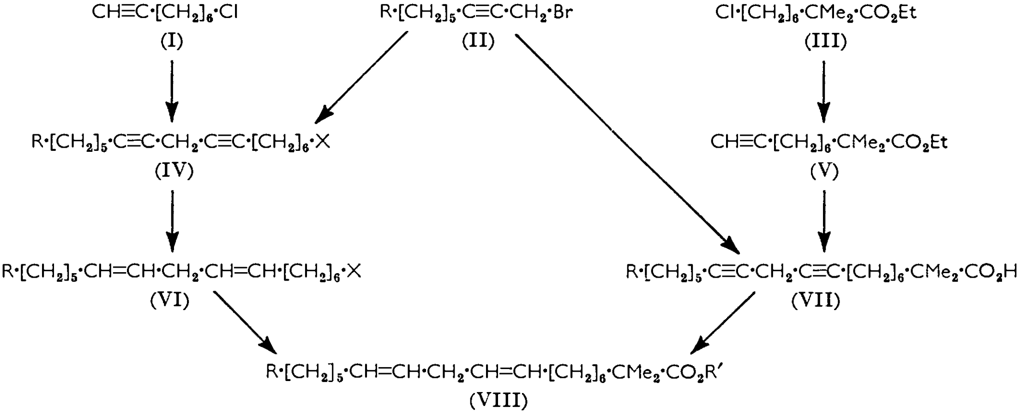
751. *Substituted Linoleic Acids.*

By J. A. Baker and P. A. McCrea.

The synthesis of 2,2-dimethyl-linoleic acid, 2,2-dimethyl-18-phenyl-linoleic acid, and 2,2-dimethyleicosa-*cis*-11,*cis*-14-dienoic acid is described.

It has been shown that high doses of linoleic acid lower serum-cholesterol levels in man.[1] The main route of metabolism for fatty acids is β-oxidation which can be blocked by disubstitution on the α-carbon atom, whereupon attack at the ω-carbon atom becomes significant.[2] 2,2-Dimethyl- (VIII; R = R′ = H) and 2,2-dimethyl-18-phenyl-linoleic acid (VIII; R = Ph, R′ = H) should be protected from normal metabolism and so be effective in lower doses.

In the synthesis of these acids, a modification of Raphael and Sondheimer's synthesis of linoleic acid[3] was tried, the alkylation of 1,1-diethylpropyl isobutyrate[4] replacing the alkylation of malonic ester in order to introduce the 2,2-dimethyl grouping. However, attempts to alkylate the isobutyrate with 16-iodohexadeca-6,9-diyne (IV; R = H, X = I) failed while 18-bromo-octadeca-*cis*-6,*cis*-9-diene, prepared from linoleic acid, reacted satisfactorily yielding on distillation 2,2-dimethyleicosa-*cis*-11,*cis*-14-dienoic acid.



Consequently 16-chlorohexadeca-6,9-diyne (IV; R = H, X = Cl) was hydrogenated to the diene (VI; R = H, X = Cl), Lindlar's catalyst being used.[5] This was converted into the iodo-compound (VI; R = H, X = I) which reacted with 1,1-diethylpropyl isobutyrate to give a product which, after hydrolysis and re-esterification, yielded ethyl 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoate (VIII; R = H, R′ = Et). Similarly, reaction of the iodo-compound (VI; R = H, X = I) with malonic ester gave a better overall yield of linoleic acid than that obtained by Raphael and Sondheimer.

In an alternative synthesis of 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoic acid (VIII; R = R′ = H) the alkylation of the isobutyric ester with an iodo-diyne was avoided by first treating 1,1-diethylpropyl isobutyrate with 1-chloro-6-iodohexane. Hydrolysis and re-esterification with ethanol gave ethyl 8-chloro-2,2-dimethyloctanoate (III). Reaction of the corresponding 8-iodo-compound with sodium acetylide yielded ethyl 2,2-dimethyldec-9-ynoate (V), the acid from which was coupled[6] with 1-bromo-oct-2-yne (II; R = H)

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[1] For a general review see Sinclair, " Essential Fatty Acids," Butterworths, London, 1958.
[2] Bergström, Borgström, Tryding, and Westöö, *Biochem. J.*, 1954, **58**, 604.
[3] Raphael and Sondheimer, *J.*, 1950, 2100.
[4] Hauser and Chambers, *J. Amer. Chem. Soc.*, 1956, **78**, 3837.
[5] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[6] Osbond and Wickens, *Chem. and Ind.*, 1959, 1288.

to give 2,2-dimethyloctadeca-9,12-diynoic acid (VII; R = H). Hydrogenation over Lindlar's catalyst gave 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoic acid (VIII; R = R' = H).

