597. *Studies in the Polyene Series. Part XXXVIII.* The Synthesis of Phenyl Analogues of Vitamin A Acid and Vitamin A.*

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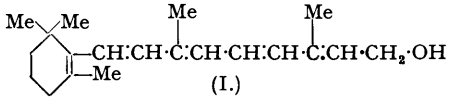
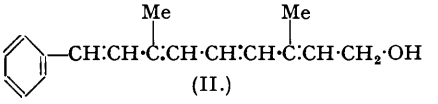
Methods have been devised for the synthesis of crystalline phenyl analogues of vitamin A acid and vitamin A. The acid was isolated in two geometrically isomeric forms, neither of which exhibited growth-promoting properties.

During the last few years the development of new synthetic methods in the polyene field has led to the preparation of a number of structural variants of the vitamin A_1 molecule (I). Growth-promotion tests on such compounds, and on derivatives of the vitamin itself, have furnished considerable information concerning the effect on biological activity of varying either the structure of the side chain or the nature of the functional group (for a review see Isler, *Chimia*, 1950, **4**, 103). Until recently conclusions regarding the specificity of the 2 : 6 : 6-trimethyl*cyclo*hex-1-enyl ring system have been drawn mainly from biological assays on cyclic and acyclic carotenoids and their degradation products (cf. Jones, *Ann. Reports*, 1940, **37**, 290). The number of structural modifications which can be examined in this way is, however, strictly limited, and furthermore the conclusions are open to criticism since structural features may determine the mode of fission of a carotenoid. The failure of the latter to exhibit activity of the pro-vitamin A type does not necessarily indicate inherent inactivity in the corresponding vitamin A_1 analogue itself (Heilbron, Jones, and Richardson, *J.*, 1949, 287).



(I.)



(II.)

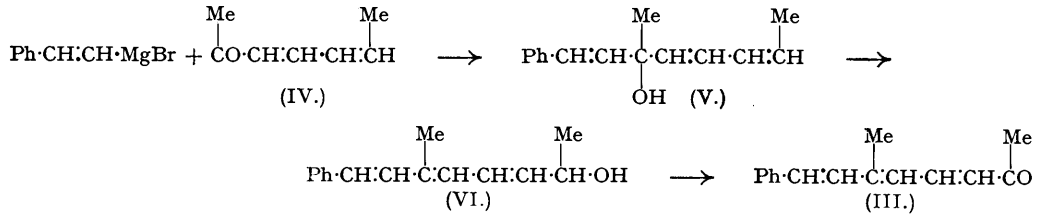
Vitamin A_2 has been shown by growth-promotion tests to possess *ca.* 40% of the biological activity of vitamin A_1 (Shantz and Brinkman, *J. Biol. Chem.*, 1950, **183**, 467). Recently a preliminary account has been published (Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49) of the synthesis of vitamin A_2, confirming its structure as 3′-dehydro-vitamin A_1, possessing an additional double bond in the ring system. A number of acetylenic analogues of vitamin A_1 and the corresponding acid, derived from ethynyl*cyclo*hexenes, have also been observed to exhibit slight, though definite, growth-promoting properties (Heilbron, Jones, and Richardson, *loc. cit.*; Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742; Heilbron, Jones, Lewis, and Weedon, *J.*, 1949, 2023; Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120). The presence in the molecule of an unmodified 2 : 6 : 6-trimethyl*cyclo*hex-1-enyl ring system is therefore not as essential for activity of the vitamin A type as has previously been suggested (cf. Karrer and Jucker, "Carotinoide," Basle, 1948), and the synthesis of compounds differing from vitamin A_1 solely in the nature of the ring system is clearly desirable. Progress in this direction has been reported in previous papers in this series.

Apart from the synthesis of vitamin A_2, the only claim to have prepared a compound containing the vitamin A side chain and a variant of the ring system is that of Linnell and Shen (*J. Pharm. Pharmacol.*, 1949, **1**, 971). These authors substituted benzylideneacetone for β-ionone in the synthesis of vitamin A_1 developed by Isler, Huber, Ronco, and Kofler (*Helv. Chim. Acta*, 1947, **30**, 1911) and obtained a biologically inactive, highly unstable product. This was presumed on the basis of light-absorption measurements to contain the phenyl analogue (II), although purification could not be effected. The present communication records the preparation of crystalline phenyl analogues of vitamin A acid and vitamin A. Comparison of the light-absorption properties of the pure carbinol (II) with those of Linnell and Shen's product indicates that the purity of the latter cannot have exceeded 15%.

An obvious intermediate for the preparation of (II) is the phenyl ketone (III), the corresponding 2 : 6 : 6-trimethyl*cyclo*hexenyl C_{18}-ketone having been used successfully for the synthesis of vitamin A_1 (Arens and van Dorp, *Rec. Trav. chim.*, 1949, **68**, 604; Schwarzkopf, Cahnmann, Lewis, Swidinsky, and Wüest, *Helv. Chim. Acta*, 1949, **32**, 443), and two routes to (III) have now been developed. Preparation of (III) from benzylideneacetone by a route analogous to that employed in the synthesis of the C_{18} ketone was found to be unsatisfactory (Linnell and Shen, *loc. cit.*).

