Total Synthesis of Isorenieratene[*], [**]

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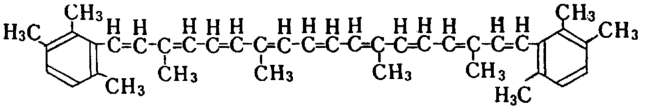
It has been shown by degradative oxidation that isorenieratene, one of the C_{40}-carotenoid hydrocarbons discovered in a sea-sponge, *Reniera japonica*[1], has a remarkable constitution I[2], in which substituted benzene rings are present as terminal groups in place of ionone rings. As the natural carotenoids have so far been aliphatic or alicyclic compounds, the above finding is very significant, and, therefore, it is of importance to make a further confirmation of this exceptional structure of isorenieratene by a synthetic study.

Recently, several routes involving many interesting intermediates have been developed for the total syntheses of carotenoids[3], some of these routes giving considerably good yields. For the present study, however, a method established by Karrer et al.[4] has been applied for the reason of the simplicity of the method, though the overall yields attained by them are not so satisfactory.

The starting material, 2,3,6-trimethylbenzaldehyde (II), was condensed with acetone to give 2,3,6-trimethylbenzalacetone (III), which corresponds to β-ionone, a starting material in the β-carotene syntheses. The ketone (III) was converted into an acetylenic alcohol (IV), which by condensation with 4-octene-2,7-dione gave a C_{40}-diynetetraol (V). Partial hydrogenation of V followed by dehydration gave



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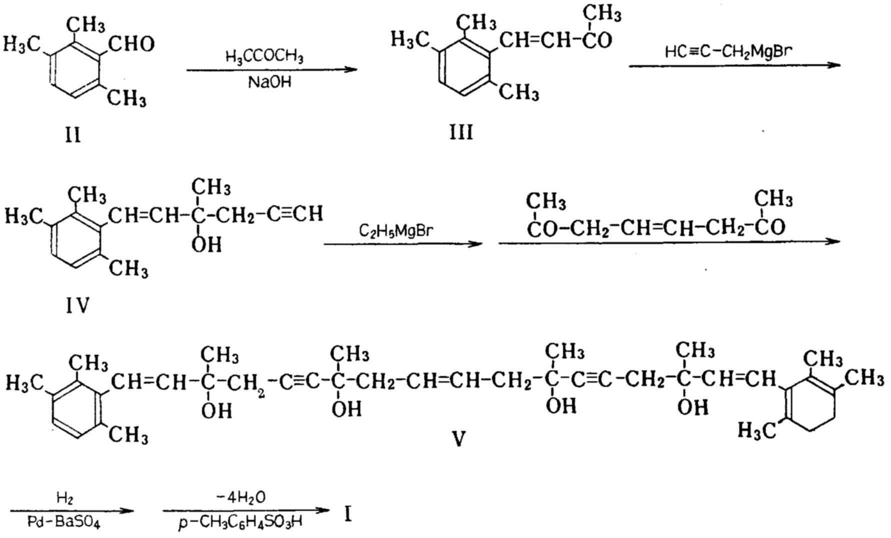

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[*] "Pigments of Marine Animals", VIII. VII of this series: T. Mukai, *Memoirs of the Faculty of Science, Kyushu University, Series C., Chemistry*, 3, No. 2, 29 (1958).

[**] Read before the 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959.

[1] T. Tsumaki, M. Yamaguchi and T. Tsumaki, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, **75**, 297 (1954).

[2] M. Yamaguchi, This Bulletin, **31**, 51 (1958).

[3] For example: H. H. Inhoffen and H. Siemer, *Fortschr. Chem. org. Naturstoffe*, **9**, 1 (1952); O. Isler et al., *Helv. Chim. Acta*, **39**, 249,274,449,454,463,2041(1956); **40**, 456,1242,1256(1957); B. C. L. Weedon et al., *J. Chem. Soc.*, **1953**, 3286,3294,3299.

[4] P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **33**, 1172 (1950); C. H. Eugster, C. Garbers and P. Karrer, ibid., **35**, 1179 (1952).

isorenieratene (I) in a small yield.

