185. *The Synthesis of Compounds related to the Antirachitic Vitamins. αβ-Di-Δ^1-*cyclo*hexenylethylene.*

By G. Norman Burkhardt and Nathan C. Hindley.

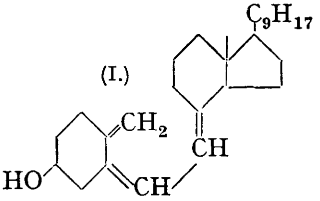
αβ-*Di*-Δ^1-cyclo*hexenylethylene* (VI) has been obtained in good yield by the removal of acetic acid from αβ-*di*-1-*acetoxy*cyclo*hexylethylene* (V), which was prepared from αβ-di-1-hydroxy*cyclo*hexylacetylene (IV) by acetylation and hydrogenation. This series of reactions provides a method for the synthesis of substances containing the conjugated triene system which corresponds with that in the most favoured of the possible structures for tachysterol (cf. II), the immediate photochemical precursor of calciferol (vitamin D_2).

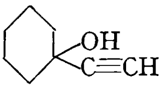
αβ-Di-Δ^1-*cyclo*hexenylethylene (VI) cyclises on heating at 255° and the product is dehydrogenated by selenium to give phenanthrene. This is apparently a new method for the formation of hydrophenanthrene derivatives and may be of particular significance in relation to the photochemical opening of sterol ring systems.

αβ-Di-1-hydroxy*cyclo*hexylethylene [of which (V) is the diacetate] is readily dehydrated by acid reagents, but, instead of forming the triene, it loses one molecule of water with the formation of a five-membered oxide ring in αβ-*di*cyclo*hexylethylene* 1 : 1'-*oxide* (VII).

The preparation of α-1-*hydroxy*-2-*methyl*cyclo*hexyl*-β-1-*hydroxy*cyclo*hexylacetylene*, a typical unsymmetrical acetylenediol, by the condensation of 1-ethinyl*cyclo*hexanol (III) with 2-methyl*cyclo*hexanone was carried out through the Grignard reagent and directly with sodamide. With potassium *tert.*-butoxide as condensing agent, some αβ-*di*-1-*hydroxy*-2-*methyl*cyclo*hexylacetylene* was obtained, indicating fission of the 1-ethinyl*cyclo*hexanol. It is concluded that the condensation of ketones with acetylene derivatives is reversible in presence of potassium *tert.*-butoxide under the conditions used.

Parallel with experiments on the synthesis of substances having the conjugated triene system of calciferol (I) (Aldersley and Burkhardt, this vol., p. 545) we have investigated methods for the preparation of compounds containing the isomeric triene system (II), which Lettré first considered to be present in tachysterol (*Annalen*, 1934, **511**, 287) and which is now favoured amongst the alternative structures for that sterol (*Z. physiol. Chem.*, 1938, **252**, 151). Whatever constitution is assigned to tachysterol, the system (II) is of interest in relation to the photochemical opening of sterol structures and the isomerisation of the products.


(I.)



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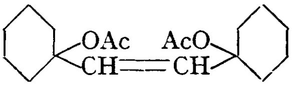

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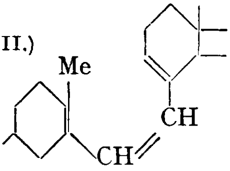
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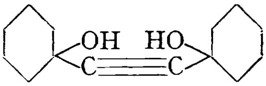

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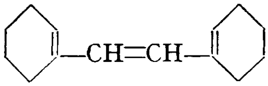
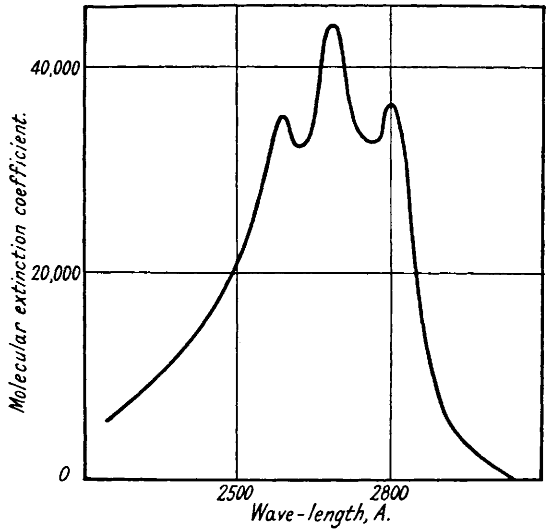


(VI.)