* Part XXXVII, *J.*, 1951, 1074.

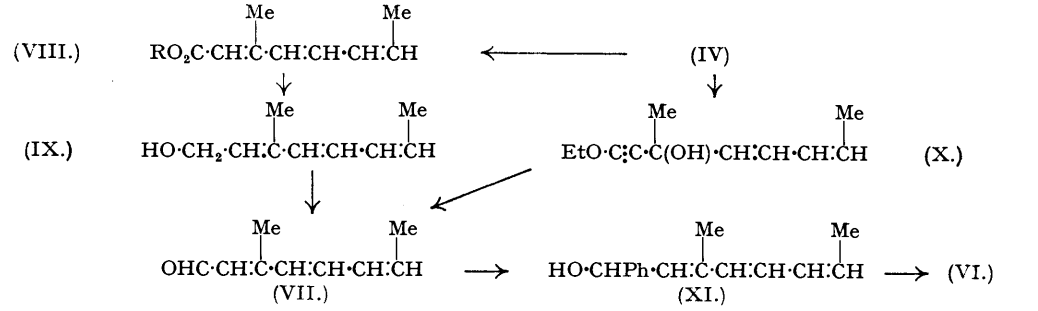
Reaction of styrylmagnesium bromide with the readily available crotonylideneacetone (IV) gave the tertiary alcohol (V), which on treatment with 0·01M-hydrochloric acid underwent anionotropic rearrangement to the crystalline alcohol (VI) (25% overall yield from IV). This was oxidised to the required ketone (III), in 77% yield, by shaking its solution in light petroleum with manganese dioxide according to the elegant method of Ball, Goodwin, and



Morton (*Biochem. J.*, 1948, **42**, 516) for the conversion of vitamin A_1 into retinene. Although few examples of its use have been recorded, this oxidation procedure obviously constitutes a valuable method for the synthesis of both polyene aldehydes (see below; Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719; Farrar, Hamlet, Henbest, and Jones, *loc. cit.*) and ketones (Bharucha and Weedon, forthcoming publication; Braude and Forbes, *J.*, in the press).

The structure of (VI) was confirmed by quantitative hydrogenation, which indicated the presence of three double bonds, and by the alternative synthesis, described below, from the C_9 aldehyde (VII).

An attempt to convert β-bromostyrene into styryl-lithium, and thence by reaction with crotonylideneacetone (IV) into (V), furnished a product similar in physical properties to (V) but giving on anionotropic rearrangement only minute amounts of the crystalline alcohol (VI). While the initial reaction product undoubtedly contained an appreciable quantity of the styryl-carbinol (V), it was probably contaminated with the corresponding phenylacetylenyl derivative. Wright (*J. Org. Chem.*, 1936, **1**, 459) has previously reported the formation of a mixture (4 : 1) of styryl-lithium and lithium phenylacetylide on reaction of β-bromostyrene with lithium. A similar mixture (5 : 1) of ethylenic and acetylenic derivatives has recently been observed in the corresponding reactions of *cis*-propenyl bromide (Braude and Coles, *J.*, in the press).



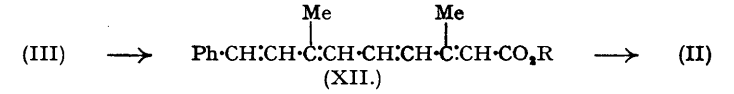
A convenient method has been developed for the synthesis of 3-methylocta-2 : 4 : 6-trienal (VII), which was required both in the present investigations and in connection with studies on the synthesis, from lithium *cyclo*hexenyls, of polyenes related to vitamin A (Braude, Bruun, Weedon, and Woods, forthcoming publication). A Reformatsky reaction of crotonylidene-acetone (IV) with methyl bromoacetate leading to the triene-ester (VIII; R = Me) in 15% yield was reported by Kuhn and Hofer (*Ber.*, 1932, **65**, 651). The corresponding ethyl ester (VIII; R = Et) has now similarly been prepared in 60% yield after dehydration of the intermediate hydroxy-ester with toluene-*p*-sulphonic acid. Reduction of (VIII; R = Et) with lithium aluminium hydride furnished in 87% yield the triene-alcohol (IX) which was oxidised with manganese dioxide to the required aldehyde (VII) in 80% yield. Catalytic hydrogenation of (VII) gave 3-methyloctanal.

