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CAROTENOID COMPOUNDS

Basil Charles Leicester Weedon, London, and Charles Kenneth Warren, Welwyn Garden City, England, assignors, by mesne assignments, to Hoffmann-La Roche Inc., Nutley, N.J.

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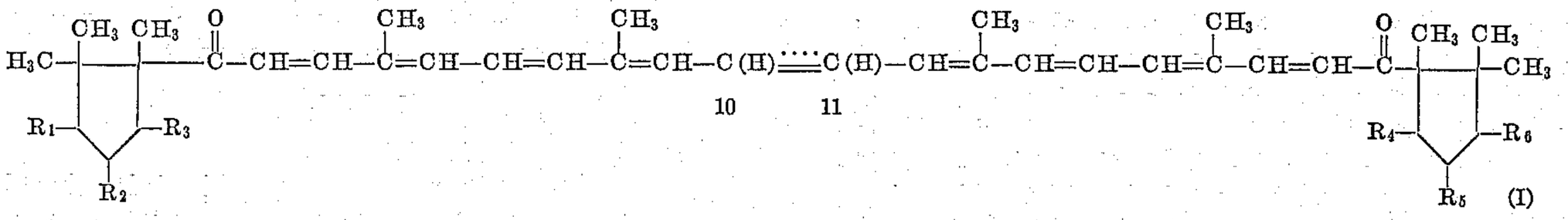
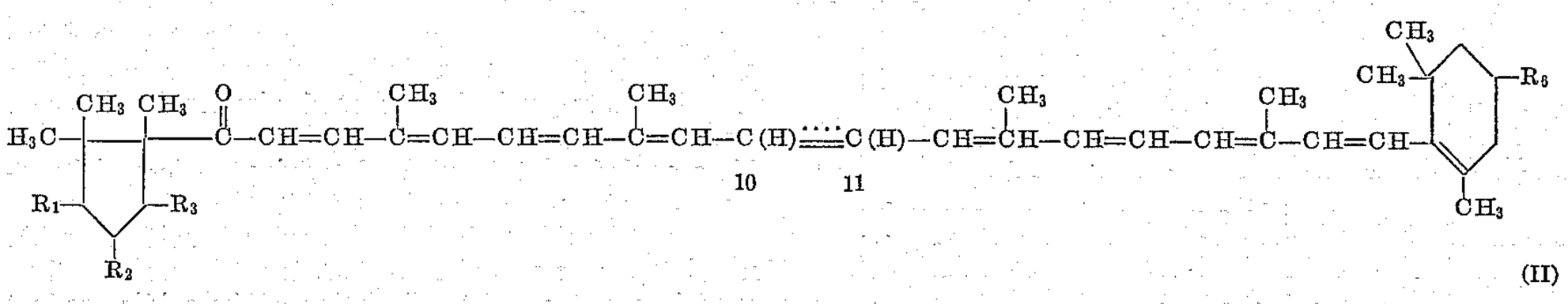
4 Claims. (Cl. 260—586)

The present invention is concerned with a process for the manufacture of carotenoid compounds and dehydro derivatives thereof, none of which has previously been synthesized. The carotenoid compounds and dehydro derivatives thereof, produced in accordance with the process of the invention, may be formulated thus:



(I)

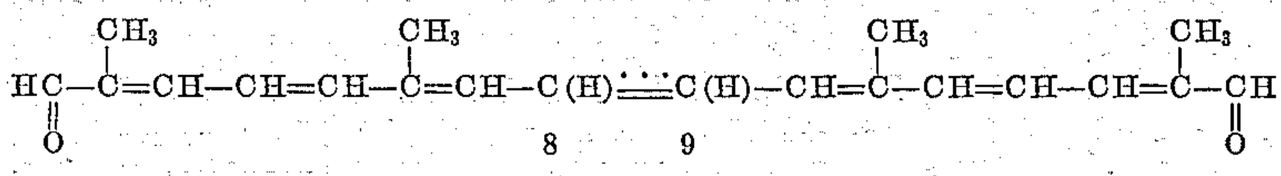
and



(II)