Evidence for the structure of this acid and the ethyl ester obtained in the first synthesis was obtained by hydrogenation to 2,2-dimethylstearic acid, identified by comparison with an authentic specimen.[2] Comparison of the ultraviolet absorption spectrum of the acid with that of octadeca-10,12-dienoic acid [7] indicated less than 1% of conjugated dienes. Similarly the ester probably contains 5% of conjugated dienes and also 2% of conjugated trienes (by comparison with β-elæostearic acid [8]). There was no absorption in the infrared region attributable to *trans*-double-bonds.

While the first synthesis is more convenient and gives higher yields, the second procedure appears to give a purer product.

16-Chloro-1-phenylhexadeca-6,9-diyne (IV; R = Ph, X = Cl), prepared by coupling 8-chloro-oct-1-yne (I) with 1-bromo-8-phenyloct-2-yne (II; R = Ph), was used to synthesise ethyl 2,2-dimethyl-18-phenyloctadeca-*cis*-9,*cis*-12-dienoate (VIII; R = Ph, R' = Et) in a similar manner to the synthesis of ethyl 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoate. There was no indication in its infrared spectrum of *trans*-double-bonds.

EXPERIMENTAL

18-*Bromo-octadeca*-cis-6,cis-9-*diene*.—Octadeca-*cis*-9,*cis*-12-dien-1-ol (144 g.) (prepared by reduction of ethyl linoleate with lithium aluminium hydride [9]), phosphorus tribromide (19 ml.), and pyridine (1·5 ml.) were refluxed for 2 hr. in dry ether (180 ml.). Water was added and the ethereal layer separated and washed with water. After the extract had been dried (Na_2SO_4) and the ether evaporated, the residue was distilled to give 18-*bromo-octadeca*-cis-6,cis-9-*diene* (90 g.), b. p. 140°/0·2 mm. (Found: C, 65·7; H, 10·3; Br, 23·7. $C_{18}H_{33}Br$ requires C, 65·7; H, 10·1; Br, 24·3%).

2,2-*Dimethyleicosa*-cis-11,cis-14-*dienoic Acid*.—1,1-Diethylpropyl isobutyrate (18·6 g.) was treated with 18-bromo-octadeca-*cis*-6,*cis*-9-diene (32·9 g.) in liquid ammonia according to Hauser and Chambers's method.[4] Vacuum distillation of the resulting 1,1-diethylpropyl ester gave 3-ethylpent-2-ene and a high-boiling acidic material which on distillation *in vacuo* yielded 2,2-*dimethyleicosa*-cis-11,cis-14-*dienoic acid* (12 g.), b. p. 163°/0·0004 mm., n_D^{20} 1·4691 [Found: C, 78·4; H, 12·2%; iodine value [10] (I.V.), 149. $C_{22}H_{40}O_2$ requires C, 78·6; H, 12·0%; I.V., 151].

16-*Chlorohexadeca*-cis-6,cis-9-*diene*.—16-Chlorohexadeca-6,9-diyne [11] (59·2 g.) in ethyl acetate (250 ml.) was hydrogenated over Lindlar's catalyst (10 g.). 11·45 l. of hydrogen were absorbed (theoretical uptake for two molecular equivalents of hydrogen = 11·48 l.). After removal of the catalyst and solvent, the residue was distilled to give 16-*chlorohexadeca*-cis-6,cis-9-*diene* (57·1 g.), b. p. 103°/0·01 mm., n_D^{20} 1·4616 (Found: C, 74·3; H, 11·1; Cl, 13·9%; I.V., 195. $C_{16}H_{29}Cl$ requires C, 74·8; H, 11·4; Cl, 13·8%; I.V., 198).