The aldehyde (VII) was also prepared, though less conveniently, by application of Arens and van Dorp's method (*Rec. Trav. chim.*, 1948, **67**, 973; cf. Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823) for the synthesis of αβ-unsaturated aldehydes. Ethoxyacetylenylmagnesium

bromide reacted with (IV) to give the alcohol (X) (44% yield), which on partial hydrogenation of the triple bond and subsequent treatment with dilute acid was converted into the aldehyde (VII).

Phenylmagnesium bromide and (VII) gave the alcohol (XI) as a crystalline solid. Treatment with 0·01M-hydrochloric acid caused anionotropic rearrangement to (VI), which was identical with the compound obtained by the alternative method and on oxidation gave (III).

A Reformatsky reaction of the ketone (III) and subsequent dehydration gave a mixture of unsaturated esters (XII; R = Et), one of which (A) was isolated as a crystalline solid. Hydrolysis of the ethyl esters furnished isomeric forms A and B, in 11 and 18% yields respectively (based on III), of the phenyl analogue (XII; R = H) of vitamin A acid. Since



these isomeric acids were both derived from the same crystalline ketone, which presumably possessed a *trans*-configuration about all three ethylenic bonds, they probably differ in geometrical configuration about the αβ-double bond. Isomerism of this type has recently been reported for vitamin A acid itself (Inhoffen, Bohlmann, and Bohlmann, *Annalen*, 1950, **568**, 47). The acids A and B yielded, with diazomethane, isomeric methyl esters (XII; R = Me), which on hydrolysis regenerated the parent acids.

Reduction of the crystalline ethyl ester (XII; R = Et) with lithium aluminium hydride, as described by Schwarzkopf *et al.* (*loc. cit.*) for vitamin A ester, furnished the crystalline phenyl analogue (II), m. p. 137°, of vitamin A, in 40% yield. This was characterised by oxidation with manganese dioxide to the corresponding aldehyde and conversion of the latter into the 2 : 4-dinitrophenylhydrazone.

The acids A and B were fed to young rats on a vitamin-A-deficient diet, as aqueous solutions (buffered to pH 10) of the potassium and sodium salts respectively. No growth responses were obtained in doses which would have revealed activity of the order of one-thousandth of that of vitamin A_1. The sodium salt of vitamin A_1 acid, when similarly tested, exhibits growth-promoting properties equal to those of the natural vitamin (Arens and van Dorp, *Nature*, 1946, **158**, 60).

The light-absorption properties of the compounds described in this paper are recorded in the Table. The phenyl analogues of vitamin A acid and vitamin A exhibit maximal absorption at wave-lengths intermediate between those of the corresponding vitamin A_1 and A_2 derivatives. More vibrational fine structure is apparent in the spectrum of (II) than in those of either vitamin A_1 or A_2.

Experimental.

Light-absorption data, the majority of which are recorded in the Table, were determined in alcohol unless otherwise stated.

All the operations were carried out in inert atmospheres.

The 2 : 4-dinitrophenylhydrazones were purified by chromatographic adsorption from benzene solutions on a column of alumina. All other chromatograms were performed on alumina which had been partially deactivated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 3120).

Manganese dioxide was selected from various commercial batches by comparing their activities in the oxidation of cinnamyl alcohol under the following conditions. A solution of crystalline cinnamyl alcohol (0·25 g.) in light petroleum (b. p. 40—60°; dried over sodium) (50 c.c.) was shaken for 2 hours at 20° with a sample (2·0 g.) of the manganese dioxide (dried over phosphoric oxide) under test. The mixture was then filtered, the filtrate evaporated, and the residue treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate in methanol. The resulting precipitate was removed and crystallised from ethyl acetate, giving cinnamaldehyde 2 : 4-dinitrophenylhydrazone. Batches of manganese dioxide giving yields of *ca.* 0·35 g. were employed in subsequent oxidations. In a blank determination without manganese dioxide only a small amount (23 mg.) of the crude derivative was obtained (cf. Braude and Forbes, *J.*, in the press).

β-Bromostyrene was prepared by Nef's method (*Annalen*, 1899, **308**, 264; cf. Dufraisse, *Ann. Chim.*, 1922, **17**, 170) and had m. p. 6—7°, b. p. 106°/23 mm., n_D^{27} 1·6040.

Ethyl 2-Methylhepta-1 : 3 : 5-triene-1-carboxylate (VIII; R = Et) (With K. R. Bharucha).—About a quarter of a mixture of crotonylideneacetone (55 g.) and ethyl bromoacetate (90 g.; freshly distilled) was added to activated zinc wool (33 g.; cf. Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 575) and benzene (150 c.c.). The mixture was heated under reflux until reaction commenced and then the remainder of the ketone–bromoacetate mixture added at such a rate that gentle refluxing was maintained. When the addition was complete (45 minutes), heating was recommenced and continued for 20 minutes.

