2. *The Synthesis of Compounds Related to the Antirachitic Vitamins. Part II.*

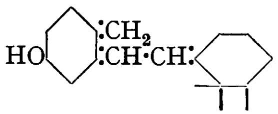
By John B. Aldersley, G. Norman Burkhardt, Albert E. Gillam, and Nathan C. Hindley.

The preparation of *cyclo*hexylideneacetaldehyde and 4-*hydroxy*cyclo*hexanone* is described together with their condensation to form the *dienone* (II) (compare Aldersley and Burkhardt, J., 1938, 545). Attempts to introduce an exocyclic methylene group in place of the carbonyl oxygen in (II) have apparently led to the formation of mixtures of isomeric hydroxytrienes, $C_{15}H_{22}O$. The predominant isomeride is considered to have the third ethylene bond in the *cyclo*hexane ring (VI) and not in the exocyclic position (I).

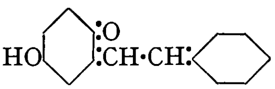
The preparation of *cyclo*hexylideneacetaldehyde by ozonolysis of 1-allyl*cyclo*hexanol is an example of a useful method for obtaining αβ-unsaturated aldehydes.

In a preliminary note, Aldersley and Burkhardt (J., 1938, 545) outlined experiments directed to the synthesis of compounds containing the triene system and hydroxyl group characteristic of the antirachitic vitamins (I). The present communication gives details and extensions of this work. In the interval Dimroth (*Ber.*, 1938, **71**, 1333, 1346, 2658) has described the synthesis, by similar methods, of substances analogous to our products but not containing the free hydroxyl group (compare also Milas and Anderson, *J. Amer. Chem. Soc.*, 1939, **61**, 2534).

(I.)

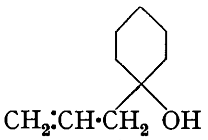


(II.)

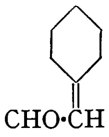


Partial hydrolysis of *trans*-quinitol diacetate (1 : 4-diacetoxy*cyclo*hexane) under carefully controlled conditions gave a 60% yield of *quinitol monoacetate*. Oxidation of the product gave 4-*acetoxy*cyclo*hexanone*, which was hydrolysed to 4-*hydroxy*cyclo*hexanone*.

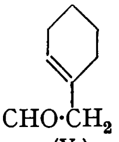
*cyclo*Hexylideneacetaldehyde (IV) was prepared, in 35% yield, by the ozonolysis of 1-allyl*cyclo*hexanol (III). 1-Hydroxy*cyclo*hexylacetaldehyde, which was an intermediate product, was partly dehydrated to give also *cyclo*hexenylacetaldehyde (V), which was removed by distillation. The formation of this isomeride can apparently be almost entirely prevented by removing all traces of alkali before distillation.



(III.)



(IV.)



(V.)

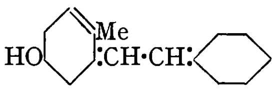
*cyclo*Hexylideneacetaldehyde was condensed with 4-hydroxy*cyclo*hexanone or with 4-acetoxy*cyclo*hexanone in presence of excess of dilute sodium hydroxide, the procedure used by Vorländer and Kunze (*Ber.*, 1926, **59**, 2078) for preparing monobenzylidene*cyclo*hexanone. The *hydroxydienone* (II) was formed together with products of higher molecular weight, which predominated when piperidine–acetic acid or hydrogen chloride was used as catalyst. (II) was converted into its *acetate* and both were characterised as derivatives.

