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Synthesis of 4,5,6,7-Tetrahydro-1,1-dimethyl-2-(4'-methyl-penta-1',3'-dien-1'-yl)-indene. A Synthetic Proof of the Chromophoric Structure of a Colour-producing Compound in the Colour Reaction of Retinoic Acid in 74% Sulphuric Acid

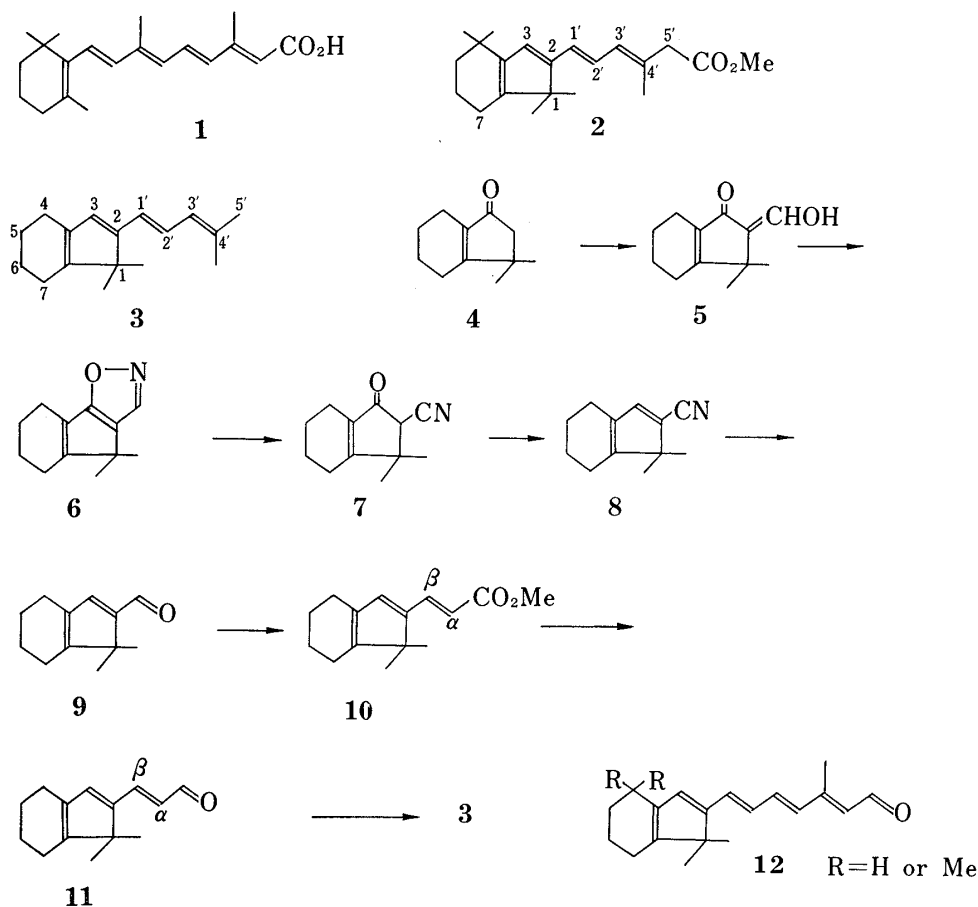
The title compound (3) which involves a new conjugated system, has been synthesised in a geometrically pure form from the indanone (4).

Keywords—colour reaction of retinoic acid; tetrahydroindene skeleton; new conjugated system; Horner reaction; Wittig reaction; visual pigment analogue

As the results of the studies¹⁾ on the chemistry of a colour reaction (in 74% H₂SO₄) of retinoic acid (vitamin A acid) (1) which is known to be closely related to the metabolism of retinol²⁾ and to prevent and inhibit the growth of epithelial tumours,³⁾ the structure of the main quenched product (isolated as methyl ester) of coloured species was proposed as 2 by its spectroscopic consideration.⁴⁾ The striking red colour of 1 in 74% sulphuric acid (λ 454 nm) was regenerated from 2 by acidification with the 74% acid. Therefore, the compound (2) which involves a new interesting conjugated system has been considered to have the same chromophoric structure as the colour-producing compound in the colour reaction of retinoic acid in 74% sulphuric acid. We now report a synthesis of 4,5,6,7-tetrahydro-1,1-dimethyl-2-(4'-methylpenta-1',3'-dien-1'-yl)-indene (3) which corroborates the *chromophoric* structure of the proposed compound (2) including the tetrahydroindene skeleton.

