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Retinoids and Related Compounds. III.[1] Synthesis of (1′*E*)-4,5,6,7-Tetrahydro-1,1-dimethyl-2-4′-methyl-penta-1′,3′-dien-1′-ylindene. A Proof of the Chromophoric Structure of a New Conjugated Compound produced from the Colour Reaction of Retinoic Acid

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The structure of a new chromophore in II has been confirmed by the synthesis of the tetraene III containing the tetrahydroindene skeleton.

Keywords——retinoid; colour reaction of retinoic acid; tetrahydroindene skeleton; new conjugated system; Wittig reaction

Retinoic acid (I) and its analogues have attracted interest because of their ability to inhibit the growth of epithelial tumours,[2] since the first successful therapeutic experiments with I were carried out with chemically induced papillomas and carcinomas.[3] On the other hand, it has been shown[4] that the colour reaction (in 74% H_2SO_4) of I was a useful method for the determination of I in tissues. As a result of our studies[5] on the chemistry of the colour reaction, the structure of the main quenched product (isolated as the methyl ester) of the coloured species was proposed to be II on the basis of a spectroscopic investigation.[5c,d] The compound II with 74% sulphuric acid regenerated the striking red colour of I in the same acid.

In a previous short communication,[6] we described a synthetic proof of the *chromophoric structure* of a colour-producing compound by the synthesis of (1′*E*)-4,5,6,7-tetrahydro-1,1-dimethyl-2-4′-methyl-penta-1′,3′-dien-1′-ylindene (III). The present paper is concerned with a full account of the experiments.

Formylation of 4,5,6,7-tetrahydro-3,3-dimethyl-1-indanone (IV)[7] with ethyl formate and sodium hydride in dry ether gave the crystalline formyl-enone (V), mp 130°C, in 81% yield. Refluxing of V with hydroxylamine hydrochloride in acetic acid for 2 h afforded the isoxazole (VI) which, without purification, was treated with sodium methoxide in dry ether followed by silica gel column chromatographic purification to yield the ketonitrile (VII) in 48% yield from V. The structure of VII was confirmed by spectral evidence: absorptions at 2250, 1712, and 1642 cm^{-1} in the infrared (IR) spectrum; a proton resonance peak (C-2) at δ 3.23 as a singlet in the nuclear magnetic resonance (NMR) spectrum. Sodium borohydride reduction of VII in methanol and subsequent dehydration of the resulting hydroxy-nitrile with phosphorous oxychloride in dry pyridine afforded the dienonitrile (VIII) in 45% yield. Its ultraviolet (UV) maximum at 295 nm, IR absorptions at 2200 and 1633 cm^{-1}, and NMR olefinic proton at δ 6.89 as a singlet established the desired structure VIII. The nitrile group of VIII was reduced with di-isobutylaluminium hydride in dry toluene to yield the dienal (IX), which was condensed with diethyl methoxycarbonylmethylphosphonate in the presence of *n*-butyl lithium to give the conjugated triene ester (X). The configuration at the newly formed double bond was confirmed to be *trans* by the NMR coupling constant (16 Hz) of the AB type quartet due to the olefinic protons. Reduction of the triene ester (X) with lithium aluminium hydride followed by oxidation with active MnO_2 and subsequent silica gel column chromatography led to the trienal (XI) in 40% yield, in which the geometry of the 1′,2′-double bond was preserved. A Wittig reaction between XI and the triphenylphosphine isopropylidene reagent[8] (prepared from isopropyltriphenylphosphonium bromide and *n*-butyl lithium in a

sealed bottle under argon) furnished the conjugated tetraene (III), an unstable yellow oil, in 72% yield. Its molecular formula was determined to be $C_{17}H_{24}$ by high resolution mass spectrometry. Its UV spectrum showed maxima at 347 (ε 18100), 331 (ε 21300), 318 (*sh.*), and 237 (ε 13000) nm. The NMR spectrum of III exhibited the signals of geminal methyl groups (δ 1.09), two olefinic methyl groups (δ 1.81), and four different olefinic protons [δ 5.92 (md, J=10 Hz), 6.19 (s), 6.22 (d, J=16 Hz), 6.60 (dd, J=16, 10 Hz)], indicating a conjugated olefinic system. The NMR spectral pattern of III in the olefinic region was similar to that of II. These physical data confirmed that II had a skeleton similar to that of III. The compound II had a UV spectrum identical to that of III. In addition, the visible light absorption spectrum of III in 74% H_2SO_4 resembled that of II very closely. These results demonstrated that the *chromophoric structure* of II was unambiguously the same as that of III. A Wittig reaction between IX and dimethylallyltriphenylphosphonium bromide in the presence of *n*-butyl lithium in dry ether produced a mixture (3: 1) of III and its *cis* isomer from which the isomers could not be separated.