wherein the dotted line between the 10-carbon atom and the 11-carbon atom means that the above compounds can optionally be either the 10-ene or 10-yn compounds corresponding to the above formulae. R_1, R_2, R_3, R_4, R_5 and R_6 in the above formulae are either hydrogen, hydroxy, or oxo; and only one of R_1, R_2 and R_3 or of R_4, R_5 and R_6, respectively, is other than hydrogen in any given compound. A single member of R_1, R_2 and R_3 and a single member of R_4, R_5 and R_6 may be other than hydrogen in the same compound.

According to the process provided by the invention, the carotenoid compounds and dehydro derivatives thereof, set forth above, are manufactured by condensing a polyen[yn]-dial or polyen[yn]al of the general formulae:



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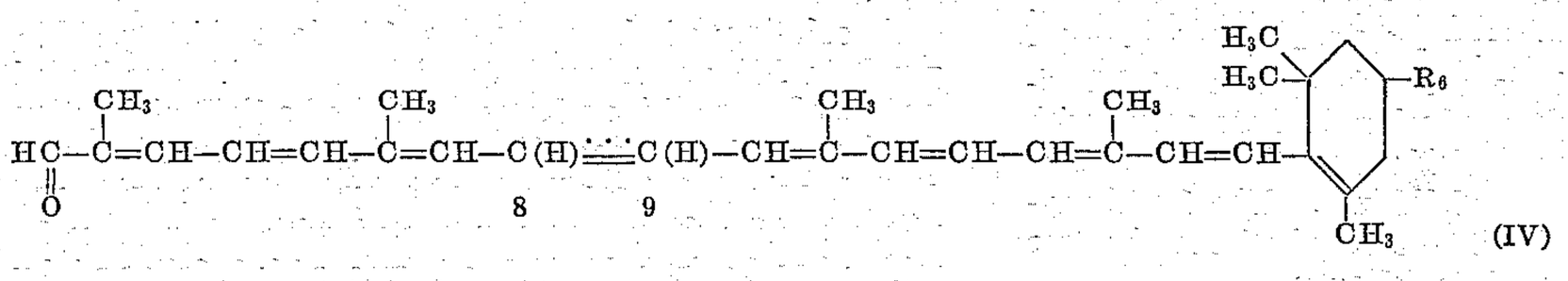
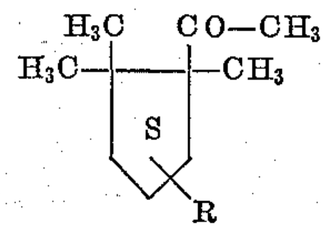


(IV)

wherein the dotted line between the 8-carbon atom and the 9-carbon atom means that the above compounds are chosen from the group consisting of 8-ene and 8-yn compounds corresponding to the above formulae, and R_6 is chosen from the group consisting of hydrogen, hydroxy and oxo,

with a compound of the formula



(V)

wherein R is chosen from the group consisting of hydrogen, hydroxy or oxo.

This condensation, when practiced with polyene dials, yields polyene diones containing two terminal 1,5,5-trimethyl-cyclopentyl groups which can be alike or unlike, which can be unsubstituted in the 2, 3, or 4 position, or which contains in the said positions oxo or hydroxy groups. When practiced with the mono-al, the condensation yields polyene-ones with a terminal 1,5,5-trimethylcyclopentyl group attached to the carbon atom of the carbonyl group. This cyclopentyl group may, as above, be unsubstituted in the 2, 3, or 4 position or contain in said positions oxo or hydroxy groups.