Formylation of 4,5,6,7-tetrahydro-3,3-dimethyl-1-indanone (4)⁶⁾ with ethyl formate and sodium hydride in dry ether gave the crystalline formyl-enone [5, mp 130°, λ 260, 283 nm, ν 1665, 1600 cm⁻¹, δ 9.95 (s, 1H, OH), 7.05 (s, 1H, =CHOH), 1.20 (s, 6H, gemCH₃)] in 81% yield. The compound (5) was reacted with hydroxylamine hydrochloride in acetic acid to yield the isoxazole (6) which, without purification, was treated with sodium methoxide in dry ether followed by column chromatographic purification (silica gel, 30% ether in *n*-hexane) to afford the ketonitrile [7, λ 238 nm, ν 2250, 1712, 1642 cm⁻¹, δ 3.23 (s, 1H, CO-CH-CN)] in 61% yield from 5. Sodium borohydride reduction of 7 and subsequent dehydration of the resulting hydroxy-nitrile with phosphorous oxychloride in dry pyridine afforded the dienonitrile [8, λ 295 nm, ν 2200, 1633, 1537 cm⁻¹, δ 6.89 (s, 1H, =CH)] in 45% yield which was converted to the dienal [9, λ 318 nm, δ 9.63 (s, 1H, CHO), 7.09 (s, 1H, =CH)] by reduction with di-isobutylaluminium hydride in dry toluene. A Horner reaction⁷⁾ between 9 and diethyl methoxycarbonylmethylphosphonate led to the conjugated triene ester (10) in which the newly formed double bond was confirmed to be *trans* by its NMR spectrum, [7.51 (d, J = 16 Hz, 1H, β -H), 5.95 (d, J = 16 Hz, 1H, α -H)]. The ester group in the compound (10) was reduced with lithium aluminium hydride followed by oxidation with active MnO₂ and subsequent column chromatography (5% H₂O-deactivated alumina, 5% ether in *n*-hexane) to

- 1) K. Tsukida, M. Ito and F. Ikeda, *Experientia*, **29**, 1338 (1973); *idem, ibid.*, **30**, 980 (1974); K. Tsukida, M. Ito, F. Tomeoka (née Ikeda) and A. Kodama, *J. Nutr. Sci. Vitaminol.*, **24**, 335 (1978).
- 2) A. Kleiner-Bössaler and H.F. DeLuca, *Arch. Biochem. Biophys.*, **142**, 371 (1971).
- 3) H. Mayer, W. Bollag, R. Hänni and R. Rüegg, *Experientia*, **34**, 1105 (1978).
- 4) 2; C₂₁H₃₀O₂, m/e 314.226 (M⁺), λ^{50} 348, 333, 318(sh.), 236 nm, ν^{50} 1740, 1150 cm⁻¹ (unconj. aliph. ester), 1622, 1592 cm⁻¹ (C=C), 958 cm⁻¹ (*trans*-CH=CH-), δ^{50} 1.08 (s, 12H, 4CH₃), 1.92 (s, 3H, 4'-CH₃), 2.13 (t, 2H, J = 5.5 Hz, 7-H₂), 3.13 (s, 2H, 5'-H₂), 3.72 (s, CO₂Me), 6.05 (d, 1H, J = 10.5 Hz, 3'-H), 6.31 (d, 1H, J = 15.5 Hz, 1'-H), 6.44 (s, 1H, 3-H), 6.61 (dd, 1H, J = 10.5, 15.5 Hz, 2'-H).
- 5) UV were taken in EtOH, IR in CHCl₃ and NMR in CDCl₃, respectively.
- 6) J.-M. Conia and M.-L. Leriverend, *Bull. Soc. Chim. Fr.*, **1970**, 2981.
- 7) J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).



give the trienal [**11**, λ 363 nm, δ 9.47 (d, $J=8$ Hz, 1H, CHO), 7.20 (d, $J=16$ Hz, 1H, β -H), 6.68 (s, 1H, =CH), 6.20 (dd, $J=16, 8$ Hz, 1H, α -H)] in 40% yield in which the geometry of the α,β -double bond was preserved. A Wittig reaction between **11** and the triphenylphosphine isopropylidene reagent prepared from isopropyltriphenylphosphonium bromide and *n*-butyl lithium in a pressure bottle under argon, furnished [**3**, unstable yellow oil, $C_{17}H_{24}$, m/e 228.1897 (M^+), λ 347, 331, 318 (sh.), 237 nm, δ 6.60 (dd, $J=16, 10$ Hz, 1H, 2'-H), 6.22 (d, $J=16$ Hz, 1H, 1'-H), 6.19 (s, 1H, 3-H), 5.92 (d, $J=10$ Hz, 3'-H), 1.81 (s, 6H, 5'-H₃ and 4'-CH₃), 1.09 (s, 6H, 1-gemCH₃)] in 72% yield. A Wittig reaction between **9** and dimethylallyltriphenylphosphonium bromide in the presence of *n*-butyl lithium in dry ether produced a mixture (3:1) of **3** and its *cis* isomer from which attempts to separate each isomer were unsuccessful. The NMR spectral pattern of **3** in olefinic region was similar to that of **2**. A striking resemblance between the ultraviolet absorption spectrum in EtOH of **3** and that of **2** and a similarity of the visible light absorption spectrum in 74% H₂SO₄ of **3** to that of **2** present unambiguous evidence in support of the *chromophoric* structure of **2**. The present synthesis of **3** which includes a new conjugated system, has resulted in the method for the preparation of **12** which is an interesting compound in the studies of visual pigment analogues.⁸⁾

