c/s), 0·92 (6H, d, J = 6 c/s), 1·0–1·85 (ca. 5H), 1·85–2·5 (ca. 8H, 2·22 (2H, s)), 3·68 (3H, s), 6·94 (1H, broad); λ_{max} (EtOH) 218 mμ (ε 12,800). (Found: C, 71·67; H, 9·64. $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%). The spectral data were identical with those of the natural product.

Methyl (±)-epitodomatuate (XVb)

The oily XVa (1·5 g) was esterified with diazomethane and the product was distilled *in vacuo* to give 1·2 g of the ester. An analytical sample boiled at 142–143°/0·1 mm, n_D^{18} 1·4832; ν_{max} (film) 1726, 1716, 1654, 1252, 1082, 1033, 920, 802, 745, 715; (CS_2) (1724 sh), 1718, 1654, 1250, 1082, 1032, 918, 800, 740, 712 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·87 (3H, d, J = 6 c/s), 0·91 (6H, d, J = 6 c/s), 1·0–1·85 (ca. 5H), 1·85–2·6 (ca. 8H, 2·22 (2H, s)), 3·66 (3H, s), 6·95 (1H). λ_{max} (EtOH) 217 mμ (ε 15,100). (Found: C, 71·50; H, 9·90; $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%).

Gas chromatographic analysis of Ib *and* XVb

(a) 2% OV-1 on Shimalite W (80–100 mesh) 180 cm × 4 mm i.d. column temp: 160°. Carrier gas: N_2 40 ml/min retention time 13·7 min.

(b) 2% OV-17 on Shimalite W (80–100 mesh) 180 cm × 4 mm i.d. Column temp: 170°, Carrier gas: N_2 80 ml/min retention time 11·25 min. Both the synthetic (Ib and XVb) and natural (Ib) products showed same retention time.

2-(4'-Carboxycyclohex-2'-enyl)6-methylheptane (=XVIII= *a mixture of* (±)-*desoxotodomatuic acid and its stereoisomer*)

A mixture of Ia and its stereoisomer XVa (3·5 g) was mixed with diethylene glycol (50 ml). KOH aq (7 g in 4 ml) and 80% hydrazine hydrate (7 ml) were added to the mixture. The mixture was heated under reflux for 30 min and then heated at 200–230° for 2·5 hr. After cooling, the mixture was diluted with water, acidified with HCl and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residual oil boiled at 160–162°/0·2 mm to give 2·6 g (79%) of the product, n_D^{16} 1·4920; ν_{max} (film) ~2600, 1685, 1646, 1280, ~930 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·86 (9H, d, J = 6 c/s), 1·0–2·0 (5H), 2·0–2·6 (4H), 7·11 (1H, broad), 11·52 (1H). (Found: C, 75·57; H, 10·96. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

2-(4'-Carboxycyclohexyl)6-methylheptane (XIXa = *a mixture of* (±)-*desoxodihydrotodomatuic acid and its stereoisomers*)

The oily XVIII (2·0 g) in AcOH (50 ml) was hydrogenated over 10% Pd–C (1 g) at room temp. After 3 hr H_2 uptake ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give 1·9 g (95%) of the product; ν_{max} (film) ~3400–~2600, 1710 (broad), ~1260, ~940 cm^{-1}. This was employed for the next step without further purification.

2-(4'-Carbomethoxycyclohexyl)6-methylheptane (XIXb = *a mixture of methyl* (±)-*desoxodihydrotodomatuate and its stereoisomers*)

The oily XIXa (1·9 g) was esterified with diazomethane to give 1·9 g (98%) of an oily ester; ν_{max} (film) 1742, 1248, 1195, 1174, 1150, 1040, 900 cm^{-1}. Water was completely removed from the crude ester by repeated addition and distillation of dry benzene. The residual oil was employed for the next reaction without further purification.

(±)-*trans-4-(1',5'-Dimethylhexyl)cyclohexane-1-carboxylic acid* (III = *the more stable epimer of* (±)-*desoxodihydrotodomatuic acid*)

A soln of XIXb (1·7 g) in MeOH (50 ml) containing NaOMe (from 0·5 g Na) was heated under reflux for 1 hr. Then KOH aq (4 g in 10 ml) was added to the soln and the refluxing was continued for further 3 hr. MeOH was removed *in vacuo*. The residue was diluted with water, acidified with HCl and extracted with ether. The ethereal soln was washed with water and brine, dried ($MgSO_4$) and concentrated to give an oil. This was distilled *in vacuo*, b.p. 150–152°/0·4 mm, to give 1·35 g (84%) of the product, n_D^{19} 1·4710; ν_{max} (film) ~3100–~2600, 1714, 1260, ~940; (CS_2) ~3100–~2600, 1710, ~1260, ~940 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4) 0·87 (9H, d, J = 6 c/s), 1·0–2·6 (18H), 10·97 (1H, s, CO_2H). (Found: C, 74·30; H, 11·83. $C_{15}H_{28}O_2$ requires: C, 74·95; H, 11·74%). *Anilide* (XX): Needles from aqueous MeOH, m.p. 88–90°; ν_{max} (Nujol) 3290, 1665, 1602, 1530, 740, 690; ($CHCl_3$) 3400, 3310, 1700, 1670, 1602, 1300, 1245, 1170, 896, 750, 690 cm^{-1}. (Found: C, 79·46; H, 10·26; N, 4·36. $C_{21}H_{33}ON$ requires: C, 79·94; H, 10·54; N, 4·44%).