The condensation is preferably carried out under alkaline conditions and can be carried out using an alcoholic solution of an alkali metal hydroxide to give the alkaline conditions. Any nuclear oxo (keto) group present in the cyclohexenyl radical of the polyen[yn]al or cyclopentyl group in the acetyl cyclopentane compound can be protected by ketalisation. Following the condensation, any protecting group can be hydrolyzed so as to obtain the corresponding oxo group originally present. Further, if desired, any triple bond present in the condensation product can be hydrogenated in the presence of a catalyst which selectively catalyzes the reduction of acetylenic linkage to an olefinic linkage. One catalyst which can be used is a palladium/lead/calcium carbonate catalyst of the kind described by Lindlar in Helv. Chim. Acta, 1952, 35, 446.

The polyen dial as one of the starting materials, namely crocetindial, can be prepared by the method of Isler et al., Helv. Chim. Acta, 1956, 39, 463. The polyenyndial used as one of the starting materials, namely 8,9-dehydro-crocetindial, may be prepared by the method of Isler et al., Helv. Chim. Acta, 1956, 39, 463.

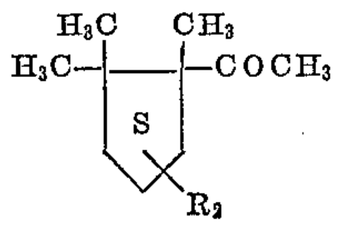
The 17-[2',6',6'-trimethyl-cyclohexen-(1')-yl]-heptadecaoctaen-(2,4,6,8,10,12,14,16)-al-(1) (for example, apo-2-β-carotenal) and the corresponding heptadecaheptaen-(2,4,6,10,12,14,16)-yn-(8)-al-(1) used as starting materials can be prepared in accordance with the method of Rüegg et al., Helv. Chim. Acta, 1959, 42, 854.

The octaene compound having a hydroxy group in the 4'-position of the trimethyl-cyclohexenyl group, which is also a starting material, is a known compound (Karrer et al., "Carotenoids," Elsevier Publishing Company, 1950, p. 218). It occurs in nature as betacitraurin and has been prepared by the oxidation of zeaxanthin. The corresponding compound having a keto in the 4'-position of the trimethyl-cyclohexenyl group which is also a starting material, may be obtained from betacitraurin by oxidation of the ring-hydroxy to a ring-keto group.

The octaenyne compound having a hydroxy group in the 4'-position of the trimethyl-cyclohexenyl group which is another starting material, is a novel compound and can be prepared from 8-[4'-acetoxy-2',6',6'-trimethyl-cyclohexen - (1') - yl]-2,6 - dimethyloctatrien - (1,3,5)-al-(1), described by Isler et al. in Helv. Chim. Acta, 1957, 40, 456, by the same method as described for the corresponding unsubstituted aldehyde by Rüegg et al. in Helv. Chim. Acta, 1959, 42, 847 and 854. The corresponding octaenyne compound having a keto group in the 4'-position of the trimethyl-cyclohexenyl group, yet another starting material, may be prepared by oxidation of the ring-hydroxy group to a ring-keto-group.

The ketals are prepared in a manner known per se by ketalisation of the acetalised aldehyde starting material and then preferentially hydrolysing the acetal group.

The 1-acetyl-1,2,2-trimethyl-cyclopentane compounds of the general formula



wherein R is chosen from the group consisting of hydrogen, hydroxy, or oxo,

used as starting materials are prepared from the corresponding 1-carboxy compounds. Thus 1-acetyl-1,2,2-trimethyl-cyclopentane is obtained from a known 1-carboxy-1,2,2-trimethyl-cyclopentane (camphonanic acid) by conversion of the carboxy group thereof into an acetyl group by the action of methyl lithium. Similarly, 1-acetyl-3-hydroxy-1,2,2-trimethyl-cyclopentane is obtained from 3-keto-camphonanic acid (camphononic acid) by reduction of the ring-keto group thereof to a hydroxyl group with the aid of lithium-boron hydride and converting the carboxy group of the resulting 3-hydroxy-camphonanic acid to an acetyl group with the aid of methyl lithium. Again, 1 - acetyl -4 - hydroxy - 1,2,2 - trimethyl-cyclopentane can be obtained from 1-carboxy-4-keto-1,2,2-trimethyl-cyclopentane by first reducing the keto group with the aid of lithium-boron hydride and then converting the carboxy group with methyl lithium. The 1-carboxy-4-keto-1,2,2-trimethyl-cyclopentane required for the two latter steps may be prepared as follows:

A solution of 4-ethoxycarbonyl-4,5,5-trimethyl-cyclohexadione-(1,3) (190 g.) [Crossley, J. Chem. Soc. 1901, 138] and toluene-p-sulphonic acid (4.5 g.) in ethanol (1.5 l.) and benzene (900 ml.) was heated under reflux under a Dean-Stark separator for four days. At intervals the condensate in the separator was run off, and the solvent in the reaction mixture was replenished. The

mixture was cooled, evaporated under reduced pressure, diluted with light petroleum (B.R. 40–60°), washed with saturated sodium hydrogen carbonate, dried with magnesium sulfate and evaporated. Distillation of the residue gave 6 - ethoxycarbonyl - 3 - ethoxy - 5,5,6 - trimethyl-cyclohexen-(2)-one (176 g.) as a colorless oil, B.P. 118° C./0.35 mm., n_D^{24} 1.4878; ν_{max} (liq. film) 1721, 1653 and 1608 cm.$^{-1}$. λ_{max} (EtOH) 256 mμ, ϵ=5,700. (Found: C, 66.0; H, 8.8. $C_{14}H_{22}O_4$ requires: C, 66.1; H, 8.7%.)

A solution of the foregoing enol-ether (10.0 g.) in ether (50 ml.) was added to lithium-aluminium hydride (2.0 g.) in ether (150 ml.). The mixture was heated under reflux for 20 hours, then cooled and treated with excess dilute sulfuric acid. Isolation of the crude product with ether gave a solid (7.0 g.). Chromatography on alumina gave 4 - hydroxymethyl - 4,5,5 - trimethyl-cyclohexen-(2)-one (2.4 g.) which crystallised from light petroleum (B.R. 40–60° C.) and had a melting point of 151° C.; λ_{max} (EtOH) 230 mμ, ϵ=7,800; ν_{max} (CCl_4) 3680, 1672 and 1600 cm.$^{-1}$. (Found: C, 71.2; H, 9.75. $C_{10}H_{16}O_2$ requires: C, 71.4; H, 9.6%). The (2,4-dinitro-phenyl)-hydrazone had a melting point of 174° C., λ_{max} (EtOH) 373 mμ, ϵ=26,000. (Found: C, 54.8; H, 5.7.

$C_{16}H_{20}O_5N_4$

requires: C, 55.15; H, 5.8%.)

The preceding crude cyclohexenone (21 g.) in ethanol (50 ml.) was shaken with hydrogen in the presence of 10% palladised charcoal (3.0 g.) until absorption was complete. Removal of catalyst and solvent gave 4-hydroxymethyl - 4,5,5 - trimethyl-cyclohexanone [ν_{max} 3497 and 1704 cm.$^{-1}$] which was used directly in the next stage.

To a cooled solution of the foregoing crude cyclohexanone (12 g.) in acetone (150 ml.) was added one of chromium tri-oxide (25 g.) in 2 N sulfuric acid (70 ml.). The mixture was stirred at 20° C. for 2 hours, and then poured into water (1 l.). Isolation of the acidic product in the usual way and crystallization from benzene/light petroleum B.R. 40–60° C.] gave 4-carboxy-3,3,4-trimethyl-cyclo-hexanone (2.0 g.), M.P. 188° C., ν_{max} ($CHCl_3$) 3,000–3,500 (broad) and 1706 cm.$^{-1}$ (unsymmetrical). (Found: C, 65.2; H, 9.0. $C_{10}H_{16}O_3$ requires; C, 65.2; H, 8.75%.) The (2,4 - dinitro-phenyl) - hydrazone crystallized from ethanol and had a melting point of 193° C., λ_{max} (EtOH) 355 mμ, ϵ=17,500.