For the preparation of αβ-di-1-hydroxy*cyclo*hexylacetylene (IV), acetylene and *cyclo*hexanone were first condensed in presence of sodium or potassium *tert.*-butoxide to form 1-ethinyl*cyclo*hexanol (III) (compare Pinkney, Nesty, Wiley, and Marvel, *J. Amer. Chem. Soc.*, 1936, **58**, 974). By further condensation of (III) with *cyclo*hexanone in presence of potassium *tert.*-butoxide in boiling ether, (IV) was produced in good yield. Sodamide proved a less satisfactory condensing agent.

By acetylation of the acetylenediol (IV) and partial hydrogenation of the diacetate in contact with a palladium catalyst on calcium carbonate, we obtained αβ-*di*-1-*acetoxy*-cyclo*hexylethylene* (V), which, on heating with copper powder at 145—150°, lost acetic acid to form *di*cyclo*hexenylethylene* (VI), which was obtained as a crystalline solid, m. p. 29°. The diacetate of (IV) and the saturated diacetate obtained from it by complete hydrogenation do not undergo appreciable decomposition in contact with copper powder below 180°.

The absorption spectrum of (VI) is very characteristic (fig.) and shows three strong



*Absorption spectrum of αβ-di-Δ¹-*cyclo*hexenylethylene in alcohol.*

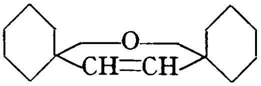
bands: $\lambda = 2595, 2690, 2810$ A.; $\varepsilon_{2690} = 42{,}600$. These bands are to be compared with those shown by tachysterol, $\lambda = 2680, 2800, 2940$ A., $\varepsilon_{2800} = 22{,}900$, and calciferol, $\lambda = 2650$ A., $\varepsilon = 18{,}100$. The absorption spectrum of αβ-di-Δ^1-*cyclo*hexenylacetylene, prepared by the method of Pinkney, Nesty, Pearson, and Marvel (*J. Amer. Chem. Soc.*, 1937, **59**, 2666), showed a similar spectrum but with the three bands not clearly resolved, $\lambda_{max.} = 2640$ A., $\varepsilon_{2640} = 17{,}300$. This material absorbed 3·8 molecular proportions of hydrogen in contact with platinum.

Di*cyclo*hexenylethylene (VI) was heated at 255° under nitrogen and the intensity of absorption fell to $\varepsilon_{2690} = 12{,}600$, a viscous liquid remaining. Dehydrogenation of this by means of selenium at 290—320° gave phenanthrene (hydrocarbon and its picrate showing no depression of m. p. with corresponding authentic specimens). The nature of the cyclised product is being examined further, particularly in view of the interesting possibility that it has a diene structure corresponding to those of ergosterol and lumisterol, in which case this cyclisation may correspond with the reversal of the photochemical opening of the ring structure of lumisterol to give tachysterol (cf. Lettré, *loc. cit.*).

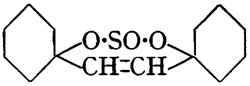
The acetylenediol (IV) was hydrogenated practically quantitatively in contact with a palladium catalyst on calcium carbonate to a single isomeride of αβ-di-1-hydroxy*cyclo*hexylethylene, m. p. 153°, corresponding with that obtained by Salkind (*J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1723) and more recently by Pinkney, Nesty, Pearson, and Marvel (*loc. cit.*). This readily undergoes dehydration with a variety of reagents, but instead of the anticipated triene (VI) an excellent yield was obtained of a neutral liquid, $C_{14}H_{22}O$, b. p. 116—118°/10 mm. This compound did not form a dinitrobenzoate or a phenylurethane and showed no active hydrogen in the Zerewitinoff estimation. It readily took up 2 molecular proportions of hydrogen in contact with a platinum catalyst, but showed no selective absorption. It is considered to be αβ-*di*cyclo*hexylethylene*

1 : 1′-*oxide* (VII) and gives a crystalline *dibromide*, $C_{14}H_{22}OBr_2$, m. p. 96°. The formation of the oxide (VII) resembles that of αβ-dibromo-αβ-di*cyclo*hexylethylene 1 : 1′-oxide, which was obtained by Salkind (*loc. cit.*) by the action of bromine on the acetylenediol (IV), and forms another example of the remarkable ease with which internal ethers are formed from ethylenediols of this type.

The action of thionyl chloride and pyridine on αβ-di-1-hydroxy*cyclo*hexylethylene gives



(VII.)