The present synthesis of III, which includes a new conjugated system, has resulted in the development of a new synthetic route to bicyclic retinoids.[9]

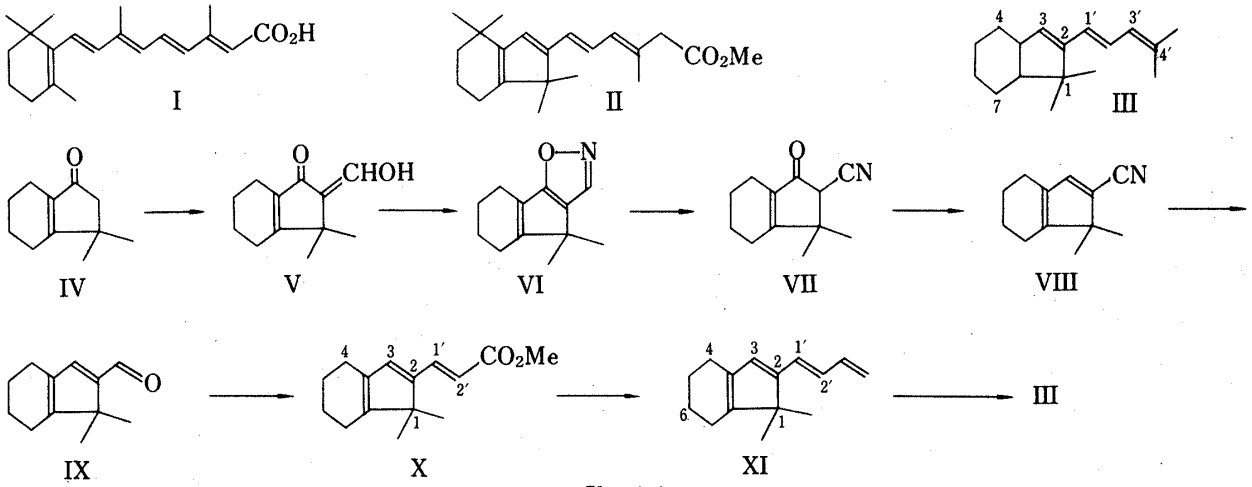

Chart 1

Experimental

UV spectra were recorded on a Shimadzu UV 200S instrument and IR spectra on a Shimadzu IR-27G spectrometer. NMR spectra at 60 or 90 MHz were determined on a JEOL JNM-PMX 60 NMR spectrometer or Varian NEVA-NV 21 spectrometer using solutions in deuteriochloroform. Mass spectra (MS) were determined on a JEOL JMS-01SG mass spectrometer; high resolution measurements were made relative to perfluorokerosene as a reference. Preparative thin layer chromatography (TLC) was carried out on silica gel plates (Merck silica gel $60F_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Alumina for column chromatography was Merck aluminium oxide 90 standardised (Aktivitätsstufe II—III). Silica gel for column chromatography was Merck Kieselgel 60 (Korngröβe 0.2—0.5 mm, 35—70 mesh ASTM).

2-Formyl-3,3-dimethyl-4,5,6,7-tetrahydro-1-indanone (V)——A mixture of indanone (IV,[7] 23.3 g) and ethyl formate (13.6 g) was added to a stirred suspension of sodium hydride (7.5 g, 50% oil dispersion) in dry ether under a stream of nitrogen during 1 h, and stirring was continued for 12 h at room temperature. Water (300 ml) was added to the reaction mixture and the organic layer was separated. The organic layer was washed with water 2 or 3 times. The combined aqueous layer was adjusted to pH 2 with dil. H_2SO_4 and extracted with ether. The ether extract was washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation gave a crystalline formate (V, 22 g (81%)) mp 130°C, UV λ_{max}^{EtOH} nm: 260, 283. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665, 1600. NMR δ (90 MHz): 1.16 (6H, s, gemCH_3), 1.62—1.79 (4H, m, CH_2), 2.13—2.31 (4H, m, CH_2), 7.04 (1H, s, =CH), 6.84—7.69 (1H, br s, OH). MS *m/e*: 192.116 (M^+, $C_{12}H_{16}O_2$ requires 192.115).

Isoxazole (VI)——A mixture of formyl ketone (V, 14.6 g) and hydroxylamine hydrochloride (11.8 g) in glacial acetic acid (380 ml) was heated under reflux for 2 h. The reaction mixture was poured into ice-water and extracted with ether. The ethereal solution was neutralised with saturated sodium bicarbonate solution, washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation yielded isoxazole (VI, 11.2 g (78%)). UV λ_{max}^{EtOH} nm: 437. NMR δ (90 MHz): 1.19 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.64—1.8 (4H, m,

CH_2), 2.13—2.36 (4H, m, CH_2), 6.82 (1H, s, =CH). MS *m/e*: 189.114 (M^+, $C_{12}H_{15}NO$ requires 189.115).