3-(p-Methoxyphenyl)butan-1-ol (XXII)

A soln of VIa (89 g) in ether (100 ml) was added dropwise to a slurry of LAH (15 g) in ether (400 ml) with stirring and ice-cooling. The mixture was stirred for 2 hr at room temp after the addition. The remaining hydride was destroyed by the addition of EtOAc. Ice and dil H_2SO_4 (from 100 ml of conc H_2SO_4) were added to the mixture. The ether layer was separated and the aqueous layer was extracted with ether. The combined ethereal soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and distilled to give 63 g (87%) of the product, b.p. 135–144°/5 mm. An analytical sample boiled at 138–140°/5 mm, n_D^{21} 1·5244; ν_{max} (film) 3400, 1612, 1585, 1515, 1250, 1180, 1040, 840 cm^{-1}. (Found: C, 72·87; H, 8·78. $C_{11}H_{16}O_2$ requires: C, 73·30; H, 8·95%).

3-(4'-Methoxycyclohexa-1',4'-dienyl)butan-1-ol (XXIII)

A soln of XXII (20 g) in THF (100 ml) and t-BuOH (100 ml) was added to liquid NH_3 (350 ml). Li (7 g) was added portion-wise to the stirred soln cooled in a dry ice–acetone bath. The stirring was continued for 4·5 hr. Subsequent treatments as described in the preparation of IX gave 19 g (95%) of an oil, b.p.

122–130°/5 mm. An analytical sample boiled at 101–102°/0·08 mm, n_D^{25} 1·5002; ν_{max} (film) 3400, 1690, 1660, 1200, 1150, ~1050, 780 cm^{-1}. (Found: C, 72·08; H, 9·51. $C_{11}H_{18}O_2$ requires: C, 72·49; H, 9·96%).

3-(4'-*Oxocyclohex*-1'-*enyl*)*butan*-1-*ol* (XXIV)

The enol XXIII (54 g) in MeOH (340 ml) was treated with aqueous oxalic acid (6 g in 70 ml) at 25° for 40 min. Subsequent treatments as described in the preparation of X gave 42 g (84%) of an oil, b.p. 130–150°/6 mm; ν_{max} (film) 3400, 1705, 1660, 1630, 1040 cm^{-1}. The IR spectrum showed that this material was a mixture of the β,γ-unsaturated ketone and its α,β-isomer. Therefore, without further purification, this was used for the next step.

3-(4'-*Oxocyclohexyl*)*butan*-1-*ol* (XXVa)

The crude XXIV (42 g) in 95% EtOH (50 ml) was hydrogenated over 10% Pd–C (4 g). Subsequent work-up gave 33 g (76%) of the product, b.p. 130–160°/7 mm. An analytical sample boiled at 120°/0·1 mm, n_D^{25} 1·4872; ν_{max} (film) 3400, 1705, 1050 cm^{-1}. (Found: C, 70·18; H, 10·43. $C_{10}H_{18}O_2$ requires: C, 70·54; H, 10·66%).

3-(4'-*Oxocyclohexyl*)*butan*-1-*ol acetate* (XXVb)

To a soln of XXVa (32 g) in ether (120 ml) and pyridine (50 ml) was added dropwise acetyl chloride (18 g). The mixture was left overnight at room temp. Subsequent treatments as described in the preparation of XIb afforded 33 g (83%) of an oily acetate. An analytical sample boiled at 114–115°/0·08 mm, n_D^{25} 1·4680; ν_{max} (film) 1740, 1710, 1230, 1030 cm^{-1}. (Found: C, 67·63; H, 9·50. $C_{12}H_{20}O_3$ requires: C, 67·89; H, 9·50%).

3-(4'-*Hydroxy*-4'-*cyanocyclohexyl*)*butan*-1-*ol acetate* (XXVI)

Powdered KCN (36 g) was suspended in a soln of XXVb (31 g) in 95% EtOH (180 ml). AcOH (38 ml) was added dropwise to the suspension at 0–5°. The stirred mixture was kept at 0–5° for 40 min then at 40° for 30 min. Subsequent treatment as described in the preparation of XII gave 32 g (94%) of an oil, which was employed for the next step without further purification; ν_{max} (film) 3400, 1740–1720 (broad), 1230, 1030 cm^{-1}.