The mixture was cooled and shaken with dilute acetic acid (1 l.; N.). Isolation of the product with benzene in the usual manner and distillation gave an oil (71 g.), b. p. 88—94°/0·5 mm., n_D^{21} 1·4800. Redistillation of a small portion gave the pure *hydroxy-ester* as a colourless oil, b. p. 83°/0·1 mm., n_D^{18} 1·4825 (Found : C, 67·0; H, 9·05. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%). Light absorption : maximum, 2280 Å; ε, 29,500.

A solution of the crude hydroxy-ester and toluene-*p*-sulphonic acid (0·48 g.) in benzene (1 l.) was heated under reflux for 6 hours, the water which separated during the first hour being removed. The solution was cooled, washed with saturated sodium hydrogen carbonate solution, dried, and evaporated. Distillation of the residue gave the *triene-ester* (53 g.) as a pale yellow oil b. p. 139—140°/18 mm., 107—108°/2 mm., 78°/0·5 mm., n_D^{21} 1·5600—1·5650 (mainly >1·5640) (Found : C, 73·3; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%). Light absorption : see Table.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
Triene-ester (VIII; R = Et) ...	2990	34,000
Triene-acid (VIII; R = H) ...	2960	42,000
	3020 *	38,000
Me·[CH:CH]$_3$·CO_2H [1]	2940	36,000
Triene-alcohol (IX)	2580 *	45,000
	2680	54,000
	2800	43,500
Me·[CH:CH]$_3$·CH_2·OH [2]	2560	42,500
	2645	53,000
	2780	46,500
Ethoxyacetylenic alcohol (X) ...	2280	20,000
Me·CH:CH·CH:CH·CMe(OH)·C:CH [3]	2270	26,500
Triene-aldehyde (VII)	3220	30,500
Me·[CH:CH]$_3$·CHO [1]	3160	37,000
Triene alcohol (XI)	2690	22,500
	2800	19,500
Styrylcarbinol (V)	2280	19,500
	2370	19,500

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
Triene-alcohol (VI)	3190	48,000
	3320	36,000
Ketone (III)	3600	42,000
Ethyl ester A (XII; R = Et)	3680	56,500
Methyl ester A (XII; R = Me)	3540 *	44,500
	3670	48,500
Methyl ester B (XII; R = Me)	3500 *	45,500
	3650	53,500
Acid A (XII; R = H)	3640	56,000
Acid B (XII; R = H)	3630	51,000
Vitamin A_1 acid [4]	3500	42,500
Vitamin A_2 acid [5]	3720	39,500
Phenyl-alcohol (II)	3300	46,500
	3430	50,500
	3620	45,000
Vitamin A_1 [6]	3280	49,000
Vitamin A_2 [5]	2880	19,000
	3520	37,500

* Inflexion.

[1] Hausser, Kuhn, Smakula, and Hoffer, *Z. physikal. Chem.*, 1935, **29**, *B*, 371. [2] Heilbron, Johnson, Jones, and Raphael, *J.*, 1943, 265. [3] Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031. [4] Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719. [5] Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49. [6] Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911.

Repetition of the Reformatsky reaction on twice the scale, and dehydration of the crude hydroxy-ester without prior distillation, gave the triene-ester in undiminished yield.

Ethyl 2-Methylheptane-1-carboxylate.—A solution of the above triene-ester (2·534 g.) in ethyl acetate (25 c.c.) was shaken in hydrogen in the presence of Adams's platinum catalyst until absorption was complete (hydrogen absorbed, 716 c.c. at 27°/759 mm., equiv. to 2·9 double bonds). Removal of catalyst and solvent, and distillation of the residue, gave the saturated *ester* (1·8 g.), b. p. 100—102°/18 mm., n_D^{24} 1·4236 (Found : C, 70·5; H, 11·85. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·9%).

2-Methylhepta-1 : 3 : 5-triene-1-carboxylic Acid.—A solution of the above triene-ester (2·0 g.) in methanolic potassium hydroxide (10% w/v; 12 c.c.) was heated under reflux for 45 minutes. After cooling, the mixture was poured into water (150 c.c.), and the non-hydrolysable portion extracted with ether. The aqueous solution was acidified (pH 4) with dilute (1 : 1) phosphoric acid, and the precipitated solid (1·33 g.), m. p. 95—115°, separated. Recrystallisation from benzene–methanol gave the acid (0·65 g.) as prismatic needles, m. p. 160—161° (Kuhn and Hoffer, *Ber.*, 1932, **65**, 651, give m. p. 160—161°). Light absorption : see Table.