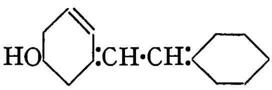
The acetate of (II) was treated with bromoacetic ester and zinc, the product successively hydrolysed with dilute alkali solution and dehydrated with acetic anhydride, the acetyl group removed, and the unsaturated acid decarboxylated (compare Wallach, *Annalen*, 1909, **365**, 255). The product readily combined with phenyl *iso*cyanate to give a solid which after recrystallisation or vacuum sublimation (m. p. 123—132°) showed an absorption spectrum indistinguishable from that of a crude sample (m. p. 105—126°) and gave the analysis required for the *phenylurethane* of the anticipated *hydroxytriene* ($C_{22}H_{27}O_2N$). This derivative was unstable in air. A dinitrobenzoate was also prepared and the crude hydroxytriene which was regenerated from it was sent to Mr. A. L. Bacharach of Glaxo Laboratories, Ltd., who kindly carried out preliminary tests for antirachitic activity but with negative results.

With excess of methylmagnesium iodide the dienone (II) gave a product very similar to the product from the Reformatsky reaction according to all the criteria examined. The mixed m. p. of the phenylurethanes showed no depression or broadening of the m. p. range.

There is a considerable difference between the absorption maximum of calciferol, λ = 2650 A., and that of the synthetic hydroxytriene, λ = 2800 A. The latter corresponds in location with the maxima shown by the unhydroxylated products obtained by Dimroth (*loc. cit.*), who also observed that the triene, which he obtained from his dienone by the Reformatsky method, was unchanged on heating in nitrogen at 200°. These results, together with the properties of our products and their derivatives, suggest that by both methods a mixture of hydroxytrienes is formed containing a predominant amount of (VI). The isomerisation of the product by irradiation and the further characterisation of its constituents are being examined.

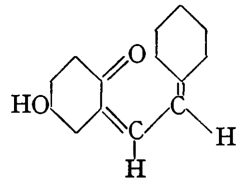
(VI.)

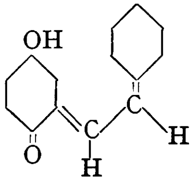




(VII.)

(VIII*a*.)

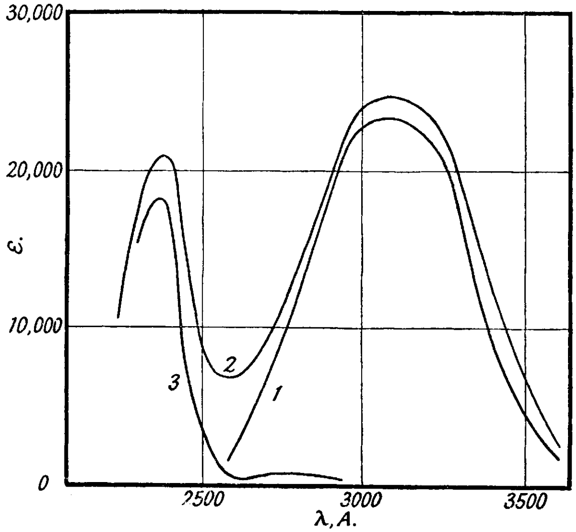




(VIII*b*.)

The reduction of the dienone (II) with aluminium *iso*propoxide gave a good yield of a hydroxytriene presumably having the constitution (VII).

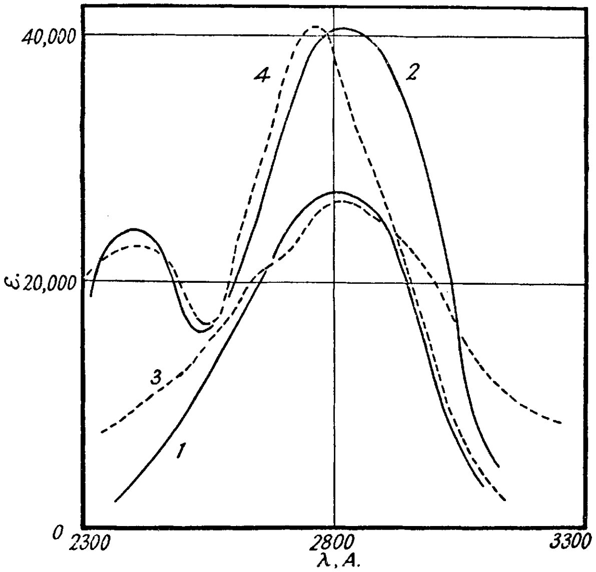
Fig. 1.