2-Cyano-3,3-dimethyl-4,5,6,7-tetrahydro-1-indanone (VII)——A solution of isoxazole (VI, 12.1 g) in dry ether (60 ml) was added to a solution prepared from sodium (3.05 g) and dry methanol (100 ml). The mixture was stirred at room temperature for 1 h. Water and ether were added and the aqueous layer was separated. The ether layer was shaken with 10% NaOH solution three times. Combined aqueous extracts were made acidic with dil. H_2SO_4 and extracted with ether. The ethereal solution was washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation afforded a brown oil which was purified by silica gel column chromatography (eluent: 25% ether in *n*-hexane) to yield the ketonitrile (VII, 7.4 g (61%)). UV λ_{max}^{EtOH} nm: 238. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1712, 1642. NMR δ (90 MHz): 1.29 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.57—1.84 (4H, m, CH_2), 2.07—2.40 (4H, m, CH_2), 3.23 (1H, s, –CO–CH–CN). MS *m/e*: 189.116 (M^+, $C_{12}H_{15}NO$ requires 189.115).

4,5,6,7-Tetrahydro-1,1-dimethyl-2-cyanoindene (VIII)——Sodium borohydride (1.5 g) was added to a solution of VII (7.4 g) in methanol (*ca.* 20 ml). The mixture was stirred at room temperature for 0.5 h. Work-up was carried out according to the usual method. The resulting hydroxy compound was dissolved in dry pyridine (100 ml), then phosphorous oxychloride (4.5 ml) was added. The mixture was stirred at 80°C for 16 h under nitrogen. The cooled reaction mixture was poured into ice-water and extracted with chloroform. The extracts were washed with dil. H_2SO_4, neutralised with sodium bicarbonate solution, washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation gave a residual brown oil which was subjected to alumina column chromatography (eluent: 20% ether in *n*-hexane) to yield the diene-nitrile (VIII, 3.04 g (45%)). UV λ_{max}^{EtOH} nm: 295. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200, 1633. NMR δ (90 MHz): 1.12 (6H, s, gemCH_3), 1.62—1.78 (4H, m, CH_2), 2.04—2.31 (4H, m, CH_2), 6.89 (1H, s, =CH). MS *m/e* 173.121 (M^+, $C_{12}H_{15}N$ requires 173.120).

4,5,6,7-Tetrahydro-1,1-dimethyl-2-formylindene (IX)——A solution of di-isobutylaluminium hydride (1.1 g) in dry toluene (4 ml) was added to a stirred solution of diene-nitrile (VIII, 550 mg) in dry toluene (1 ml) with ice-cooling under a stream of nitrogen. When addition was complete, the mixture was stirred at room temperature for 4 h. The reaction was stopped by addition of dil. H_2SO_4 under ice-cooling. The mixture was extracted with ether, and the ethereal solution was washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation gave an orange oil which was purified by alumina column chromatography (eluent: 5% ether in *n*-hexane) to afford the dienal (IX, 234 mg (43%)). UV λ_{max}^{EtOH} nm: 318. NMR δ (90 MHz). 1.17 (6H, s, gemCH_3), 1.64—1.80 (4H, m, CH_2), 2.09—2.41 (4H, m, CH_2), 7.09 (1H, s, =CH), 9.63 (1H, s, CHO). MS *m/e*: 176.120 (M^+, $C_{12}H_{16}O$ requires 176.120).

(1′*E*)-4,5,6,7-Tetrahydro-1,1-dimethyl-2-2′-methoxycarbonylethenylindene (X)——Diethyl methoxycarbonylmethylphosphonate (885 mg) was added to a stirred suspension of sodium hydride (240 mg, 50% oil dispersion) in dry dimethylformamide (1 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 2—3 h and dienal (300 mg) in dry dimethylformamide (1—2 ml) was then added dropwise. The reaction mixture was stirred at *ca.* 50°C for 2—3 h, cooled to room temperature, poured into water, and extracted with ether. The ethereal extract was washed with brine, dried (Na_2SO_4) and concentrated to yield an oil which was purified by chromatography (SiO_2 or Al_2O_3, eluent: *n*-hexane) to give the triene ester (X, 200 mg (67%)). UV λ_{max}^{EtOH} nm: 345. NMR δ (60 MHz): 1.12 (6H, s, gemCH_3), 1.62—1.85 (4H, m, CH_2), 2.15—2.32 (4H, m, CH_2), 3.8 (3H, s, CO_2Me), 5.95 (1H, d, J=16 Hz, C-2′-H), 6.62 (1H, s, C-3 –H), 7.52 (1H, d, J=16 Hz, C-1′-H).