3-Methylocta-2 : 4 : 6-trien-1-ol (IX).—A solution of the triene ester (VIII; R = Et) (45 g.) in ether (100 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (13·5 g.; *ca.* 80% pure) in ether (500 c.c.) at −40°. The temperature of the mixture was then allowed to rise to −20° and stirring continued for 1 hour at −20°. Ethyl acetate (28 c.c.) was added, to decompose the excess of hydride, and then a saturated solution of ammonium chloride (58 c.c.). The temperature of the mixture was allowed to rise to 20° and the mixture then filtered and the solid washed well with ether. The combined ethereal washings and filtrate were dried and evaporated. Distillation of the residue gave the *alcohol* (30 g.) as a colourless oil, b. p. 85°/0·8 mm., n_D^{27} 1·5656 (Found : C, 78·45; H, 10·25. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). Light absorption : see Table. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 80—100°) in yellow prisms, m. p. 124° (Found : N, 8·65. $C_{16}H_{16}O_6N_2$ requires N, 8·45%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 106° (Found : C, 77·7; H, 7·25. $C_{20}H_{21}O_2N$ requires C, 78·15; H, 6·9%).

1-Ethoxy-3-methylocta-4 : 6-dien-1-yn-3-ol (X).—Crotonylideneacetone (12·2 g.) in ether (50 c.c.) was added dropwise to an ice-cooled, stirred suspension of ethoxyacetylenylmagnesium bromide (from

3·0 g. of Mg and 10·0 g. of ethoxyacetylene, according to Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823) in ether (300 c.c.). After the mixture had been stirred at 0° for a further 20 minutes, the Grignard complex was decomposed by addition of a saturated aqueous solution of ammonium chloride, and the product then isolated in the usual manner. Distillation gave the *ethoxyacetylene-alcohol* (9·2 g.), b. p. 82°/0·3 mm., n_D^{20} 1·4920—1·4971 (Found: C, 73·85; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%). Light absorption: see Table.

3-*Methylocta*-2 : 4 : 6-*trienal* (VII).—(*a*) A solution of the triene-alcohol (IX) (24·8 g.) in light petroleum (b. p. 40—60°) (1250 c.c.) was shaken with manganese dioxide (120 g.) at 20° for 4 hours. The mixture was filtered and the filtrate was evaporated. Distillation of the residue gave the *aldehyde* (20·0 g.) as a pale yellow oil, b. p. 70—75°/0·1 mm., n_D^{24} 1·6005 (Found: C, 79·2; H, 9·15. $C_9H_{12}O$ requires C, 79·4; H, 8·9%). Light absorption: see Table. The 2 : 4-*dinitrophenylhydrazone*, crystallised from ethyl acetate, had m. p. 192—193° (Found: N, 17·7. $C_{15}H_{16}O_4N_4$ requires N, 17·7%). Light absorption in chloroform (main band only): maximum, 4050 Å; ε, 44,000. A portion (150 mg.) was converted into the *semicarbazone* which crystallised from aqueous methanol in pale yellow plates (195 mg.), m. p. 178—179° (decomp.), and decomposed rapidly even when kept at 0° (Found: C, 60·75; H, 10·55. $C_{10}H_{15}ON_3$ requires C, 60·25; H, 10·6%). Light absorption: maxima, 3250 and 3390 Å; ε, 36,500 and 33,000 respectively.

(*b*) A solution of the ethoxyacetylene-alcohol (X) (6·4 g.) in ethyl acetate (40 c.c.) was shaken in the presence of 1% palladium–calcium carbonate (0·5 g.) in an atmosphere of hydrogen. When one molar proportion (800 c.c. at 19°/765 mm.) of hydrogen had been absorbed the reaction was interrupted. After removal of catalyst and solvent the residue was distilled, giving an oil (2·8 g.), b. p. 64—65°/0·4 mm., n_D^{18} 1·5316. A portion (2·0 g.) of the latter was shaken in ether (10 c.c.) with 0·2N-sulphuric acid (20 c.c.) at 20° for 40 minutes. Isolation of the product as usual gave the aldehyde (1·2 g.), b. p. 63°/0·2 mm.; n_D^{21} 1·600. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate and had m. p. 191°, undepressed on admixture with the specimen described above. A portion (200 mg.) of the aldehyde was converted into the semicarbazone which crystallised from aqueous methanol in yellow plates (214 mg.), m. p. 179° (decomp.).

3-*Methyloctanal*.—The preceding aldehyde [3·7 g., from (*a*)] in methanol (20 c.c.) was shaken in an atmosphere of hydrogen, in the presence of platinic oxide, until absorption was complete (hydrogen absorbed, 1910 c.c. at 20°/749 mm., equiv. to 2·8 double bonds). After removal of catalyst and solvent the crude product was distilled giving 3-*methyloctanal* (2·13 g.), b. p. 79°/15 mm., n_D^{22} 1·4320 (Found: C, 76·05; H, 12·65. $C_9H_{18}O$ requires C, 76·0; H, 12·75%). The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in needles, m. p. 79—80° (Found: N, 17·5. $C_{15}H_{22}O_4N_4$ requires N, 17·4%). The *semicarbazone* crystallised from aqueous methanol in plates, m. p. 86° (Found: C, 60·25; H, 10·55; N, 21·3. $C_{10}H_{21}ON_3$ requires C, 60·25; H, 10·6; N, 21·1%).

