Diels–Alder Reactions. Part I. The Dienophilic Properties of *cis*- and *trans*-β-Formylcrotonic Acid and their Derivatives

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Methyl *trans*-β-formylcrotonate (2) and 4-hydroxy-3-methylbut-2-en-4-olide (*cis*-β-formylcrotonic acid) gave Diels–Alder adducts with dimethylbuta-1,3-diene with preservation of the steric arrangement of the substituents on the dienophile. The dienophile (2) similarly gave adducts with the 1,2,4-trisubstituted diene, 6,6-ethylenedioxy-3-methylhexa-2,4-dienyl acetate, which might prove of value in the synthesis of kitol-like dimers of retinol.

KITOL (1),[1,2] a naturally occurring dimer of retinol, can be regarded as a 1,4-cycloaddition product involving the 11,13-double bonds of the first and the 13-double bond of the second retinol molecule, leading to the formation of the central cyclohexene ring. Retinol is known to undergo such 1,4-addition reactions at the 11,13-double bonds, when treated with suitable dienophiles.[3] The

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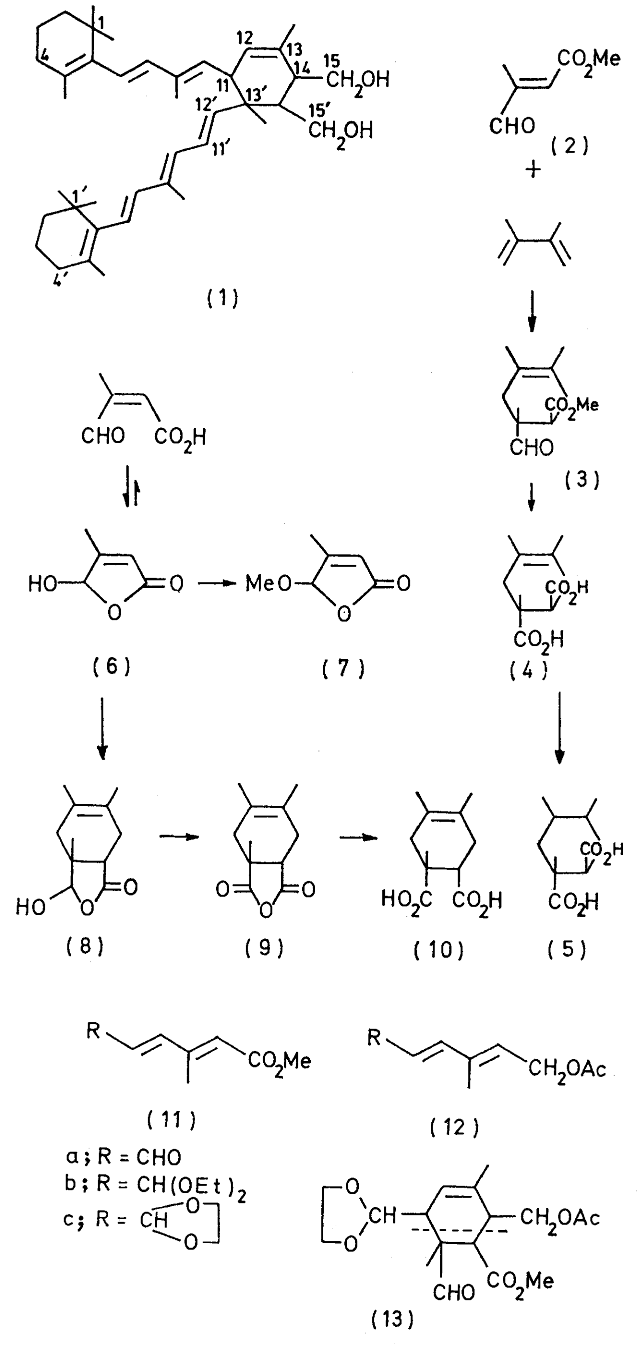
synthesis of kitol by condensation of retinol, its acetate, or other suitable dienes, 6,6-ethylenedioxy-3-methylhexa-2,4-dienyl acetate (12c) with a dienophile that would furthermore allow completion of the conjugated tetraene unit of kitol, was therefore considered. β-Formylcrotonic acid and derivatives thereof appeared to fit these requirements as possible dienophiles, and in this paper their condensation with reactive 1,2,4-trisubstituted dienes is described. This investigation was followed by exploration of the influence of hydroxy- and acetoxy-methyl groups on the diene on the orientation and steric arrangement [4,5] of substituents in the adducts with methyl *trans*-β-formylcrotonate.[6]



Methyl *trans*-β-formylcrotonate (2), obtained from γ-bromosenecioate [7] by a Kröhnke oxidation,[8] on heating with dimethylbuta-1,3-diene yielded the adduct (3), which, on oxidation with silver oxide in alkaline medium followed by saponification, gave the *trans*-diacid (4), which did not yield an anhydride on sublimation. The *trans*-ester (2) was converted into *cis*-β-formylcrotonic acid by hydrolysis in aqueous hydrochloric acid; [9] and was isolated as 4-hydroxy-3-methylbut-2-en-4-olide (6), which at elevated temperatures gave the adduct (8) with dimethylbuta-1,3-diene. Chromic acid oxidation [10] of adduct (8) and sublimation of the product yielded the anhydride (9) which upon hydrolysis gave the *cis*-diacid (10), with properties similar to those reported by Rivett [11] for an acid (10) obtained in a different way.

