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Retinoids and Related Compounds. IV.[1] Synthesis of Bicyclic Retinoates

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The bicyclic retinoates (VII) and (XII) were synthesised.

Keywords——retinoid; bicyclic retinoate; antitumour effect; Grignard reaction; Horner condensation; coplanarity

It is well known that retinoic acid (Ia) shows a prophylactic as well as a therapeutic effect on skin papillomas and carcinomas in mice.[2,3] Extensive chemical modifications of the acid (Ia) have resulted in the discovery of arotinoids (aromatic retinoids) as a new class of highly active retinoids.[4] In a previous series of studies, we developed a new route for the synthesis of bicyclic retinoids.[1,5] In this paper, we describe the synthesis of the new bicyclic retinoates (VII) and (XII) as a part of a series of studies[6,7] to obtain new retinoids with antitumour effect.

A Grignard reaction of the bicyclic dienal (II),[1,5] the key intermediate in the synthesis of X, with methylmagnesium bromide in dry tetrahydrofuran (THF) gave a dienal [ν_{OH} 3600 cm^{-1}] which, without purification, was treated with active MnO_2[8] followed by silica gel column chromatographic purification to afford the methyl ketone (III) in 50.7% yield from II. The structure of the dienone (III) was characterised by its spectral data. Attempts to obtain the dienone (III) from the nitrile (VIII)[1,5] through the intermediate imine (IX) using methylmagnesium bromide resulted in low yield [6.1% from VIII]. The dienone (III) was condensed with diethyl cyanomethylphosphonate using *n*-butyl-lithium as the base under reflux in dry THF under nitrogen for 2 h to give the (*E*)-triene-nitrile (IV) [ν_{CN} 2207 cm^{-1}] exclusively in 51.5% yield. The newly formed trisubstituted double bond was determined to have the *E*-configuration from the chemical shift (δ 2.27 ppm)[9] of the C-1'-methyl signal. The nitrile group of IV was reduced with di-isobutylaluminium hydride followed by preparative thin-layer chromatography (TLC) to provide the (*E*)-trienal (V) in 50.7% yield. A Horner condensation of the (*E*)-trienal (V) with the phosphonate (VI)[10] in the presence of *n*-butyl-lithium in dry THF at ice-cooling temperature under nitrogen for 0.5 h led to the all-(*E*)-bicyclic retinoate (VII) in 69.2% yield. The structure of VII was confirmed by its spectral data (ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS)). Characteristic data are shown in the Table I compared with those of methyl retinoate (Ib). The UV maximum of VII suggests that the bicyclic retinoate (VII) has high coplanarity in its conjugated system as compared with the retinoate (Ib). It is very interesting that all the olefinic

Table I

	Bicyclic retinoate VII	Retinoate Ib
UV λ_{max}^{EtOH} nm	397 (ε 37500)	354 (ε 44400)[11]
NMR	6.40 (3-H)	6.27 (7-H)[12]
δ_{ppm}	—	6.11 (8-H)
	6.32 (2'-H)	6.13 (10-H)
	7.07 (3'-H)	6.99 (11-H)
	6.34 (4'-H)	6.27 (12-H)
	5.77 (6'-H)	5.79 (14-H)