3-*Methyl*-1-*phenylocta*-2 : 4 : 6-*trien*-1-*ol* (XI).—A solution of the triene-aldehyde (VII) (6·5 g.) in ether (50 c.c.) was added during 20 minutes to a stirred solution of phenylmagnesium bromide (from 2·4 g. of Mg) at 0°. Stirring was continued for a further hour at 20° and the complex was then decomposed by the addition of ammonium chloride (15 g.) in water (60 c.c.). The ethereal layer was separated, washed with water, dried ($MgSO_4$ + trace of K_2CO_3), and evaporated. The residual pale yellow oil (10·0 g.) was kept in light petroleum (b. p. 60—80°; 25 c.c.) at 0° for 40 hours. The solid which separated was recrystallised from the same solvent, giving the *alcohol* (3·3 g.) as colourless needles, m. p. 73° (Found: C, 83·75; H, 8·45. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%). Light absorption: see Table.

Evaporation of the mother-liquors and distillation of the residue gave a further quantity (4·3 g.), b. p. 80° (bath-temp.)/10^{-4} mm., n_D^{18} 1·5856, which solidified when seeded and had m. p. 70°.

3-*Methyl*-1-*phenylocta*-1 : 4 : 6-*trien*-3-*ol* (V).—A solution of crotonylideneacetone (49·5 g.; freshly distilled) in ether (200 c.c.) was added during 45 minutes to a filtered solution of styrylmagnesium bromide (prepared from 91·6 g. of β-bromostyrene and 36·5 g. of magnesium powder according to Gilman, *Rec. Trav. chim.*, 1935, **54**, 590) in ether (300 c.c.) at 0°. Stirring was continued for 30 minutes at 20°, and then a solution of ammonium chloride (150 g.) in water (500 c.c.) was added. The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed with water and dried ($MgSO_4$ + trace of K_2CO_3). The solvent was removed, finally at 60°/0·2 mm. for ½ hour, the residue (80 g.) dissolved in light petroleum (b. p. 60—80°; 40 c.c.), and the solution kept at 0° for 12 hours. Diphenylbutadiene (4·3 g.) separated as plates, m. p. 136—137°, which after one crystallisation from the same solvent had m. p. 150—151° (Pinckard, Wille, and Zechmeister, *J. Amer. Chem. Soc.*, 1948, **70**, 1938, give m. p. 152—153°). The mother-liquors were evaporated. Distillation of a small portion (1·0 g.) of the residue gave the tertiary *alcohol* (0·65 g.) as a viscous oil, b. p. 85° (bath-temp.)/10^{-4} mm., n_D^{25} 1·5743 (Found: C, 84·15; H, 8·55%). Light absorption: see Table. The majority of the crude product was used for the preparation of (VI) without further purification.

An attempt to convert β-bromostyrene into styryl-lithium (cf. Wright, *J. Org. Chem.*, 1936, **1**, 459) and thence by reaction with crotonylideneacetone into the required tertiary carbinol (V) gave in good yield an oil, b. p. 120° (bath-temp.)/10^{-3} mm., n_D^{25} 1·5745 (Found: C, 84·25; H, 8·45%). Light absorption: maxima, 2280, 2370, and 2420 Å; $E_{1\,cm.}^{1\%}$, 1120, 1100, and 1180 respectively. Anionotropic rearrangement of this product in the manner described below for (V) gave only traces of the crystalline carbinol (VI).

6-*Methyl*-8-*phenylocta*-3 : 5 : 7-*trien*-2-*ol* (VI).—(*a*) 3-Methyl-1-phenylocta-2 : 4 : 6-trien-1-ol (6·0 g.; m. p. 71°) was dissolved in a 0·01M-solution of hydrochloric acid in water (160 c.c.)–acetone (240 c.c.), and the resulting solution kept at 20° overnight. A saturated solution of sodium hydrogen carbonate was added until the pH of the mixture rose to 7—8. The bulk of the acetone was then removed under reduced pressure and the product (5·5 g.) isolated with ether in the usual way. Light absorption: maxima, 2690, 2800, 3190, and 3300 Å; $E_{1\,cm.}^{1\%}$, 840, 840, 1090, and 700 respectively. Recrystallisation from light

petroleum (b. p. 60—80°) gave 6-*methyl*-8-*phenylocta*-3 : 5 : 7-*trien*-2-*ol* (1·95 g.) as colourless prisms, m. p. 102·5° (Found : C, 83·75; H, 8·55. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%). Light absorption : see Table.

(*b*) The crude tertiary carbinol (V) (50 g.) was dissolved in a 0·01M-solution of hydrochloric acid in water (540 c.c.)–acetone (1260 c.c.), and the solution kept at 20° for 60 hours. The product, isolated as described in (*a*), was an oil (48·7 g.), n_D^{21} 1·6170. Light absorption : maxima, 3180 and 3280 Å; $E_{1\,cm.}^{1\%}$, 950 and 800 respectively.