16-*Iodohexadeca*-cis-6,cis-9-*diene*.—16-Chlorohexadeca-*cis*-6,*cis*-9-diene (56·8 g.) was added to sodium iodide (80 g.) in acetone (500 ml.) and heated under reflux with stirring for 18 hr. After removal of the acetone on the water bath, the residue was extracted with sufficient anhydrous ether to give 250 ml. of ethereal solution of 16-iodohexadeca-*cis*-6,*cis*-9-diene.

Ethyl 2,2-*Dimethyloctadeca*-cis-9,cis-12-*dienoate*.—1,1-Diethylpropyl isobutyrate (26·6 g.) was added to sodamide [from sodium (3·3 g.)] in liquid ammonia (500 ml.) and stirred for 1¼ hr. Ethereal 16-iodohexadeca-*cis*-6,*cis*-9-diene (120 ml. ≡ 32·8 g. of the chloro-compound) was added and the mixture stirred for 20 hr. The work-up and hydrolysis of the diethylpropyl ester followed Hauser and Chambers's procedure. The resulting crude 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoic acid was heated under reflux in ethanol (250 ml.) for 24 hr., portions (12 ml.) of saturated ethanolic hydrogen chloride being added after 0, 3, 6, and 21 hr. The solution was concentrated under reduced pressure on the water bath, and the residue, in light petroleum (b. p. 30—50°), was washed with 0·2N-sodium hydroxide in 10% aqueous ethanol and with

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[7] Holman, Lundberg, and Burr, *J. Amer. Chem. Soc.*, 1945, **67**, 1386.
[8] Crombie and Jacklin, *J.*, 1957, 1633.
[9] Ligthelm, von Rudloff, and Sutton, *J.*, 1950, 3187.
[10] British Pharmacopœia. 1958, p. 873.
[11] Gensler and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 4601.

water, and dried ($MgSO_4$), and the solvent removed. Distillation of the residue gave *ethyl* 2,2-*dimethyloctadeca*-cis-9,cis-12-*dienoate* (15·8 g.), b. p. 106°/10^{-4} mm., n_D^{20} 1·4590 (Found: C, 78·5, 78·6; H, 11·9, 12·3%; I.V., 146. $C_{22}H_{40}O_2$ requires C, 78·6; H, 12·0%; I.V., 151); $\lambda_{max.}$ ($E^{1\%}_{1\,cm.}$) 232 (42·9) (indicates 5% of conjugated diene), 259 (26·5), 268 (34·2) and 278 mμ (27·0) (indicates 2% of conjugated triene). The infrared absorption spectrum showed no band at 10·3μ attributable to *trans*-CH=CH.

Linoleic Acid.—Ethyl malonate (5·1 g.) was heated under reflux for 1 hr. with sodium ethoxide [from sodium (0·7 g.)] in anhydrous ethanol (50 ml.). Ethereal 16-iodohexadeca-*cis*-6,*cis*-9-diene (17·5 ml. ≡ 4 g. of the chloro-compound) was added, and the ether allowed to distil off. The residual alcoholic solution was heated under reflux for 16 hr. The resulting substituted malonic ester was hydrolysed and decarboxylated by Raphael and Sondheimer's method.[3] Distillation of the product *in vacuo* gave linoleic acid (2·02 g., 50%), b. p. 175°/0·2 mm., n_D^{20} 1·4690, I.V., 179. The tetrabromide had m. p., and mixed m. p. with a specimen obtained [12] from corn oil, 115—116°.