Isorenieratene thus obtained forms purplish-red fine needles, m. p. 199~200°C, and is indistinguishable in the appearance from the specimen isolated from the sea-sponge. Furthermore, a mixed melting point, a mixed chromatography, and UV- and IR-spectra established perfect identity. (IR-spectra : Fig. 1).

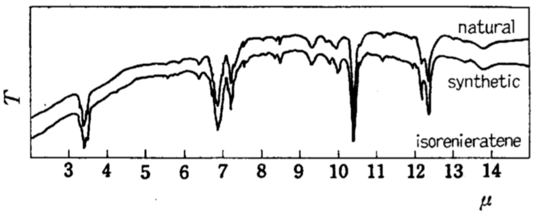

Fig. 1. Infrared spectra of isorenieratene (nujol mull).

Experimental

Solutions were evaporated under diminished pressure unless otherwise mentioned. Anhydrous sodium sulfate was employed for drying solutions.

4-(2, 3, 6-Trimethylphenyl)-3-buten-2-one (III).—A 10% aqueous sodium hydroxide solution (3.1 cc.) was added dropwise during five minutes to a stirred mixture of 2,3,6-trimethylbenzaldehyde (14 g.), acetone (16 g.) and water (10 cc.) at room temperature. After stirring for eight hours, the upper layer was separated, combined with the extract (benzene, 20 cc.) of the lower aqueous layer, washed successively with water, 3% hydrochloric acid and water, dried and evaporated. Distillation of the residue gave at first trimethylbenzaldehyde (2.5 g.) and then 4-(2,3,6-trimethylphenyl)-3-buten-2-one (11 g.) as an almost colorless oil, b.p. 127~132°C/6 mmHg.

Anal. Found: C, 82.98; H, 8.67. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57%.

The semicarbazone, colorless needles, m.p. 223~225°C.

Anal. Found: C, 68.37; H, 7.83. Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81%.

The 2,4-dinitrophenylhydrazone, red plates, m.p. 178~180°C.

Anal. Found: C, 61.79; H, 5.37. Calcd. for $C_{19}H_{20}O_4N_4$: C, 61.95; H, 5.47%.

The residue of the distillation solidified on cooling, which on recrystallization from benzene-ethanol gave 1,5-bis(2,3,6-trimethylphenyl)-1,4-pentadien-3-one (1.9 g.) in pale yellow plates, m.p. 153~154°C.

Anal. Found: C, 86.67; H, 8.15. Calcd. for $C_{23}H_{26}O$: C, 86.74; H, 8.23%.

The 2,4-dinitrophenylhydrazone, red needles from acetic acid, m.p. 166~168°C.

Anal. Found: C, 70.11; H, 5.95. Cacld. for $C_{29}H_{30}O_4N_4$: 69.86; H, 6.07%.

1-(2, 3, 6-Trimethylphenyl)-3-methyl-1-hexen-5-yn-3-ol (IV).—A Grignard solution was prepared by dropwise addition (1.5 hr.) of propargyl bromide (5.9 g.) in dry ether (20 cc.) to magnesium (1.5 g.) covered with dry ether (60 cc.) under vigorous stirring. Magnesium was previously activated with a 1% aqueous solution of mercuric chloride. The excess of magnesium was removed by filtration and the solution was added during a half hour to a well stirred solution of the above C_{13}-ketone (III) (9 g.) in dry ether (20 cc.). The mixture was refluxed under stirring for additional one hour, and then decomposed with ice and 5% aqueous sulfuric acid. The ethereal layer was washed with water, dried and evaporated. The oily residue was dissolved in absolute ethanol (80 cc.), a solution of Girard reagent P (6 g.) in acetic acid (6.3 g.) was added, and the mixture was refluxed for an hour. The cooled solution was poured into ice water (300 cc.) containing sodium hydrogen carbonate (7.95 g.) and extracted with ether (3×50 cc.). The ethereal solution was washed, dried and evaporated. Distillation of the residue gave 1-(2,3,6-trimethylphenyl)-3-methyl-1-hexen-5-yn-3-ol (4.3 g.) as a faint colored viscus oil, b.p. 110~115°C/0.04 mmHg.

Anal. Found: C, 83.92; H, 9.05. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83%.