(VIII.)

a neutral *sulphurous* ester, m. p. 83°, for which the formula (VIII) is suggested. It is hydrolysed to the original diol by alkali.

The preparation of α-(2-methyl*cyclo*hexenyl)-β-*cyclo*hexenylethylene and αβ-di-2-methyl*cyclo*hexenylethylene by similar methods is under investigation. A mixture of stereoisomerides of α-1-*hydroxy*-2-*methyl*cyclo*hexyl*-β-1-*hydroxy*cyclo*hexylacetylene* was obtained by the Grignard method (Pinkney, Nesty, Wiley, and Marvel, *loc. cit.*) and a similar mixture was obtained by the two-stage method outlined above with sodamide as condensing agent, methyl*cyclo*hexanone being used in the first stage and *cyclo*hexanone in the second and vice versa. From all three products the same isomeride of α-1-hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene, m. p. 97·5°, was isolated by crystallisation. When potassium *tert.*-butoxide was used as condensing agent, however, the mixture of acetylenediols produced had a higher melting point and from this αβ-*di*-1-*hydroxy*-2-*methyl*cyclo*hexylacetylene*, m. p. 149°, was isolated, and compared with that obtained by the condensation of 2-methyl*cyclo*hexanone with acetylene with either sodamide or potassium *tert.*-butoxide as condensing agent. This redistribution of the ketonic components used in the two stages of this synthesis suggests that the combination of ketones with acetylene derivatives, in presence of basic catalysts, is a reversible reaction resembling cyanohydrin formation in certain respects. The synthetic reaction presumably takes place between the ketone and the ion of the acetylene derivative, notwithstanding the common procedure of treating the sodio-derivative of the ketone with acetylene.

EXPERIMENTAL.

αβ-*Di*-1-*hydroxy*cyclo*hexylacetylene.*—1-Ethinyl*cyclo*hexanol (62 g.), prepared from *cyclo*hexanone and acetylene as described by Pinkney, Nesty, Wiley, and Marvel (*J. Amer. Chem. Soc.*, 1936, **58**, 974), with *cyclo*hexanone (53 c.c.) in anhydrous ether (100 c.c.) was added during 1 hour to a boiling suspension of potassium *tert.*-butoxide (from potassium, 20 g., and anhydrous *tert.*-butyl alcohol, 350 c.c., in ether, 300 c.c.). At half time the reaction mixture was clear and yellow, but solid was again precipitated before the addition was complete. After refluxing for a further 6 hours, the product was decomposed with dilute sulphuric acid, and the ethereal layer washed with water and dried. Removal of solvent left a clear yellow viscous oil, which gave αβ-di-1-hydroxy*cyclo*hexylacetylene, m. p. 109°, on treatment with benzene–light petroleum and recrystallisation from this solvent (yield, 70%).

αβ-*Di*-1-*acetoxy*cyclo*hexylacetylene.*—This was obtained by acetylating the acetylenediol (Rupe, Messner, and Kambli, *Helv. Chim. Acta*, 1928, **11**, 449) and purified by distillation (130—135°/0·5 mm.) and recrystallisation from light petroleum; m. p. 47° (Found: C, 70·7; H, 8·7. Calc. for $C_{18}H_{26}O_4$: C, 70·6; H, 8·6%).

Hydrogenation.—The diacetate (60 g.) was hydrogenated in methyl alcohol with a palladium catalyst on calcium carbonate until 1 mol. of hydrogen had been absorbed. Control experiments indicated a marked fall in the rate of absorption after this. Removal of the catalyst and solvent, followed by distillation, gave a nearly quantitative yield of αβ-*di*-1-*acetoxy*cyclo*hexylethylene* as a colourless oil, b. p. 143—145°/1 mm. (Found: C, 70·3; H, 9·3. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·2%). Hydrolysis of a small portion of this product with alcoholic potassium hydroxide gave αβ-di-1-hydroxy*cyclo*hexylethylene, m. p. 153° (90% of the theoretical yield).