The methoxybutenolide (7) was obtained by heating the hydroxybutenolide (6) with sulphuric acid in methanol.[12] This product, which is known to react in the open chain form with Wittig reagents,[13] did not however yield an adduct under the conditions where both the dienophiles (2) and (6) gave the expected Diels–Alder adducts. This could be due to steric effects and/or the inductive effect of the *O*-methyl group.

As outlined in the introductory paragraph, the adducts (13) could in principle be used for the synthesis of kitol-like dimers of retinol by employing the formyl and ethylenedioxymethyl groups successively for the construction of the conjugated tetraene and triene units respectively.

Methyl 3-methyl-6-oxohexa-2,4-dienoate (11a), prepared by condensing the diethyl acetal of methyl *trans*-β-formylcrotonate (2) with ethyl vinyl ether,[14] was converted into methyl 6,6-diethoxy-3-methylhexa-2,4-dienoate (11b) by treatment with ethyl orthoformate and toluene-*p*-sulphonic acid. On reduction with lithium aluminium hydride followed by acetylation with acetic anhydride and pyridine, *compound* (11b) gave 6,6-diethoxy-3-methylhexa-2,4-dienyl acetate (12b). During distillation under reduced pressure or during gas chromatography this product was partially converted into the corresponding aldehyde (12a), and was therefore considered too unstable for Diels–Alder addition to the unreactive dienophile (2). The ethylene acetal (12c), although also relatively thermally unstable was eventu-

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ally employed as dienophile, and gave a mixture of adducts (13) in 17% yield. The n.m.r. spectrum of this mixture showed aldehyde resonances at τ 0·52, 0·30, 0·23, and 0·22, indicative of the presence of at least four different isomeric adducts.

These introductory experiments confirmed the utility of methyl *trans*-β-formylcrotonate (2) and the hydroxybutenolide (6) as dienophiles, and confirmed the principle of preservation of the steric arrangement of the substituents on the dienophile.[4,5]

EXPERIMENTAL

Combustion analyses were by Dr. F. Pascher, Bonn. I.r. spectra were recorded with a Perkin-Elmer model 21 spectrometer. G.l.c. analyses were obtained with a Perkin-Elmer model 116E gas chromatograph. Helium was used as carrier gas.

4-Methoxy-3-methylbut-2-en-4-olide (7).—The hydroxybutenolide [9] (6) (10 g), methanol (10 ml), and sulphuric acid (0·5 ml) were refluxed for 15 h. The mixture was then poured into water, the aqueous layer extracted with ether, and the extracts were washed successively with aqueous sodium carbonate and water. After drying, the ether was evaporated, and distillation of the residue gave the methoxybutenolide (7) (9·2 g), b.p. 75—76° at 1·5 mmHg (Found: C, 56·0; H, 6·3. Calc. for $C_6H_8O_3$: C, 56·2; H, 6·2%). I.r. and n.m.r. data were identical to published values.[13] A mixture of the methoxybutenolide (7) (2 g), dimethylbuta-1,3-diene (2 g), and hydroquinone (0·1 g) was heated in a sealed tube at 150° for 40 h. Distillation of the product gave no adduct. Similarly a mixture of the methoxybutenolide (7), dimethylbuta-1,3-diene, and hydroquinone in benzene (7 ml) on heating at 150° for 4 h also yielded no adduct.

Condensation of Hydroxybutenolide (6) *with* 2,3-*Dimethylbutadiene*.—A mixture of the hydroxybutenolide (6) (2 g), dimethylbutadiene (2·5 g), hydroquinone (0·1 g), and benzene (10 ml) was heated in a sealed tube at 150° for 40 h. Distillation of the reaction mixture gave *9-hydroxy-1,3,4-trimethyl-7-oxo-8-oxabicyclo*[4.3.0]*non-3-ene* (8) (2·54 g), b.p. 120—121° at 0·01 mmHg (Found: C, 67·7; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

1,4,5-*Trimethylcyclohex*-4-*ene*-cis-1,2-*dicarboxylic Acid* (10).—To the adduct (8) (0·96 g) in acetone (50 ml) at room temperature chromic acid [10] [2 ml of a solution containing CrO_3 (18 g)–6N-H_2SO_4 (100 ml)] was added over 2 h. The mixture was diluted with water and extracted with ether. The combined extracts were washed with water, dried, and the ether evaporated. Distillation of the residue gave the crude anhydride (9), b.p. 60—65° (bath temperature) at 0·1 mmHg (Found: C, 67·3; H, 7·9. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%). The anhydride (9) (0·6 g) was heated with water (7 ml),[15] after which the mixture was cooled and extracted with ether. The extract was dried (Na_2SO_4), the ether evaporated, and the residue recrystallised from ether to yield the *cis*-diacid (10), m.p. 181—191° (lit.,[11] 183—190°) (Found: C, 62·3; H, 8·2. Calc. for $C_{11}H_{16}O_4$: C, 62·3; H, 7·6%).