Trituration of the crude product with light petroleum (b. p. 60—80°) gave a solid which on recrystallisation from the same solvent yielded 6-methyl-8-phenylocta-3 : 5 : 7-trien-2-ol (15·0 g.), m. p. 103°, undepressed on admixture with a specimen from (*a*). Attempts to isolate further quantities of the crystalline alcohol by evaporation of the mother-liquors and chromatography of the residual oil (32 g.) were unsuccessful.

When a solution of the crystalline alcohol (523 mg.) in ethyl acetate (15 c.c.) was shaken in hydrogen and in the presence of a platinum catalyst (30 mg.), 179 c.c. of hydrogen were adsorbed at 21·5°/761 mm., equiv. to 2·95 double bonds.

6-*Methyl*-8-*phenylocta*-3 : 5 : 7-*trien*-2-*one* (III).—A solution of the preceding alcohol [10·0 g.; m. p. 101°, prepared by method (*b*)] in light petroleum (b. p. 40—60°; 900 c.c.) was shaken with manganese dioxide (90 g.) at 20° for 5 hours. The mixture was filtered and the filtrate evaporated, giving a solid (10·0 g.) which on recrystallisation from light petroleum (b. p. 60—80°) yielded the *ketone* (7·7 g.) as yellow plates, m. p. 102°, depressed to 83—89° on admixture with the parent alcohol (Found : C, 84·45; H, 7·55. $C_{15}H_{16}O$ requires C, 84·85; H, 7·6%). Light absorption : see Table. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate and had m. p. 192° (Found : N, 15·2. $C_{21}H_{20}O_4N_4$ requires N, 15·45%). Light absorption in chloroform (main band only) : maximum 4130 Å; ε, 33,500.

A specimen of the ketone prepared by oxidation of the alcohol from (*a*) had m. p. 100°, undepressed on admixture with the specimen described above. It yielded a 2 : 4-dinitrophenylhydrazone, m. p. 191°, undepressed on admixture with the specimen described above.

2 : 6-*Dimethyl*-8-*phenylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylic Acids* (XII; R = H).—A solution of the preceding ketone (5·0 g.) and ethyl bromoacetate (4·4 g.; freshly distilled) in benzene (15 c.c.) was added dropwise to a mixture of activated zinc (1·7 g.; cf. Fieser and Johnson, *loc. cit.*), benzene (45 c.c.), and a trace of iodine. When about one-fifth of the ketone solution had been added, the mixture was refluxed until reaction commenced (15 minutes), and then the remainder of the ketone solution added at such a rate as to maintain a gentle reflux. The mixture was heated under reflux for a further ½ hour—all the zinc had by then reacted—cooled, and shaken with 5% acetic acid (150 c.c.). The benzene layer was separated, washed well with sodium hydrogen carbonate solution, and dried ($MgSO_4$).

The resulting solution of hydroxy- and unsaturated esters was diluted to *ca.* 150 c.c. with benzene, toluene-*p*-sulphonic acid (30 mg.) was added, and the mixture heated under reflux for 5 hours (the water which separated during the first ½ hour was removed by azeotropic distillation with benzene). The benzene solution was cooled, washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, giving a red oil (6·0 g.), n_D^{23} 1·675. This was dissolved in light petroleum (b. p. 40—60°) (8 c.c.), and the solution was poured on to a column of partially deactivated alumina (350 g.; Grade IV; cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with the same solvent and the least strongly adsorbed band eluted. Evaporation of the solvent gave a yellow oil (4·2 g.), n_D^{25} 1·671, which exhibited a light-absorption maximum at 3680 Å; $E_{1\,cm.}^{1\%}$, 1270. On storage of a solution of the oil in light petroleum (b. p. 60—80°) at 0° for a few hours, a solid separated which was recrystallised from benzene and from ether, giving *ethyl* 2 : 6-*dimethyl*-8-*phenylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (ethyl ester A) (1·07 g.) as yellow needles, m. p. 122—123° (Found : C, 80·75; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%). Light absorption : see Table. Evaporation of the mother-liquors gave a crude ester as an oil (3·1 g.).

A solution of the crystalline ethyl ester (0·3 g.; m. p. 121°) in methanolic potassium hydroxide (10% w/v; 7 c.c.) was warmed for 1 hour at 60° and then cooled. The potassium salt (216 mg.) crystallised and was separated and washed with methanol. The potassium salt was dissolved in water (20 c.c.), and the solution acidified with phosphoric acid. The solid which separated was recrystallised from benzene giving the *acid A* (132 mg.) as yellow plates, m. p. 195° (Found : C, 80·25; H, 7·15. $C_{17}H_{18}O_2$ requires C, 80·45; H, 7·15%). Light absorption : see Table. The methanolic mother-liquors were diluted with water, and the non-hydrolysable material was extracted with ether. Acidification of the aqueous solution gave a further quantity (52 mg.) of acid A.