4,5,6,7-Tetrahydro-1,1-dimethyl-2-2′-formylethenylindene (XI)——The ester (X, 200 mg) was dissolved in dry ether (4 ml) and treated with lithium aluminium hydride (32 mg) at room temperature for 1 h. The reaction mixture was decomposed with moist ether and dil. H_2SO_4. The ether layer was washed with brine and dried (Na_2SO_4). Removal of the solvent by evaporation gave a corresponding alcohol, which was dissolved in *n*-hexane (10 ml). The hexane solution was shaken with active MnO_2 (1.7 g) at room temperature for 1.5 h, then filtered. The filtrate was concentrated to give a yellow oil, which was purified by silica gel column chromatography (eluent: 5% ether in *n*-hexane) to afford the trienal (XI, 50 mg (27%)). UV λ_{max}^{EtOH} nm: 363 (ε 16300). NMR δ (60 MHz): 1.12 (6H, s, gemCH_3), 1.62—1.85 (4H, m, CH_2), 2.12—2.38 (4H, m, CH_2), 6.2 (1H, dd, J=8, 16 Hz, C-2′-H), 6.68 (1H, s, C-3-H), 7.2 (1H, d, J=16 Hz, C-1′-H), 9.47 (1H, d, J=8 Hz, CHO). MS *m/e* 202.1354 (M^+, $C_{14}H_{18}O$ requires 202.1356).

(1′*E*)-4,5,6,7-Tetrahydro-1,1-dimethyl-2-4′-methyl-penta-1′,3′-dien-1′-ylindene (III)——Isopropyltriphenylphosphonium bromide[8] (385 mg) and *n*-butyl lithium (1 ml of 15% hexane solution) in dry ether (3 ml) were stirred together at room temperature for *ca.* 10 h in a sealed bottle under argon. A solution of the trienal (50 mg) in dry ether (1 ml) was added to the alkylidene solution in a sealed bottle under argon. The mixture was stirred in the sealed bottle at room temperature for 1 h then filtered, and the solid material was washed several times with ether. The ether extract was concentrated to give a gum, which was purified by preparative TLC (10% ether in *n*-hexane) to yield the tetraene (III, 40 mg (71%)). UV λ_{max}^{EtOH} nm 347 (ε 18100), 331 (ε 21300), 318 (sh.), 237 (ε 13000); $\lambda_{max}^{74\%\ H_2SO_4}$ nm: 462. NMR δ (90 MHz): 1.09 (6H, s, gemCH_3), 1.62—1.78 (4H, m, CH_2), 1.81 (6H, s, $=\langle^{CH_3}_{CH_3}$), 2.07—2.29 (4H, m, CH_2), 5.92 (1H, md, J=10 Hz, C-3′-H), 6.19 (1H, s, C-3-H), 6.22 (1H, d, J=16 Hz, C-1′-H), 6.60 (1H, dd, J=10, 16 Hz, C-2′-H). MS *m/e*: 228.1897 (M^+, $C_{17}H_{24}$ requires 228.1879).

References and Notes

1) Part II: M. Ito, A. Kodama, and K. Tsukida, *Chem. Pharm. Bull.*, **29**, 3385 (1981).
2) W. Bollag, *Cancer Chemother. Pharmacol.*, **3**, 207 (1979).
3) W. Bollag, *Experientia*, **27**, 90 (1971).
4) C. Kawasaki, Y. Ito, and K. Tanino, *Vitamins* (Japan), **36**, 430 (1967).
5) *a*) K. Tsukida, M. Ito, and F. Ikeda, *Experientia*, **29**, 1338 (1973); *b*) *Idem*, *ibid.*, **30**, 980 (1974); *c*) K. Tsukida, M. Ito, F. Tomeoka (née Ikeda), and A. Kodama, *J. Nutr. Sci. Vitaminol.*, **24**, 335 (1978); *d*) K. Tsukida, M. Ito, F. Tomeoka and A. Kodama, *J. Chem. Soc., Perkin Trans 1*, **1981**, 2472.
6) M. Ito, A. Kodama, and K. Tsukida, *Chem. Pharm. Bull.*, **28**, 679 (1980).
7) J.-M. Conia and M.-L. Leriverend, *Bull. Soc. Chim. Fr.*, **1970**, 2981.
8) U.H.M. Fagerlund and D.R. Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1975).
9) P. Loeliger and H. Mayer, *Helv. Chim. Acta*, **63**, 1604 (1980).