Absorption spectra (in ethyl alcohol).

1. *The hydroxydienone (II).*
2. *Phenylurethane of the hydroxydienone (II).*
3. *Phenylurethane of* cyclo*hexanol.*

Fig. 2.



Absorption spectra (in ethyl alcohol).

1. *The hydroxytriene from the Reformatsky method.*
2. *Phenylurethane of the hydroxytriene from the Reformatsky method.*
3. *The hydroxytriene from the Grignard method.*
4. *Phenylurethane of the hydroxytriene from the Grignard method.*

The dienone (II) and its acetate have each been isolated in a single isomeric form only. (VIII*a*) and (VIII*b*) represent the two theoretically possible isomerides, written so as to retain the opened-phenanthrene skeleton. The two forms should be readily convertible through enolisation, but heating for several hours, with piperidine–acetic acid as a condensing catalyst, gave no evidence of cyclisation to hydroxyoctahydrophenanthrene. This suggests that the carbonyl group is stereochemically remote from the active ε position as in (VIII*b*), but the action of other condensing agents is being examined.

It is perhaps worthy of note that the evidence on the corresponding stereochemistry of the antirachitic vitamins is not conclusive either. The general resemblance between the crystal structures of calciferol and ergosterol and the easy cyclisation of calciferol to pyrocalciferol suggest a formula corresponding to (VIII*a*), but the unexpectedly short length of the calciferol molecule according to *X*-ray data (Bernal and Crowfoot, *Chem. and Ind.*, 1935, **13**, 701) would be accounted for on a formula analogous to (VIII*b*) and the conditions used for ring opening from lumisterol or for recyclisation might be expected to permit any necessary change of geometrical isomerism.

EXPERIMENTAL.

Quinitol Diacetate.—Quinitol (50 g.) and acetic anhydride (200 c.c.) were refluxed for an hour and then poured into hot water. The diacetate (90% yield) separated on cooling and was recrystallised from dilute alcohol; m. p. 102—103° (*trans*-isomeride; Palfrey and Rothstein, *Comp. rend.*, 1928, **186**, 1007).

Quinitol Monoacetate.—Potassium hydroxide (11 g. pure) in 50% alcohol (50 c.c.) was dropped during 5 minutes into quinitol diacetate (50 g.) dissolved in 50% alcohol (350 c.c.) at 40—50° with vigorous stirring. The alcohol was removed under reduced pressure and the unchanged diacetate (5 g.), which crystallised on cooling, was separated. The monoacetate (24 g.; 60% of the theoretical) was isolated by chloroform extraction of the aqueous liquor and distilled, b. p. 136—137°/15 mm. This material, which generally still contained a small amount of quinitol diacetate, was oxidised without further purification.

By this method Mr. J. Wardleworth has recently obtained crystalline *quinitol monoacetate*, m. p. 68—72° (Found: C, 60·4; H, 8·9. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%).

4-*Acetoxy*cyclo*hexanone.*—Quinitol monoacetate (22 g.) in glacial acetic acid (50 c.c.) was oxidised in the cold with chromic acid (12 g.) in acetic acid (12 c.c. of glacial acid, 8 c.c. of water). After leaving overnight, water (100 c.c.) was added, and the solution extracted with chloroform (500 c.c.). The extract was washed with a little water, dried, and distilled, giving a colourless liquid (15 g.), b. p. 124—126°/14 mm., 110°/8 mm., 235°/760 mm. The semicarbazone had m. p. 182° (Found: N, 19·8. Calc. for $C_9H_{15}O_3N$: N, 19·7%). The 2:4-dinitrophenylhydrazone recrystallised from alcohol had m. p. 176°.