A solution of the crude liquid ethyl ester (3·1 g.) in methanolic potassium hydroxide (10% w/v; 45 c.c.) was kept at 20° for 54 hours. Isolation of the acidic product in the usual manner gave a solid (1·86 g.), m. p. 151—154°, which was recrystallised from 1 : 3 benzene–light petroleum (b. p. 60—80°), yielding *acid B* (1·085 g.) as yellow plates, m. p. 165° which was depressed on admixture with acid A (Found : C, 80·25; H, 7·35%). Light absorption : see Table. Acid B was also prepared in a subsequent experiment by hydrolysing the crude liquid ester at 60° for 1 hour.

Methyl 2 : 6-*Dimethyl*-8-*phenylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylates* (XII; R = Me).—A solution of acid A (140 mg.; m. p. 195°) in ether (10 c.c.) was treated at 0° with ethereal diazomethane (50% excess; standardised against benzoic acid). After 5 minutes at 0° the mixture was warmed to 30° to expel the excess of diazomethane, and the solvent was then removed under reduced pressure. The solid residue was dissolved in benzene (3 c.c.) and the solution poured on to a column of alumina (10 g.; Grade IV). The chromatogram was developed with light petroleum (b. p. 40—60°), and the single yellow band eluted. Evaporation of the solvent and crystallisation of the residue from 1 : 3 benzene–

light petroleum (b. p. 60—80°) gave the *methyl ester A* (114 mg.) as yellow needles, m. p. 125° (Found : C, 80·35; H, 7·55. $C_{18}H_{20}O_2$ requires C, 80·55; H, 7·5%). Light absorption : see Table.

Hydrolysis of a portion (73 mg.) of the ester by heating it under reflux with methanolic potassium hydroxide (10% w/v; 3 c.c.) and isolation of the acidic product in the usual manner gave acid A (51 mg.), m. p. 192°, undepressed on admixture with an authentic specimen.

Esterification of acid B (200 mg.; m. p. 162°) as described for the isomeric material gave a crude oil (210 mg.) which was dissolved in light petroleum (b. p. 40—60°) (10 c.c.). The solution was poured on to a column of alumina (30 g.; Grade IV). The chromatogram was developed with the same solvent and the single yellow band was eluted. Evaporation of the solvent and crystallisation of the residue from light petroleum (b. p. 60—80°) gave the *methyl ester B* (107 mg.) as pale yellow needles, m. p. 123° (Found : C, 80·7; H, 7·55%). Light absorption : see Table. A mixture of the two isomeric methyl esters had m. p. 121°.

The methyl ester B (200 mg.) was hydrolysed in the usual manner by boiling methanolic potassium hydroxide (10% w/v; 6 c.c.) for 1 hour and gave a crude acid (138 mg.), m. p. 143°, which was crystallised from 1 : 3 benzene–light petroleum (b. p. 60—80°), yielding acid B, m. p. 163°, undepressed on admixture with an authentic specimen.

3 : 7-*Dimethyl*-9-*phenylnona*-2 : 4 : 6 : 8-*tetraen*-1-*ol* (II).—A solution of the crystalline ethyl ester (560 mg.; m. p. 122—123°) of acid A in ether (25 c.c.) was added during 10 minutes to a stirred ethereal solution of lithium aluminium hydride (1·87% w/v; 9·5 c.c.) at −30°. The temperature of the mixture was allowed to rise to −15° (15 minutes) and stirring continued for a further ½ hour. Ethyl acetate (0·5 c.c.) was added and then saturated aqueous ammonium chloride (1 c.c.). The mixture was filtered and the filtrate dried and evaporated. The residual solid was crystallised from benzene–light petroleum (b. p. 60—80°), giving the *alcohol* (196 mg.) as pale yellow plates, m. p. 137° (Found : C, 85·35; H, 8·35. $C_{17}H_{20}O$ requires C, 85·15; H, 8·4%). Light absorption : see Table. Attempts to isolate further quantities of the pure alcohol by evaporation of the mother-liquors and chromatography of the residue were unsuccessful.

A solution of the crystalline material (33 mg.) in light petroleum (b. p. 40—60°; 7 c.c.) and benzene (2 c.c.) was shaken with manganese dioxide (300 mg.) for 4 hours. The mixture was filtered, the solid washed with benzene, and the combined filtrate and washings were evaporated. The residue was converted into the 2 : 4-*dinitrophenylhydrazone* which crystallised from 1 : 1 ethyl acetate–methanol and had m. p. 213—214° (Found : N, 13·1. $C_{23}H_{22}O_4N_4$ requires N, 13·4%). Light absorption in chloroform (main band only) : maximum, 4400 Å; ε, 49,000.

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