αβ-*Di*-Δ^1-cyclo*hexenylethylene.*—αβ-Di-1-acetoxy*cyclo*hexylethylene (58 g.) was heated with copper-bronze (10 g.) for 2 hours at 145—150°/30 mm., and the acetic acid formed (80% of theoretical) distilled off. The dark reddish liquid residue was taken up in ether, filtered from copper, and washed with dilute sodium bicarbonate solution and water. After drying and removal of solvent the residue was fractionated at 1 mm., and gave a colourless main fraction (29 g.), b. p. 110—115°/1 mm. Recrystallisation from methyl alcohol, with cooling to − 15°, gave the triene as a crystalline solid, m. p. 29° (Found : C, 89·6; H, 10·5. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%). A quantitative hydrogenation with a platinum oxide catalyst in acetic acid gave a value corresponding to 3·01 double bonds. A very characteristic triplet absorption spectrum (fig.) is obtained. Intensity measurements also showed that the liquid distillate before recrystallisation contained 80% of this absorbing component. αβ-*Di*-Δ^1-cyclo*hexenylethylene* loses its crystalline form in air and changes to a colourless sticky oil; it instantaneously absorbs bromine, giving a dark oily product which has not been obtained crystalline.

Cyclisation. αβ-Di*cyclo*hexenylethylene (5 g.), heated at 255° for 4 hours in nitrogen, gave a viscous, pale yellow oil showing two maxima in its absorption spectrum, $\lambda = 2600$—2700 and 2800 A., $\varepsilon_{2690} = 12{,}600$ (cf. $\varepsilon_{2690} = 42{,}600$ originally). No crystalline material was obtained by treatment with solvents. Without further purification the product (4 g.) was dehydrogenated with selenium (9 g.) for 48 hours at 290—320°. Ether extracted a dark oil, which, on heating at 70°/0·008 mm. for 4 hours, gave a white crystalline sublimate, m. p. 97°. Recrystallised from alcohol, this gave no depression in m. p. with an authentic sample of phenanthrene, nor did the corresponding picrates, m. p. 143°.

Dehydration of αβ-*Di*-1-*hydroxy*cyclo*hexylethylene.*—This was brought about by refluxing the diol (19·5 g.) for 2 hours with saturated oxalic acid solution (200 c.c.). The product was extracted with ether, and the extract washed with sodium bicarbonate solution and dried. After removal of solvent, distillation of the residue at 10 mm. gave a liquid (17·4 g.), b. p. 116—118°/10 mm. (Found : C, 81·2; H, 10·8. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%) (yield, 97% of the theoretical). Quantitative hydrogenation gave a value corresponding to 2·0 double bonds, but the compound exhibited no selective absorption in the ultra-violet region, nor would it condense with maleic anhydride. Attempts to prepare a 3 : 5-dinitrobenzoate and a phenylurethane were unsuccessful and a Zerewitinoff determination gave a zero value for the percentage of active hydrogen. We conclude that this is αβ-*di*cyclo*hexylethylene* 1 : 1′-*oxide* (VII), the oxide ring opening on hydrogenation. By the action of bromine in chloroform or of bromine water, a solid dibromide was obtained, m. p. 96° (from alcohol), which is considered to be αβ-*dibromo*-αβ-*di*cyclo*hexylethane* 1 : 1′-*oxide* (Found : C, 45·8; H, 6·3; Br, 43·9. $C_{14}H_{22}OBr_2$ requires C, 45·9; H, 6·1; Br, 43·7%). The addition in chloroform takes place very readily in sunlight. Dehydration of αβ-di-1-hydroxy*cyclo*hexylethylene was not effected by distillation at atmospheric pressure either alone or with alumina or thoria. Treatment with potassium hydrogen sulphate at 140°, or with catalytic amounts of iodine at 160° or with phosphorus tribromide in pyridine all yielded the same mono-dehydration product as was obtained with oxalic acid, characterised as the dibromide.

Action of thionyl chloride. Thionyl chloride (7·2 c.c.) was added to αβ-di-1-hydroxy*cyclo*hexylethylene (10 g.) in anhydrous ether and excess of dry pyridine with stirring at 0°. After standing overnight, ice-water was added, the mixture extracted with ether, and the extract washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution, and water. Removal of solvent and recrystallisation of the residue gave a white crystalline product (6 g.), m. p. 83°. On alkaline hydrolysis it gave αβ-di-1-hydroxy*cyclo*hexylethylene, m. p. 153°. It is considered to be the neutral cyclic *sulphurous* ester (VIII) [Found : S, 11·9; *M* (Rieche method), 268. $C_{14}H_{22}O_3S$ requires S, 11·9%; *M*, 270].