Ethyl 8-*Chloro*-2,2-*dimethyloctanoate.*—1,1-Diethylpropyl iosbutyrate (111 g.) was treated with 1-chloro-6-iodohexane (147 g.) according to Hauser and Chambers's method [4] during 3 hr., giving crude 1,1-diethylpropyl 8-chloro-2,2-dimethyloctanoate, which was hydrolysed by hydrochloric acid and dioxan to crude 8-chloro-2,2-dimethyloctanoic acid. The acid was refluxed with ethanol (200 ml.), toluene (400 ml.), and toluene-*p*-sulphonic acid (10 g.), the water–ethanol–toluene azeotrope being continuously removed by distillation until no more water was generated. After the solution had been washed with sodium carbonate solution and water, the solvents were removed, and the residue distilled, yielding *ethyl* 8-*chloro*-2,2-*dimethyloctanoate* (82 g., 58·5%), b. p. 62°/0·03 mm., n_D^{20} 1·4429 (Found: C, 61·4; H, 9·8; Cl, 15·3. $C_{12}H_{23}ClO_2$ requires C, 61·4; H, 9·9; Cl, 15·1%).

In one preparation the crude 1,1-diethylpropyl ester was distilled *in vacuo* to give pure 1,1-*diethylpropyl* 8-*chloro*-2,2-*dimethyloctanoate*, b. p. 111°/0·18 mm., n_D^{20} 1·4540, in 65% yield (Found: C, 67·4; H, 11·3; Cl, 11·5. $C_{17}H_{33}ClO_2$ requires C, 67·0; H, 10·9; Cl, 11·6%).

Ethyl 8-*Iodo*-2,2-*dimethyloctanoate.*—The chloro-ester (80 g.) and sodium iodide (65 g.) were refluxed with stirring in acetone (500 ml.) for 60 hr. After the mixture had cooled, sodium chloride was filtered off and the filtrate concentrated under reduced pressure. Water was added and the mixture extracted with light petroleum (b. p. 30—50°). After being dried ($MgSO_4$), the petrol extract was evaporated and the residue distilled to give *ethyl* 8-*iodo*-2,2-*dimethyloctanoate* (105 g., 94·5%), b. p. 102°/0·14 mm., n_D^{20} 1·4812 (Found: C, 44·5; H, 7·2; I, 38·8. $C_{12}H_{23}IO_2$ requires C, 44·2; H, 7·1; I, 38·9%).

Ethyl 2,2-*Dimethyldec*-9-*ynoate.*—Ethyl 8-iodo-2,2-dimethyloctanoate (30 g.) in dimethylformamide (50 ml.) was added during 10 min. to sodium acetylide [from sodium (2·5 g.)] in liquid ammonia (75 ml.). The ammonia was allowed to evaporate during 1 hr. and the residue stirred for a further hour at room temperature. Solid ammonium chloride was added, followed by water. The mixture was twice extracted with light petroleum (b. p. 30—50°), and the extracts were washed with water. After the extracts had been dried ($MgSO_4$) and the petroleum evaporated, the residue was fractionated to give (*a*) b. p. 38°/0·1 mm., n_D^{20} 1·4303 (3·5 g.), thought to be ethyl 2,2-dimethyloct-7-enoate (Found: C, 72·6; H, 11·7%; I.V., 128. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%; I.V., 128), and (*b*) *ethyl* 2,2-*dimethyldec*-9-*ynoate* (11·5 g., 56%), b. p. 58°/0·05 mm., n_D^{20} 1·4380 (Found: C, 75·2; H, 11·2. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%).

2,2-*Dimethyldec*-9-*ynoic Acid.*—Ethyl 2,2-dimethyldec-9-ynoate (23 g.) was refluxed for 72 hr. with ethanol (200 ml.) and 30% aqueous potassium hydroxide (70 ml.). The ethanol was evaporated under reduced pressure and the residue diluted with water. After extraction with light petroleum (b. p. 30—50°) the aqueous solution was acidified and then extracted twice with light petroleum. The latter extracts were washed with water and, after being dried (Na_2SO_4), the petroleum was evaporated. Vacuum distillation of the residue yielded 2,2-*dimethyldec*-9-*ynoic acid* (18·5 g., 92%), b. p. 104°/0·1 mm., n_D^{20} 1·4540 (Found: C, 73·1; H, 10·4. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·3%).

2,2-*Dimethyloctadeca*-9,12-*diynoic Acid.*—To the Grignard reagent from ethyl bromide (20·7 g.) and magnesium (4·6 g.) in tetrahydrofuran (75 ml.) was added 2,2-dimethyldec-9-ynoic acid (18·5 g.), and the mixture was refluxed with stirring until gas was no longer evolved.