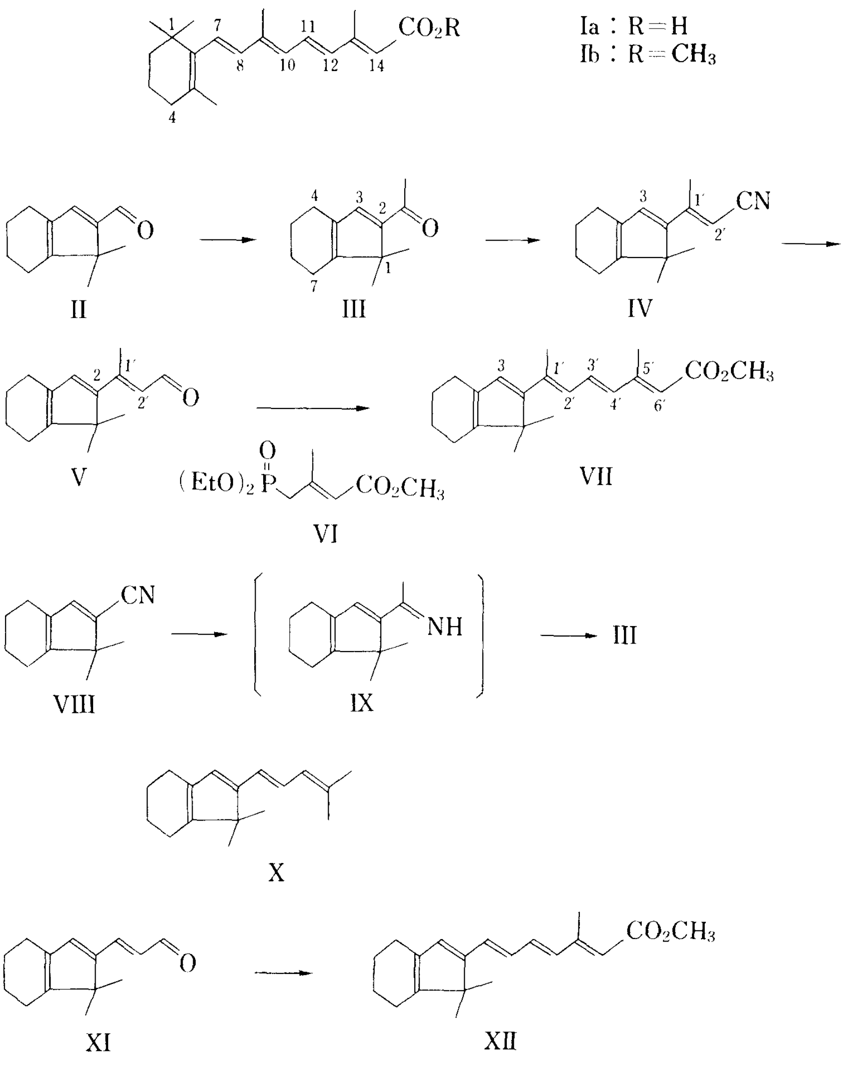

Chart 1

protons except for 6'-H (14-H) in the NMR spectrum of VII appear at lower field than the corresponding protons in methyl retinoate (Ib). In the same manner, a 9-des-methyl analogue (XII) was prepared from the trienal (XI).[1] The biological activities of VII and XII are now under investigation.

Experimental

UV spectra were recorded on a Shimadzu 200S instrument and IR spectra on a Shimadzu IR-27G spectrometer. NMR spectra at 60 or 200 MHz were determined on a JEOL PMX 60 NMR spectrometer or a Varian XL-200 superconducting FT-NMR spectrometer using solutions in $CDCl_3$. MS were determined on a JEOL JMS-01SG mass spectrometer; high resolution measurements were made relative to perfluorokerosene as a reference. Preparative TLC was carried out on silica gel plates (Merck silica gel $60F_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Silica gel for column chromatography was Merck Kieselgel 60 (Korngröβe 0.2—0.5 mm, 35—70 ASTM).

4,5,6,7-Tetrahydro-1,1-dimethyl-2-acetylindene (III)——A solution of 4,5,6,7-tetrahydro-1,1-dimethyl-2-formylindene (II,[1] 436 mg) in dry THF (3 ml) was added dropwise to a 1 M solution (6.3 ml) of methylmagnesium bromide in dry THF with ice-cooling under a stream of nitrogen. When addition was complete, the mixture was stirred at room temperature for 0.5 h. Ether (5 ml) was added and then saturated aq. NH_4Cl solution (10 ml) was added under ice-cooling. The mixture was extracted with ether and the extract was washed with brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave an oil (356 mg), which was dissolved in *n*-hexane (15 ml). The hexane solution was shaken with active MnO_2[8] (3.1 g) at room temperature for 20 h, then filtered. The filtrate was concentrated *in vacuo* to give a yellow oil, which was purified by silica gel column chromatography (eluent: 10% ether in benzene) to afford the methyl ketone (III, 243 mg (50.7%)). UV λ_{max}^{EtOH}: 320 nm (ε 14000); IR $\nu_{max}^{CHCl_3}$: 1640, 1625 cm^{-1}; NMR δ (60 MHz): 1.17 (6H, s, gemCH_3), 2.30 (3H, s, $COCH_3$), 7.03 (1H, s, 3-H); MS *m/e*: 190.135 (M^+, $C_{13}H_{18}O$ requires 190.136).

(1′*E*)-4,5,6,7-Tetrahydro-1,1-dimethyl-2-1′-methyl-2′-cyanoethenylindene (IV)——*n*-Butyl-lithium (15% in *n*-hexane, 1.6 ml) was added to a solution of diethyl cyanomethylphosphonate (677 mg) in dry THF (4 ml) with ice-cooling under nitrogen. The mixture was stirred at room temperature for 0.5 h and then a solution of the methyl ketone (III, 241 mg) in dry THF (4 ml) was added dropwise. The reaction mixture was refluxed for 2 h, cooled to room temperature, poured into water, and extracted with ether. The ethereal extract was washed with brine, then dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded an oil which was purified by preparative TLC (developing solvent: 2% ether in benzene) to afford the (1′*E*)-nitrile (IV, 138 mg (51.5%)). UV λ_{max}^{EtOH}: 341 nm; IR $\nu_{max}^{CHCl_3}$: 2207 cm^{-1}; NMR δ (60 MHz): 1.08 (6H, s, gemCH_3), 2.27 (3H, s, 1′-CH_3), 5.18 (1H, s, 2′-H), 6.60 (1H, s, 3-H).