3-(4'-*Cyanocyclohex*-3'-*enyl*)*butan*-1-*ol acetate* (XXVII)

$POCl_3$ (36 g) was added to an ice-cooled soln of XXVI (32 g) in pyridine (150 ml). The mixture was left at room temp for 2 days and then treated under reflux for 30 min. After cooling, it was poured into ice and HCl (from 200 ml of conc HCl). Subsequent treatment as described in the preparation of XIII afforded 27 g (90%) of an oil. An analytical sample boiled at 130–132°/0·08 mm, n_D^{25} 1·4818; ν_{max} (film) 2220, 1740, 1640, 1250, 1040 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln) 0·88 (3H, d, J = 6 c/s), 1·94 (3H, s), 3·96 (2H, t, J = 6 c/s) 6·50 (1H, broad). (Found: C, 70·53; H, 8·56; N, 5·84. $C_{13}H_{19}O_2N$ requires: C, 70·55; H, 8·65; N, 6·33%).

3-(4'-*Carboxycyclohex*-3'-*enyl*)*butan*-1-*ol* (XXVIIIa *and* XXIXa)

A soln of crude XXVII (25 g) in diethylene glycol (150 ml) was mixed with KOH aq (35 g in 120 ml) and the mixture was heated under reflux for 42 hr. Subsequent treatment as described in the preparation of XIV gave an oil (18 g, 80%). This was triturated with ether to give 9 g of crystals, m.p. 96–100°. This acid (XXVIIIa) was recrystallized from EtOAc–petrol as prisms, m.p. 110–111°; ν_{max} (Nujol) ~3300, ~2600, 1688, (1675 sh), 1646, 1050, 1006, ~950; ($CHCl_3$) 1692, 1650 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·88 (3H, d, J = 6 c/s), 3·64 (2H, m, CH_2OH), 6·80 (2H, broad, OH + CO_2H), 7·05 (1H CH=C). (Found: C, 66·91; H, 9·36. $C_{11}H_{18}O_3$ requires: C, 66·64; H, 9·15%).

Concentration of the mother liquor afforded oily XXIXa (7·7 g); ν_{max} (film) ~3350, ~2600, (1710 sh), 1698, 1650, 950; ($CHCl_3$) 1692 (broad), 1650 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln) 0·88 (3H, d, J = 6 c/s), 3·64 (2H, m, CH_2OH), 6·80 (2H, broad, OH + CO_2H), 7·05 (1H CH=C).

3-(4'-*Carbomethoxycyclohex*-3'-*enyl*)*butan*-1-*ol* (XXVIIIb *and* XXIXb)

The crystalline XXVIIIa was esterified with diazomethane to give an oily ester XXVIIIb, b.p. 130°/0·1 mm, n_D^{27} 1·4912; ν_{max} (film) 3400, 1700, 1640, 1250, 1080, 1040 cm^{-1}. (Found: C, 67·30; H, 9·52. $C_{12}H_{20}O_3$ requires: C, 67·89; H, 9·50%).

The oily XXIXa was also esterified with ethereal diazomethane to give an oily ester XXIXb, b.p. 122–124°/0·08 mm, n_D^{27} 1·4892; ν_{max} (film) 3400, 1705, 1640, 1240, 1080, 1040 cm^{-1}. (Found: C, 67·63; H, 9·61. $C_{12}H_{20}O_3$ requires: C, 67·89; H, 9·50%).

3-(4'-Carbomethoxycyclohex-3'-enyl)butan-1-ol (XXI)

A soln of t-butyl chromate was prepared by mixing CrO_3 (3·0 g), t-BuOH (6 ml) and benzene (20 ml) and dried over $MgSO_4$. A soln of XXVIIIb (4·2 g) in benzene (20 ml) was added to an ice-cooled soln of t-butyl chromate and the mixture was left at room temp for 2 days. Then the excess oxidant was destroyed by aqueous oxalic acid. The benzene layer was separated, diluted with ether and shaken with dil H_2SO_4 to remove Cr ion. The organic layer was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated. The residual oil was dissolved in a small amount of ether and shaken with sat $NaHSO_3$ aq. The precipitated bisulphite adduct was collected on a filter and washed with ether. The adduct was dissolved in a small amount of hot water. Powdered $NaHCO_3$ was added to the aqueous soln to decompose the adduct. The separated oily aldehyde was extracted with ether. The ethereal soln was washed with brine, dried ($MgSO_4$) and concentrated to give 0·5 g (13%) of an oil; ν_{max} (film) 2720, 1720, 1705, 1640, 1250, 1080 cm^{-1}. The *2,4-dinitrophenylhydrazone*: fine yellow needles from EtOAc petrol m.p. 148 150°; ν_{max} (Nujol) 3270, 3120, 1718, 1650, 1615, 1592, 1512, 1338, 1322, 1304, 1255, 1134, 1080 cm^{-1}. (Found: C, 55·12; H, 5·58; N, 13·90. $C_{18}H_{22}O_6N_4$ requires: C, 55·38; H, 5·68; N, 14·35%).

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