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[12] McCutcheon, *Org. Synth.*, 1942, **22**, 76.

While a slow stream of nitrogen was passed through the apparatus, cuprous chloride (0·5 g.) and then 1-bromo-oct-2-yne (17·9 g.) were added, and the mixture was refluxed for 7 hr. After the mixture had cooled, dilute sulphuric acid was added and the mixture extracted twice with ether, the ether extracts being washed with water and dried (Na_2SO_4). After removal of the ether, the residue was distilled *in vacuo* giving a viscous oil (11 g.), b. p. 162°/0·005 mm., n_D^{20} 1·4759, which rapidly became brown in air. This was considered to be 2,2-dimethyloctadeca-9,12-diynoic acid, although an analytically pure sample could not be obtained.

2,2-*Dimethyloctadeca*-cis-9,cis-12-*dienoic Acid.*—2,2-Dimethyloctadeca-9,12-diynoic acid (8·9 g.) in ethyl acetate (100 ml.) and quinoline (0·5 ml.) were shaken with Lindlar's catalyst (2 g.) in hydrogen. Hydrogenation ceased when the hydrogen uptake was 99% of the theoretical 2 mols. The catalyst was filtered off and the filtrate washed with dilute hydrochloric acid and water. After being dried (Na_2SO_4) the ethyl acetate was evaporated and the residue distilled *in vacuo* to give 2,2-*dimethyloctadeca*-cis-9,cis-12-*dienoic acid* (7·3 g., 82%), b. p. 140°/0·0002 mm., n_D^{20} 1·4680 (Found: C, 77·6; H, 11·7%; I.V., 161. $C_{20}H_{36}O_2$ requires C, 77·9; H, 11·8%; I.V. 165); $\lambda_{max.}$ 232 mμ ($E^{1\%}_{1\,cm.}$ 8·78, indicating less than 1% conjugation). The absence of infrared absorption at 10·3 μ indicated less than 5% of *trans*-CH=CH.

2,2-*Dimethylstearic Acid.*—(*a*) Ethyl 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoate (900 mg.) in ethyl acetate (25 ml.) was fully hydrogenated, palladium–charcoal (250 mg.) being used as catalyst (absorption, 130 ml. Theory, 128 ml.). Removal of the catalyst and solvent left an oil which solidified at 0°. Hydrolysis with 10% methanolic potassium hydroxide (25 ml.) for 9 hr. and recrystallisation of the acidic product from light petroleum (b. p. 60—80°) gave 2,2-dimethylstearic acid (400 mg.), m. p. 57·5—58·5° undepressed by admixture with an authentic specimen.

(*b*) 2,2-Dimethyloctadeca-*cis*-9,*cis*-12-dienoic acid (200 mg.) in ethyl acetate (10 ml.) was hydrogenated over palladium–charcoal until absorption of hydrogen ceased. Filtration, evaporation, and crystallisation from light petroleum (b. p. 60—80°) gave material, m. p. 57·5—58·5° undepressed by admixture with an authentic specimen of 2,2-dimethylstearic acid or with the product from (*a*).

7-*Phenylhept*-1-*yne.*—1-Bromo-5-phenylpentane (315 g.) reacted with sodium acetylide [from sodium (34·5 g.)] in liquid ammonia (1 l.) with vigorous stirring for 10 hr. Water was then added and the ammonia allowed to evaporate. The product was isolated by ether extraction and the ethereal extracts washed with dilute hydrochloric acid and sodium hydrogen carbonate solution, and dried (Na_2SO_4). After evaporation of the ether the residue was fractionated to give 7-*phenylhept*-1-*yne* (171 g.), b. p. 80·5°/0·4 mm., n_D^{20} 1·5089 (Found: C, 90·2; H, 9·4. $C_{13}H_{16}$ requires C, 90·7; H, 9·3%).