8) M. Ito, K. Hirata (née Akutsu), A. Kodama, K. Tsukida, H. Matsumoto, K. Horiuchi and T. Yoshizawa, *Chem. Pharm. Bull.*, **26**, 925 (1978); S. Kawamura, T. Yoshizawa, K. Horiuchi, M. Ito, A. Kodama and K. Tsukida, *Biochim. Biophys. Acta*, **548**, 147 (1979); M. Ito, A. Kodama, M. Murata, M. Kobayashi, K. Tsukida, Y. Shichida and T. Yoshizawa, *J. Nutr. Sci. Vitaminol.*, **25**, 343 (1979).

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Isolation of Agarofuran-type Sesquiterpenes from *Alpinia japonica* (THUNB.) MIQ.¹⁾

A new sesquiterpene, 3 α ,4 α -oxidoagarofuran (2) was isolated besides 4-hydroxydihydroagarofuran (1), α -agarofuran (3) and β -eudesmol (4) from the rhizomes of *Alpinia japonica*.

Biogenetically, it is interesting that β -eudesmol is isolated from same plant together with agarofurans, which possess 10-epimeric eudesmane carbon skeleton.

Keywords—Zingiberaceae; *Alpinia japonica* (THUNB.) MIQ.; sesquiterpene; 4 α -hydroxydihydroagarofuran; 3 α ,4 α -oxidoagarofuran; α -agarofuran; β -eudesmol; 10-epi-eudesmane-type

The seeds of *Alpinia japonica* (THUNB.) MIQ. (Zingiberaceae) are used as an aromatic stomachic under the name, "Izu-shukusha" (伊豆縮砂), in Japan.

Several flavonoids (alpinon, izalpinin, kumatakenin and rhamnocitrin) and monoterpenes (camphor and cineole) have been isolated from the seeds by Kimura and co-workers.²⁾ They have also reported the presence of sesquiterpene alcohols in the essential oil of the seeds, but little has been known about their structures.^{2d)}

In this paper, we wish to report the isolation and characterization of four sesquiterpenes including a new compound from the rhizomes of this plant.

The fresh rhizomes were extracted with methanol, and the aqueous methanolic extracts were partitioned with petroleum ether. The petroleum ether soluble fraction was repeatedly separated and purified by silica gel and silver nitrate impregnated silica gel chromatography to give four compounds (1-4).

Compound (1), C₁₅H₂₆O₂, colorless needles, mp 128.5-129.5°, showed a strong hydroxyl absorption band at 3430 cm⁻¹ in the IR spectrum. The ¹H-NMR spectrum (CDCl₃) revealed four tertiary methyl signals (δ 1.17, 1.21, 1.27, 1.36), and the ¹³C-NMR spectrum (CDCl₃) indicated the presence of ether linkage [δ 82.1 (s), 87.8 (s)]. Taking account of its molecular formula, we assumed from above facts that compound (1) might be 4 α -hydroxydihydroagarofuran

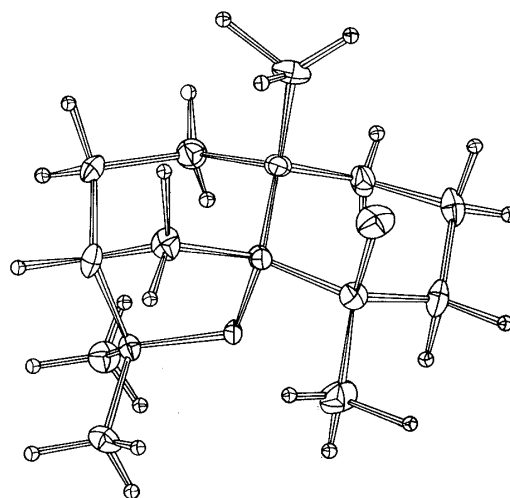


Fig. 1. Perspective View of the Molecular Structure of Compound 1

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2) a) Y. Kimura and M. Hoshi, *Yakugaku Zasshi*, **57**, 147 (1937); b) Y. Kimura and M. Hoshi, *ibid.*, **55**, 1101 (1935); c) Y. Kimura, M. Takido and S. Takahashi, *ibid.*, **87**, 1132 (1967); d) Y. Kimura and M. Hoshi, *ibid.*, **53**, 794 (1933).