A solution of the preceding keto-acid (4.4 g.) in 1 N potassium t. butoxide (200 ml.) was shaken in oxygen until absorption was complete (equivalent to 1.05 mol of oxygen). The solution was poured into water and acidified with 10% hydrochloric acid. Isolation of the product with chloroform gave solid 4-carboxy-4,5,5-trimethyl-cyclohexanedione-(1,2) (4.6 g.) (ultraviolet spectrophotometry indicated a purity of 89%). Crystallization of the product from another similar experiment gave the 1,2-dione having a melting point of 136–137° C.; ν_{max} 3,100–3,500, 1695 and 1672 cm.$^{-1}$; λ_{max} (EtOH) 268 mμ, ϵ=6,500; λ_{max} (aq. alkali) 312 mμ, ϵ=5,200. (Found: C, 60.65; H, 7.05. $C_{10}H_{14}O_4$ requires: C, 60.6; H, 7.1%.)

A solution of the preceding 1,2-dione (4.2 g. 89% pure) in 5% potassium hydroxide (100 ml.) was boiled under reflux until it no longer exhibited a light absorption maximum at 312 mμ (20 hours). The solution was cooled, acidified (to pH 4) with hydrochloric acid, and filtered. The filtrate was extracted with ether (3 x 20 ml.) phosphoric acid (9.0 g.) was added followed by analytically pure sodium bismuthate (9.0 g.). The suspension was left for ca. 16 hours and then stirred vigorously for 2 hours. Extraction with ether (4 x 50 ml.), evaporation of the extract, and crystallization of the residue from benzene/light petroleum [B.R. 60–80° C.] gave the required 1-carboxy-4-keto-1,2,2-trimethyl-cyclopentane; M.P. 216° C. (sealed tube) (on admixture with

camphononic acid, M.P. 228° C., the melting point was depressed to 207–209° C.); ν_{max} ($CHCl_3$) 3100–3500, 1736 and 1701 cm.$^{-1}$. (Found: C, 62.95; H, 8.25. $C_9H_{14}O_3$ requires: C, 63.5; H, 8.25%.) The (2,4-dinitrophenyl)-hydrazone crystallized from methanol and had a melting point of 223° C. (Found: C, 52.0; H, 5.3. $C_{15}H_{18}O_6N_4$ requires: C, 51.4; H, 5.2%.)

It has been found that the products of this invention (represented by Formulae I and II, supra), are highly colored compounds and are useful for the coloration of foodstuffs and animal feeds.

The following examples illustrate the compounds and processes of the invention.

EXAMPLE 1

1,20 - di(1',2',2' - trimethyl-cyclopentyl)-4,8,13,17-tetramethyleicosanonaene - (2,4,6,8,10,12,14,16,18) - dione-(1,20)

Camphononic acid (Appel, Zeit. Phys. Chem., 1938, 218, 202) (3.5 g.) in ether (40 ml.) was added dropwise to a stirred ethereal solution (50 ml.) of methyl lithium (from 10 g. of methyl iodide). The mixture was refluxed for 18 hours and cooled. Iced water was added cautiously. Isolation of the neutral product gave 1-acetyl-1,2,2-trimethyl-cyclopentane; B.P.=88°–92° C./23 mm., ν_{max} 1692 cm.$^{-1}$.