8-*Phenyloct*-2-*yn*-1-*ol.*—7-Phenylhept-1-yne (17·2 g.) was added to ethylmagnesium bromide [from ethyl bromide (13·6 g.) and magnesium (2·92 g.)] in ether (100 ml.), and the mixture refluxed for 1 hr. Gaseous formaldehyde, formed by heating paraformaldehyde (6 g.) in a stream of dry nitrogen, was then bubbled through the solution, and the mixture kept overnight. After decomposition with dilute sulphuric acid, the product was extracted with ether, and the extract washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). After removal of the ether the residue was fractionated to give 8-*phenyloct*-2-*yn*-1-*ol* (17·2 g.), b. p. 129°/0·25 mm., n_D^{20} 1·5281 (Found: C, 82·8; H, 9·0. $C_{14}H_{18}O$ requires C, 83·2; H, 9·0%).

1-*Bromo*-8-*phenyloct*-2-*yne.*—Phosphorus tribromide (20 ml.) was added gradually to a solution of 8-phenyloct-2-yn-1-ol (115 g.) and pyridine (1·4 ml.) in ether (170 ml.). The mixture was refluxed for 2 hr. and then poured on ice. The ether layer was separated, washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Evaporation of the ether, and fractionation of the residue gave 1-*bromo*-8-*phenyloct*-2-*yne* (95 g.), b. p. 115°/0·15 mm., n_D^{20} 1·5483 (Found: C, 63·35; H, 6·4; Br, 30·15. $C_{14}H_{17}Br$ requires C, 63·4; H, 6·5; Br, 30·1%).

16-*Chloro*-1-*phenylhexadeca*-6,9-*diyne.*—8-Chloro-oct-1-yne (39 g.) was added to ethylmagnesium bromide [from ethyl bromide (30·5 g.) and magnesium (6·7 g.)] in ether (200 ml.) and the mixture heated under reflux until evolution of ethane had ceased (2½ hr.). A stream of nitrogen was passed through the apparatus, cuprous chloride (0·75 g.) was added, and the heating continued for 15 min. 1-Bromo-8-phenyloct-2-yne (63·3 g.) was added and the reflux continued for a further 20 hr. The cooled mixture was poured on ice (200 g.) and 2N-sulphuric acid (100 ml.) and extracted with ether. The ether solution was washed with sodium hydrogen carbonate solution and dried ($MgSO_4$). After removal of the solvent the residue was distilled to give 16-*chloro*-1-*phenylhexadeca*-6,9-*diyne* (63 g., 80%) b. p. 170°/0·006 mm., n_D^{20} 1·5217 (Found: C, 80·0; H, 9·4; Cl, 10·5. $C_{22}H_{29}Cl$ requires C, 80·3; H, 8·9; Cl, 10·8%).

16-*Chloro*-1-*phenylhexadeca*-cis-6,cis-9-*diene*.—16-Chloro-1-phenylhexadeca-6,9-diyne (58·8 g.) was hydrogenated in a similar manner to 16-chlorohexadeca-6,9-diyne, taking up 8·34 l. of hydrogen (8·36 l. required for semi-hydrogenation of two acetylenic linkages), to give 16-*chloro*-1-*phenylhexadeca*-cis-6,cis-9-*diene* (54·2 g., 90·5%), b. p. 145°/0·002 mm., n_D^{20} 1·5096 (Found: C, 79·3; H, 10·3; Cl, 10·3. $C_{22}H_{33}Cl$ requires C, 79·4; H, 10·0; Cl, 10·3%).

Ethyl 2,2-*Dimethyl*-18-*phenyloctadeca*-cis-9,cis-12-*dienoate*.—This was prepared from 16-chloro-1-phenylhexadeca-*cis*-6,*cis*-9-diene (26·7 g.) in a similar manner to the preparation of ethyl 2,2-dimethyloctadeca-*cis*-9,*cis*-12-dienoate from 16-chlorohexadeca-*cis*-6,*cis*-9-diene. *Ethyl* 2,2-*dimethyl*-18-*phenyloctadeca*-cis-9,cis-12-*dienoate* (22·6 g., 68·2%), b. p. 174°/0·0004 mm., n_D^{20} 1·4913, was obtained (Found: C, 81·25; H, 10·55. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·7%). The infrared absorption spectrum showed no band at 10·3 μ attributable to *trans*-CH=CH.

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