4-*Hydroxy*cyclo*hexanone.*—Crude 4-acetoxy*cyclo*hexanone (50 g.), which gave an acetyl value corresponding to the presence of 16% of quinitol diacetate, was hydrolysed by standing for 24 hours at room temperature with 2N-sodium hydroxide (300 c.c.). The clear light brown liquid was neutralised with dilute acid, and the water removed by prolonged heating on a steam-bath. The residue was taken up with ethyl acetate and treated with anhydrous sodium sulphate. On evaporation and fractionation through a Widmer column it gave 4-*hydroxy*cyclo*hexanone* as a colourless mobile liquid (28 g.), b. p. 83—85°/0·6 mm. (Found: C, 63·4; H, 9·0. $C_6H_{10}O_2$ requires C, 63·1; H, 8·8%). A higher fraction distilling at 95—100°/0·6 mm. crystallised on cooling and was identified as quinitol.

Acetylation of 4-*Hydroxy*cyclo*hexanone.*—4-Hydroxy*cyclo*hexanone (7 g.) was refluxed with acetic anhydride (60 c.c.) for 3 hours, and the bulk of the acetic anhydride removed under reduced pressure. After standing with water (30 c.c.) for 24 hours the acetate was isolated by chloroform extraction, yielding pure 4-*acetoxy*cyclo*hexanone* as a colourless liquid, b. p. 112—114°/11 mm. (Found: C, 61·0; H, 7·9. $C_8H_{12}O_3$ requires C, 61·4; H, 7·8%).

The Oxidation of Quinitol.—This was carried out by adding chromic anhydride (23 g.) in acetic anhydride (100 c.c.) to a cooled (10—15°) and vigorously stirred solution of quinitol (40 g.) in acetic anhydride (200 c.c.). After standing overnight, the solvent was removed under reduced pressure. Water (100 c.c.) was added to the sticky residue. After 2 hours, chloroform extraction gave a liquid (17 g.), b. p. 235°, containing 67% of 4-acetoxy*cyclo*hexanone (estimated as dinitrophenylhydrazone). The other constituent was shown to be quinitol diacetate, which was precipitated by adding water, from which acetoxy*cyclo*hexanone was extracted with chloroform and distilled. The aqueous liquors from the first chloroform extractions were evaporated and from the residue 1 : 4-*cyclo*hexanedione (m. p. 79°, b. p. 121—124°/11 mm.) was isolated (compare Sabetay and Bléger, *Compt. rend.*, 1930, **191**, 104).

4-*Acetoxy*-2 : 6-*dibenzylidene*cyclo*hexanone*.—Dry hydrogen chloride was passed into 4-acetoxy*cyclo*hexanone (5·2 g.) and benzaldehyde (3·5 g.; 1 mol.) in glacial acetic acid (15 c.c.). After leaving overnight, the solid was filtered off, washed and recrystallised from 95% alcohol; m. p. 165° (Found : C, 79·3; H, 5·7. Calc. for $C_{22}H_{20}O_3$: C, 79·5; H, 6·0%). No monobenzylidene derivative was detected in the mother-liquors.

1-*Allyl*cyclo*hexanol*.—This was prepared by the method of Jaworski (*Ber.*, 1909, **42**, 436; compare Mazurewitsch, *Chem. Zentr.*, 1911, II, 1922) and was obtained as a colourless liquid (55% yield), b. p. 72—75°/11 mm., together with *cyclo*hexenyl*cyclo*hexanone, b. p. 138—142°/11 mm. (semicarbazone, m. p. 202° after recrystallisation), and a higher fraction, b. p. 210—215°/11 mm. 1-Allyl*cyclo*hexanol on treatment with 3 : 5-dinitrobenzoyl chloride in the presence of excess of pyridine readily yielded the 3 : 5-*dinitrobenzoate*, which crystallised from benzene–light petroleum in needles, m. p. 101—103° (Found : N, 8·6. $C_{16}H_{18}O_6N_2$ requires N, 8·4%).