(1′*E*)-4,5,6,7-Tetrahydro-1,1-dimethyl-2-1′-methyl-2′-formylethenylindene (V)——A solution of diisobutylaluminium hydride (180 mg) in *n*-hexane (2 ml) was added to a solution of the (1′*E*)-nitrile (IV, 132 mg) in *n*-hexane (2 ml) with ice-cooling under nitrogen. The mixture was stirred at room temperature for 0.5 h, poured into cold dil. H_2SO_4, and extracted with ether. The extract was neutralised with sodium bicarbonate solution, washed with brine, and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave an oil, which was purified by preparative TLC (developing solvent: 15% ether in *n*-hexane) to yield the (1′*E*)-trienal (V, 68 mg (50.7%)) as orange crystals, mp 94—96°C, UV λ_{max}^{EtOH}: 370 nm (ε 18200); IR $\nu_{max}^{CHCl_3}$: 1640, 1580 cm^{-1}; NMR δ (60 MHz): 1.15 (6H, s, gemCH_3), 2.38 (3H, s, 1′-CH_3), 6.12 (1H, d, J=8 Hz, 2′-H), 6.83 (1H, s, 3-H), 10.12 (1H, d, J=8 Hz, CHO); MS *m/e*: 216.149 (M^+, $C_{15}H_{20}O$ requires 216.151).

All-(*E*)-4,5,6,7-tetrahydro-1,1-dimethyl-2-1′,5′-dimethyl-6′-methoxycarbonyl-hexa-1′,3′,5′-trien-1′-ylindene (VII)——*n*-Butyl-lithium (15% in *n*-hexane, 0.2 ml) was added to a solution of (*E*)-diethyl 3-methoxycarbonyl-2-methylprop-2-enyl-phosphonate (VI,[10] 122.8 mg) in dry THF (2 ml) with ice-cooling under nitrogen and the reaction mixture was stirred for 0.5 h. Then a solution of the aldehyde (V, 68 mg) in dry THF (2 ml) was added dropwise. When addition was complete, the mixture was stirred at room temperature for 0.5 h, poured into water, and extracted with ether. The ethereal extract was washed with brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave an oil, which was purified by preparative TLC (developing solvent: 10% ether in *n*-hexane) to afford the all-(*E*)-ester (VII, 68 mg (69.2%)) as yellow needles, mp 127—128.5°C, UV λ_{max}^{EtOH}: 397 nm (ε 37500); IR $\nu_{max}^{CHCl_3}$: 1700 cm^{-1}; NMR δ (200 MHz): 1.17 (6H, s, gemCH_3), 2.07 (3H, s, 1′-CH_3), 2.37 (3H, s, 5′-CH_3), 3.71 (3H, s, $COOCH_3$), 5.77 (1H, s, 6′-H), 6.32 (1H, d, J=11 Hz, 2′-H), 6.34 (1H, d, J=15 Hz, 4′-H), 6.40 (1H, s, 3-H), 7.07 (1H, dd, J=15, 11 Hz, 3′-H); MS *m/e*: 312.208 (M^+, $C_{21}H_{28}O_2$ requires 312.209).

All-(*E*)-4,5,6,7-tetrahydro-1,1-dimethyl-2-5′-methyl-6′-methoxycarbonyl-hexa-1′,3′,5′-trien-1′-ylindene (XII)——According to the same method as used for the ester (VII), the 9-desmethyl analogue (XII, 18.7 mg (23.3%)) was obtained from the (*E*)-trienal (XI,[1] 54.8 mg). UV λ_{max}^{EtOH}: 390 nm; NMR δ (200 MHz): 1.11 (6H, s, gemCH_3), 2.33 (3H, s, 5′-CH_3), 3.71 (3H, s, $COOCH_3$), 5.75 (1H, s, 6′-H), 6.28 (1H, d, J=12 Hz, 1′-H), 6.32 (1H, s, 3-H), 6.49 (1H, dd, J=12, 9 Hz, 2′-H), 6.61 (1H, d, J=14.5 Hz, 4′-H), 6.71 (1H, dd, J=14.5, 8 Hz, 3′-H); MS *m/e*: 298.189 (M^+, $C_{20}H_{26}O_2$ requires 298.193).

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