A mixture of 1-acetyl-1,2,2-trimethyl-cyclopentane (0.5 g.) and crocetindial (50 mg.) in the 5% ethanolic potassium hydroxide (3 ml.) was kept for 4 days and shaken and warmed occasionally. The mixture was refluxed for 30 minutes, cooled, and diluted with benzene. The solution was washed with water, dried (sodium sulfate) and evaporated. Chromatography of the residue in (1:1) benzene/light petroleum (B.P.=60°–80° C.) on alumina (Brockmann et al., Ber., 1941, 74, 73; Grade IV), isolation of the main red band, and crystallization from benzene/light petroleum (B.P.=60°–80° C.) gave the polyene diketone as violet crystals; M.P.=205°–206° C.; λ_{max} 517 and 483 mμ, ϵ=95,000 and 105,000 respectively, ν_{max} 1664 cm.$^{-1}$.

EXAMPLE 2

1,20 - di(3' - hydroxy - 1',2',2' -trimethyl - cyclopentyl)-4,8,13,17 - tetramethyl - eicosanonaene - (2,4,6,8,10,12,14,16,18)-dione-(1,20)

Potassium borohydride (4.0 g.) was added in small portions to a warm solution of camphononic acid (Appel, Zeit. Phys. Chem, 1938, 218, 202) (10.0 g.) and sodium hydroxide (3.3 g.) in water (130 ml.). The resulting mixture was heated on a steam bath for 16 hours and cooled. Concentrated sulfuric acid (13.3 ml.) in water (70 ml.) was added, and the solution was heated on a steam bath for 1 hour, cooled and extracted thoroughly with ether. The ethereal solution was extracted with saturated sodium hydrogen carbonate. Acidification of the extract, isolation of the product with ether, and crystallization from a mixture of ethyl acetate and light petroleum (B.P.=60°–80° C.) gave 3-hydroxy-camphonanic acid as a mixture of epimers; M.P.=220°–222° C., ν_{max} 1695 cm.$^{-1}$. Its methyl ester boiled at 132°–135° C./17 mm.; ν_{max} 3450 and 1718 cm.$^{-1}$.

3-hydroxy-camphonanic acid (5.7 g.) in ether (50 ml.) was added dropwise to a stirred ethereal solution of methyl lithium (from 18 g. of methyliodide). The mixture was refluxed for 18 hours and cooled. Iced water was added cautiously and the neutral product isolated, giving 1-acetyl-3-hydroxy-1,2,2-trimethyl-cyclopentane (1 g.), ν_{max} 3425 and 1686 cm.$^{-1}$.

A mixture of 1-acetyl-3-hydroxy-1,2,2-trimethyl-cyclopentane, crocetindial (100 mg.) and 5% methanolic potassium hydroxide (3 ml.) was kept at 20° C. for 19 hours and then refluxed for 2.5 hours. The mixture was cooled, diluted with benzene, washed with water, dried (sodium sulfate) and evaporated. Isolation of the product as in the previous example, and crystallization from benzene/light petroleum (B.P.=60°–80° C.) gave the polyene diketone as violet crystals; M.P.=187°–188° C., ν_{max} 3401 and 1661 cm.$^{-1}$, λ_{max} (benzene) 520 and 485 mμ, ϵ=104,000 and 118,000 respectively.

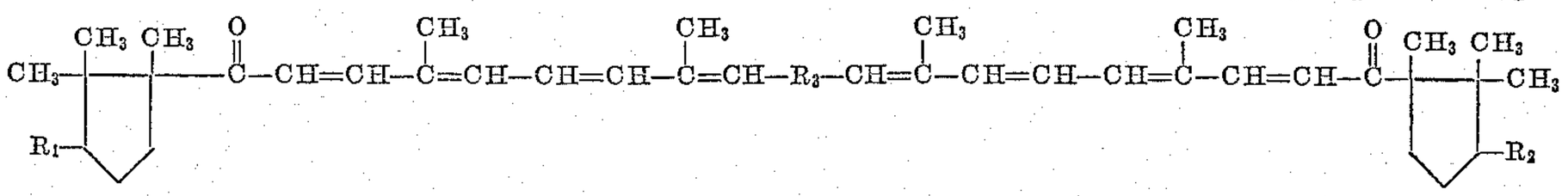
EXAMPLE 3

1-[2',6',6'-trimethylcyclohexen - (1') - yl] - 19 - (1',2',2-trimethyl - cyclopentyl) - 3,7,12,16 - tetramethylnonadecanonaen-(1,3,5,7,9,11,13,15,17)-one-(19)