cyclo*Hexylideneacetaldehyde*.—1-Allyl*cyclo*hexanol (36·5 g.) in acetic acid (150 c.c.) at 0° was ozonised for 20 hours, and the ozonide warmed under reflux with zinc dust (10 g.). The vigorous decomposition was moderated by cooling in ice, and the reaction then completed on the steam-bath (½ hour). The brown liquid was diluted with ether, filtered, and just neutralised with a suspension of sodium bicarbonate in water. The ethereal layer was washed with very dilute sulphuric acid and several times with water and dried over alkali-free sodium sulphate, and the solvent distilled. The residue on fractionation gave a small first fraction and a main fraction, b. p. 85—87°/9 mm. (35% yield), showing a single absorption band in alcohol, $\lambda =$ 2400 A., $\varepsilon_{max.} = 15,900$. Dimroth (*loc. cit.*) found $\lambda = 2320$ A., $\varepsilon_{max.} = 17,400$ in ether, a solvent which apparently gives a displacement of maximum to shorter wave-length (~50 A.) and slightly higher ε values for the pure dienone (II). The residue in the distillation flask, presumably containing hydroxy-aldehyde, on slow distillation with catalytic amounts of iodine yielded further quantities of impure aldehyde.

Condensation of 4-*Hydroxy*cyclo*hexanone and* cyclo*Hexylideneacetaldehyde*.—4-Hydroxy*cyclo*hexanone (36·4 g.; 0·41 mol.) in 0·086N-sodium hydroxide (1 l.) was shaken in nitrogen with *cyclo*hexylideneacetaldehyde (28·2 g.; 0·23 mol.), added in five equal parts during 24 hours. Shaking was continued for a further 24 hours, the mixture titrated to neutrality with sulphuric acid, and the thick yellow oil which had separated taken up with ether. After drying, distillation gave a main fraction (21 g.), b. p. 168—173°/0·01 mm., as a thick yellow oil which partly crystallised on prolonged standing and gave needles of 2-*keto*-5-*hydroxy*-αβ-*di*cyclo*hexylidene-ethane* (II), m. p. 65—69°, from light petroleum–acetone (Found : C, 76·0; H, 9·5. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·2%), showing a single maximum in its absorption spectrum, $\lambda = 3090$ A., $\varepsilon_{max.} = 23,200$ in alcohol, characteristic of the conjugated dienone system. The pure dinitrophenylhydrazone (m. p. 170—171°) and the phenylurethane (m. p. 180°) (Aldersley and Burkhardt, *loc. cit.*) were prepared by the usual methods.

Acetylation of the Condensation Product (II).—The total main fraction, b. p. 168—173°/0·01 mm. (6 g.), was refluxed in nitrogen for 2 hours with acetic anhydride (80 c.c.), and the bulk of the acetic anhydride removed under reduced pressure. Water (100 c.c.) was added to the residue, and the mixture heated on the steam-bath for 1 hour in nitrogen, cooled, and ether-extracted. The extract was washed to neutrality with sodium bicarbonate solution and water and dried, and solvent removed. Distillation of the residue gave a main fraction (5·2 g.), b. p. 140—150°/0·002 mm., $\lambda = 3070$ A., $\varepsilon_{max.} = 17,930$, as a pale yellow oil which crystallised completely on standing. Recrystallisation from acetone–light petroleum gave colourless needles, m. p. 80—82° (Found : C, 73·05; H, 8·5. $C_{16}H_{22}O_3$ requires C, 73·2; H, 8·5%). Absorption maximum, $\lambda = 3090$ A., $\varepsilon_{max.} = 23,300$. This *acetoxydienone* gave a deep red 2 : 4-*dinitrophenylhydrazone*, m. p. 187—189° (Found : C, 59·4; H, 6·1; N, 12·6. $C_{22}H_{26}O_6N_4$ requires C, 59·7; H, 5·9; N, 12·7%), which was very sparingly soluble in alcohol, in contrast to the corresponding hydroxy-derivative. The acetoxydienone and aqueous alcoholic semicarbazide acetate gave a pale yellow solid, m. p. 205—210° (decomp.) after recrystallisation from absolute alcohol, which was sensitive to air, turning deep yellow, and showed a single absorption band $\lambda = 3120$ A., $\varepsilon_{max.} = 22,030$ (Found : N, 12·9. $C_{17}H_{25}O_3N_3$ requires N, 13·2%).