Condensation of Methyl trans-β-*Formylcrotonate* (2) *with Dimethylbuta*-1,3-*diene*.—The ester (2) (2·4 g), dimethylbuta-1,3-diene (5 g), and hydroquinone were heated at 150° for 51 h in a sealed tube. Distillation gave *methyl 6-formyl-3,4,6-trimethylcyclohex-3-enecarboxylate* (3) (2·5 g, 64%), b.p. 88° at 0·1 mmHg, n_D^{20} 1·4795, $\nu_{max.}$ (film) 1730 cm^{-1} (Found: C, 69·0; H, 8·9. $C_{12}H_{18}O_3$ requires C, 68·5; H, 8·6%). A *dinitrophenylhydrazone*, prepared according to the method of Johnson,[16] had m.p. 133·5—134° (from EtOH) (Found: C, 55·5; H, 5·8; N, 14·15. $C_{18}H_{22}N_4O_6$ requires C, 55·4; H, 5·7; N, 14·35%).

1,4,5-*Trimethylcyclohex*-4-*ene*-trans-1,2-*dicarboxylic Acid* (4).—Adduct (3) (1 g) was suspended in an aqueous solution of silver nitrate (2·3 g in 5 ml) at room temperature. Aqueous sodium hydroxide (1·2 g in 5 ml) was added and the reaction mixture was shaken for 3 h, followed by heating on a steam-bath for 1 h. Solid material was filtered off, the filtrate was acidified with 3N-H_2SO_4, and the product extracted with ether. Saponification was incomplete, so the isolated product was resaponified with ethanolic sodium hydroxide (1 g in 25 ml). The acid was purified by recrystallisation from acetone–light petroleum (yield 500 mg). Sublimation yielded the pure *diacid* (4), m.p. 178—179° (Found: C, 62·0; H, 7·75. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%).

1,4,5-*Trimethylcyclohexane*-trans-1,2-*dicarboxylic Acid* (5).—Hydrogenation of the diacid (4) in acetic acid over Adams catalyst led to the absorption of 0·94 mol. equiv. of hydrogen to yield the trans-*diacid* (5), which was purified by sublimation, m.p. 253—254° (sealed tube) (Found: C, 61·8; H, 8·75. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

Methyl 6,6-*Ethylenedioxy*-3-*methylhexa*-2,4-*dienoate* (11c).—A mixture of methyl 3-methyl-6-oxohexa-2,4-dienoate [14] (11a) (10 g), benzene (50 ml), ethylene glycol (8 g), and toluene-*p*-sulphonic acid (0·2 g) was refluxed in a Dean–Stark apparatus until no more water separated. The solution was treated with potassium carbonate, filtered, and the solvent was evaporated under reduced pressure. Distillation of the residue yielded the required *product* (11c) (10·5 g), b.p. 93—95° at 0·01 mmHg, n_D^{25} 1·5060, $\nu_{max.}$ (film) 1715 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 255 nm (Found: C, 60·8; H, 7·15. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

6,6-*Ethylenedioxy*-3-*methylhexa*-2,4-*dienyl Acetate* (12c).—A solution of the ester (11c) (10·5 g) in dry ether (50 ml) was reduced at 0° with lithium aluminium hydride (1·2 g) in ether (25 ml). Excess of reducing agent was destroyed after 10 min by the addition of ethyl acetate (6 ml). The product was isolated and distilled to yield 6,6-ethylenedioxy-3-methylhexa-2,4-dienol (6·87 g), b.p. 107—108° at 0·01 mmHg, $\nu_{max.}$ (film) 3395 cm^{-1} (OH). This dienol (5·87 g) was acetylated by treatment with acetic anhydride (4 g) and pyridine (3·5 g) for three days at room temperature, and yielded the *acetate* (12c) (6 g), b.p. 96—98° at 0·02 mmHg, n_D^{25} 1·4871, $\nu_{max.}$ (film) 1730 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 232 nm (ε 23,400) (Found: C, 62·4; H, 7·8. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·55%).

Diels–Alder Addition Products (13).—The dienyl acetate (12c) (5 g) and methyl *trans*-β-formylcrotonate (2) (3·5 g) were heated for 116 h at 110°. Distillation of the product yielded a mixture of the adducts (13) (1·2 g, 17%), b.p. 150—160° (air-bath) at 2×10^{-4} mmHg (Found: C, 59·7; H, 6·4. Calc. for $C_{12}H_{24}O_7$: C, 60·0; H, 7·05%).

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