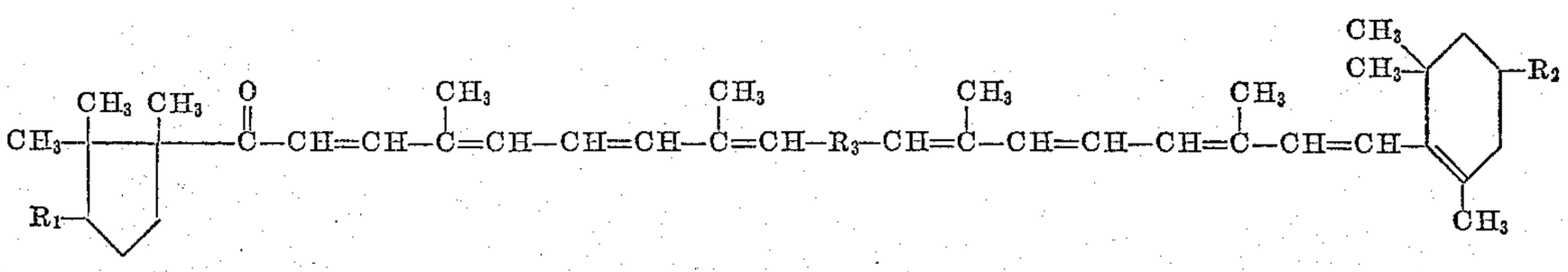
A mixture of apo-2-β-carotenal (200 mg.), 1-acetyl-1,2,2 - trimethylcyclopentane (1.0 g.), and 5% ethanolic potassium hydroxide (15 ml.) was warmed, kept at 20° for 2 days, and finally boiled under reflux for 30 minutes. The mixture was cooled, diluted with light petroleum (B.P. 60–80°) (250 ml.) washed with aqueous methanol (1:9), and then with water. The solution was dried and evaporated. Chromatography of the residue in benzene or alumina, isolation of the main red band, evaporation, and crystallization of the residue from benzene/methanol gave the polyene ketone as needles, M.P.=164–165°; λ_{max} (C_6H_6) 483 mμ, ϵ=101,000; ν_{max} ($CHCl_3$) 1667 cm.$^{-1}$; ϵ=200; τ=8.03, 8.28, 8.82, 8.89, 8.97, 9.15 p.p.m. (Found: C, 86.8; H, 10.5. $C_{40}H_{56}O$ requires: C, 86.9; H, 10.2%.)

We claim:

1. A compound selected from the group consisting of



and



wherein R_1 and R_2 are selected from the group consisting of hydrogen and hydroxy, and R_3 is selected from the group consisting of —CH=CH— and —C≡C—.

2. 1,20 - di(1',2',2' - trimethyl - cyclopentyl) - 4,8,13,17-tetramethyl - eicosanonaene - (2,4,6,8,10,12,14,16,18)-dione-(1,20).

3. 1,20 - di(3' - hydroxy - 1',2',2', - trimethyl - cyclopentyl) - 4,8,13,17 - tetramethyl - eicosanonaene - (2,4,6,8,10,12,14,16,18)-dione-(1,20).

4. 1 - [2',6',6' - trimethylcyclohexen - (1') - yl] - 19-(1',2',2' - trimethyl - cyclopentyl) - 3,7,12,16 - tetramethyl-nonadecanonaen-(1,3,5,7,9,11,13,15,17)-one-(19).

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LORRAINE A. WEINBERGER, *Acting Primary Examiner.*

CHARLES B. PARKER, LEON ZITVER, *Examiners.*