Reaction of the Hydroxydienone (II) *with Methylmagnesium Iodide*.—A solution of the hydroxydienone (II) (2 g.; $\lambda = 3070$ A., $\varepsilon_{max.} = 16,060$) in absolute ether (30 c.c.) was added during 5 minutes to a solution of methylmagnesium iodide (from methyl iodide, 6·4 g.) in absolute ether (50 c.c.) with precipitation of a pale yellow solid. The mixture was refluxed for 20 minutes, cooled, and decomposed with ice-cold ammonium chloride solution. The ethereal layer was washed to neutrality with dilute sulphuric acid and water, dried over alkali-free sodium sulphate, and evaporated. The residual orange-coloured oil showed a main band, λ = 2450 A., $\varepsilon_{max.}$ = 16,400, indicating that the tertiary alcohol had not been dehydrated. A second band, λ = 3080 A., $\varepsilon_{max.}$ = 8200, corresponded to unchanged ketone. Distillation of the product gave a main fraction (0·8 g.), b. p. 140—150°/0·003 mm., as a viscous, pale yellow oil showing a single absorption band, λ = 2815 A., $\varepsilon_{max.}$ = 24,500. This material readily gave a phenylurethane which after one recrystallisation under nitrogen from benzene–petrol and one from acetone–water had m. p. 105—127°, and showed two absorption bands, λ = 2770 A., $\varepsilon_{max.}$ = 38,150; λ = 2390 A., $\varepsilon_{max.}$ = 20,900.* Repeated crystallisation from acetone–water gave fine white needles, m. p. 125—135°, and further recrystallisation from a variety of solvents failed to increase the m. p. or decrease the m. p. range. Exposure to air gave rise to a broadening of the m. p. range. A sample of the phenylurethane was distilled in a high vacuum (furnace temp. 140°), giving a white crystalline sublimate, m. p. 123—132°, showing two absorption bands, λ = 2770 A., $\varepsilon_{max.}$ = 40,780; λ = 2390 A., $\varepsilon_{max.}$ = 23,000.