C_{40}-diyntetraol (V).—A solution (ca. 30 cc.) of ethylmagnesium bromide prepared from ethyl bromide (3.9 g.) was filtered, and added dropwise during one and a half hour to a well stirred mixture of above acetylenic alcohol (4.1 g.), cuprous chloride (50 mg.) and dry ether (16 cc.). The mixture was refluxed for an additional one hour. A solution of 4-octene-2,7-dione[5] (840 mg.) in dry ether (18 cc.) was then added dropwise during thirty minutes under efficient stirring. After refluxing for one hour, the mixture was allowed to stand overnight, and decomposed with 1 N sulfuric acid under ice-cooling. Ether (30 cc.) was added, and the ethereal layer was washed with dilute sulfuric acid, an aqueous solution of sodium hydrogen carbonate and water, dried and evaporated. The yellow brown oily residue was adsorbed on alumina (95 g., standardized according to Brockmann), from a benzene solution (15 cc.). The column was washed successively with benzene (115 cc., the elute gave an oily residue, 1.7 g.), with ether (100 cc., it gave 1.4 g. of residue), and with ether-methanol (10:1, 180 cc.). The last fraction contained C_{40}-tetraol, which is obtained by evaporation of the solvent as a yellowish colored glasslike mass (1.8 g.).

Anal. Found: C, 79.39; H, 8.82. Calcd. for $C_{40}H_{52}O_4$: C, 80.50; H, 8.78%.

It showed somewhat low C-value, and was employed for the next step without further purification.

Isorenieratene (I).—A solution of tetraol (300 mg.) in ethyl acetate (10 cc.) was agitated with active charcoal (100 mg.) for 10 min., filtered, and shaken with palladium barium sulfate catalyst (1%, 20 mg.) in an atmosphere of hydrogen. Occasional additions of the catalyst (ca. 5 mg.) were necessary until 2 mol. (23.6 cc., 13°C/760 mmHg) of hydrogen was adsorbed (2.5

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[5] P. Karrer and C. H. Eugster, ibid. ,32, 1934 (1949).

hr.). The catalyst was removed and the solution was evaporated to give a glassy residue. A boiling solution of toluene-*p*-sulfonic acid (40 mg., dehydrated by melting in vacuo) in toluene (5 cc.) was added at a time to a boiling solution of the above residue in toluene (10 cc.) and the mixture was boiled for ca. eighty seconds, the water which formed being removed by azeotropic distillation. The greenish brown solution was cooled and poured into a mixture of a saturated aqueous solution of sodium hydrogen carbonate and petroleum ether (50 cc.). On shaking, the color changed into deep red. The petroleum ether solution was then washed once with water and thrice with 90% methanol, dried and evaporated. The reddish brown residue was dissolved in petroleum ether and chromatographed on alumina (2×20 cm.). The chromatogram was developed with petroleum ether, giving (i) a diffuse faint yellow band (least strongly adsorbed); (ii) an orange zone which is somewhat heterogeneous due to the presence of *cis*-isomer; (iii) a small orange brown zone; (iv) a small brown zone. The orange zone (ii) was eluted with benzene-methanol (10:1). The residue of the elute was treated with a mixture of petroleum ether and ethanol (1 : 1, 3 cc.), and left to stand overnight in an ice chamber to giv a red precipitate (4.5 mg.). From the mother liquor was obtained an additional quantity of the pigment (1 mg.) after isomerization with iodine. In this way, 900 mg. in total of the tetraol was worked up giving 14 mg. of the pigment. Several recrystallizations from benzene-methanol gave the analytically pure pigment (9 mg.), in purplish red fine needles, m.p. 199~200°C. The mixed melting point with isorenieratene (m.p. 199~200°C) which was isolated from the sea-sponge, *Reniera japonica*, was 199~200°C. A mixed chromatography of the synthetic and the natural pigments showed no separation. They gave the same UV-curves with maxima at 492 ($\varepsilon=12.3\times10^4$) and 463 m$\mu$ ($\varepsilon=10.4\times10^4$) (in benzene, spectrophotoelectric method). IR-curves: Fig. 1.

Anal. Found: C, 90.58; H, 9.24. Calcd. for $C_{40}H_{48}$: C, 90.85; H, 9.15%.

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