Homologues of αβ-*Di*-1-*hydroxy*cyclo*hexylacetylene.*—2-Methyl-1-ethinyl*cyclo*hexanol was prepared by the method of Cook and Lawrence (this vol., p. 58) and isolated by steam distillation. The product, b. p. 69—71°/10 mm., solidified at room temperature and crystallised from light petroleum in hard needles, m. p. 57° (Found : C, 78·0; H, 10·3. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·2%). The non-steam-volatile portion of the reaction product distilled at 181—183°/8 mm. and solidified on cooling, m. p. 108—125°. This solid was presumably a mixture of isomers of αβ-*di*-1-*hydroxy*-2-*methyl*cyclo*hexylacetylene*, as only after several recrystallisations from petrol and dilute methyl alcohol was constant-melting material obtained. From the latter solvent fine white needles were obtained, m. p. 149° (Found : C, 76·4; H, 10·4. $C_{16}H_{26}O_2$ requires C, 76·75; H, 10·5%).

For comparison this isomer was also isolated from the non-steam-volatile portion of the reaction product obtained by condensing 2-methyl-1-ethinyl*cyclo*hexanol with 2-methyl*cyclo*hexanone, sodamide being used as condensing agent as described for α-1-hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene.

When 1-ethinyl*cyclo*hexanol was condensed with 2-methyl*cyclo*hexanone, potassium *tert.*-butoxide being used as condensing agent, under the conditions used for the preparation of αβ-di-1-hydroxy*cyclo*hexylacetylene, the non-steam-volatile portion of the product had b. p. 179—182°/10 mm. and melted at 75—86°. Repeated recrystallisation gave fine needles, m. p. 149°, not depressed by αβ-di-1-hydroxy-2-methyl*cyclo*hexylacetylene obtained by the above unequivocal methods (Found: C, 76·9; H, 10·3. Calc. for $C_{16}H_{26}O_2$: C, 76·75; H, 10·5%). A similar crude product and the same pure substance were obtained by condensing 2-methyl-1-ethinyl*cyclo*hexanol with *cyclo*hexanone under similar conditions. The crude product presumably also contains α-1-hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene, the anticipated product and possibly αβ-di-1-hydroxy*cyclo*hexylacetylene produced by redistribution of the *cyclo*hexanone liberated by the reversal of the acetylene–ketone condensation.

α-1-*Hydroxy*-2-*methyl*cyclo*hexyl*-β-1-*hydroxy*cyclo*hexylacetylene*.—2-Methyl*cyclo*hexanone (40 c.c.) in anhydrous ether (60 c.c.) was added during ½ hour to a stirred suspension of finely ground sodamide (18 g.) in anhydrous ether (60 c.c.) at 0°. After a further 2 hours 1-ethinyl*cyclo*hexanol (40 g.) in anhydrous ether (50 c.c.) was added during 3 hours, and stirring continued for 60 hours at 0°. The deep orange reaction mixture was decomposed with ice and acidified with dilute acid. The ethereal layer was washed with water, the solvent removed, and the residue steam-distilled. The reddish oil which remained was taken up in ether and dried, and the solvent evaporated. On fractionation at 15 mm., 90% of the liquid distilled at 186—189° (32 g.; 42% of the theoretical) and solidified on cooling. Trituration with light petroleum (b. p. 40—60°) gave a white solid, m. p. 70—78°. Constant-melting material was obtained only after ten recrystallisations of the product from light petroleum (b. p. 60—80°). The *isomeride* of α-1-hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene thus obtained crystallised in feathery needles, m. p. 97·5° (Found: C, 76·0; H, 9·9. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

Condensation of molecular quantities of 2-methyl-1-ethinyl*cyclo*hexanol and *cyclo*hexanone under analogous conditions gave a 13% yield of non-steam-volatile material distilling at 186—188°/15 mm. and melting at 70—78°. Repeated crystallisation from petrol gave feathery needles, m. p. 97·5°, showing no depression with α-1-hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene isolated in the previous condensation.

α-1-Hydroxy-2-methyl*cyclo*hexyl-β-1-hydroxy*cyclo*hexylacetylene was also obtained through the Grignard derivative of 1-ethinyl*cyclo*hexanol by the method of Pinkney, Nesty, Wiley, and Marvel (*loc. cit.*). The non-steam-volatile portion of the product distilled at 179—182°/11 mm. (Found: C, 76·3; H, 10·2. Calc. for $C_{15}H_{24}O_2$: C, 76·2; H, 10·2%) and melted, after one recrystallisation from benzene–petrol, at 76—84°. After 17 recrystallisations, feathery needles were isolated, m. p. 97·5°, not depressed by the corresponding products obtained previously.

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