Attempted Introduction of an Exocyclic Methylene Group (compare Wallach, *loc. cit.*).—Zinc needles (2·6 g.) were covered with absolute benzene (40 c.c.), and redistilled Kahlbaum's ethyl bromoacetate (6·7 g.) added, followed by a solution of the acetoxydienone (5·2 g.; λ = 3070 A., $\varepsilon_{max.}$ = 17,930). Warming under reflux with the slow passage of dry nitrogen through the mixture induced a steady reaction and after 3 hours the deep red liquid was decomposed with dilute sulphuric acid and washed five times with water. Drying over alkali-free sodium sulphate and removal of solvent, finally under vacuum, furnished an orange-coloured oil, which showed a single absorption band, λ = 2460 A., $\varepsilon_{max.}$ = 18,800, consistent with the presence of two exocyclic double bonds. This product was hydrolysed by refluxing for 1 hour in nitrogen with a solution of caustic potash (6 g. pure) in methyl alcohol (100 c.c.). The dark liquid was cooled and diluted with water, and the neutral fraction extracted in ether. The deep red aqueous layer was acidified with dilute sulphuric acid, and the product extracted with ether. After washing to neutrality and drying over alkali-free sodium sulphate, removal of solvent gave a yellow flaky solid, completely soluble in alkali and reprecipitated on acidification. On spectrographic examination the same single band was exhibited, λ = 2470 A., $\varepsilon_{max.}$ = 13,700, consistent with the presence of two conjugated exocyclic double bonds and indicating that the hydroxy-acid had not been dehydrated at this stage. The hydrolysis product was dissolved in acetic anhydride (27 c.c.), and the deep red solution heated in nitrogen for 45 minutes at 95°, followed by refluxing for 20 minutes. Removal of acetic anhydride under reduced pressure, followed by gentle warming in a water-bath under a high vacuum, gave a clear red oil, λ = 2790 A., $\varepsilon_{max.}$ = 11,700 (Found: C, 71·9; H, 8·6. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%). The dehydration product was hydrolysed by refluxing in nitrogen for 40 minutes with a solution of caustic potash (2 g.) in methyl alcohol (60 c.c.). The reaction mixture was titrated with dilute sulphuric acid to a slightly acid reaction, the colour changing from red to yellow. The product was ether-extracted, and the extract washed to neutrality with water and dried over alkali-free sodium sulphate in nitrogen. Removal of solvent gave an orange-coloured oil, which on slow distillation in a vacuum gave a main lower fraction (0·6 g.), b. p. 140—150°/0·002 mm. This material in alcohol showed a single band, λ = 2815 A., $\varepsilon_{max.}$ = 26,400. Treatment of a sample of the above fraction (0·2 g.) in absolute benzene with 3 : 5-dinitrobenzoyl chloride and excess of pyridine yielded a solid 3 : 5-dinitrobenzoate, m. p. 70° after one recrystallisation from alcohol. Hydrolysis of this material (80 mg.) in nitrogen with 2% methyl-alcoholic caustic potash gave a deep-coloured oil, which was distilled on a molecular still under a high vacuum. The temperature bath being maintained at 110°, a first fraction was collected as a pale yellow oil showing a single band in alcohol, λ = 2805 A., $\varepsilon_{max.}$ = 28,000 (Found: C, 81·2; H, 10·2. $C_{15}H_{22}O$ requires C, 82·5; H, 10·2%). The hydroxytriene distilling at 140—155°/0·002 mm. (0·3 g.) gave a solid *phenylurethane* (m. p. 105—126°; from acetone–water after one crystallisation from benzene–light petroleum), which after recrystallisation and high-vacuum distillation had m. p. 123—132° (Found: C, 77·9; H, 8·3. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·1%). This product gave no depression of m. p. with the phenylurethane of the corresponding Grignard product, which it closely resembled spectrographically, exhibiting two bands, λ = 2805 A., $\varepsilon_{max.}$ = 40,440; λ = 2380 A., $\varepsilon_{max.}$ = 24,260, which show little

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* The phenylurethane of *cyclo*hexanol, m. p. 84°, showed two absorption bands, λ = 2720 A., ϵ = 826, and λ = 2380 A., ϵ = 17,380. It is therefore concluded that the position and intensity of absorption maxima near 2800 A., shown by these highly absorbing hydroxytrienes, should approximate to those of their phenylurethanes (see Figs. 1 and 2).

difference from the bands given by the crude phenylurethane, m. p. 105—126° (above), *viz.*, λ = 2805 A., $\varepsilon_{\text{max.}}$ = 42,100; λ = 2400 A., $\varepsilon_{\text{max.}}$ = 24,780.

Reduction of the Hydroxydienone.—The hydroxydienone (2 g.) was refluxed overnight with aluminium *iso*propoxide (22 g.) in *iso*propyl alcohol (100 c.c.), and the bulk of the alcohol removed on the steam-bath. The residue was poured into a solution of caustic potash (22 g.) in methyl alcohol (320 c.c.) and kept for ½ hour. After dilution with water the product was ether-extracted, and the extract washed to neutrality and dried over sodium sulphate. Evaporation of the solvent left a yellow oil, which gave no ketonic reactions and formed hard prisms, m. p. 81—83°, after three recrystallisations from benzene–light petroleum (Found : C, 81·9; H, 10·0. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). 0·96 Active hydrogen atom was found by the Zerewitinoff method. The product showed an absorption spectrum having two strong bands, λ = 2705 A., $\varepsilon_{\text{max.}}$ = 42,100; λ = 2820 A., $\varepsilon_{\text{max.}}$ = 40,900.

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