Studies in the Vitamin D Field. Part I. Synthesis of Trienes containing the Tachysterol Chromophore.

By E. A. Braude and O. H. Wheeler.

[Reprint Order No. 5729.]

*cyclo*Hexylidene- and 2′-methyl*cyclo*hexylidene-acetaldehyde have been prepared by a number of methods. Reaction of the aldehydes with *cyclo*hexenyl-lithium, followed by anionotropic rearrangement and dehydration, gave the trienes (IV*a* and *b*). These model experiments adumbrate a synthetical route to tachysterol derivatives.

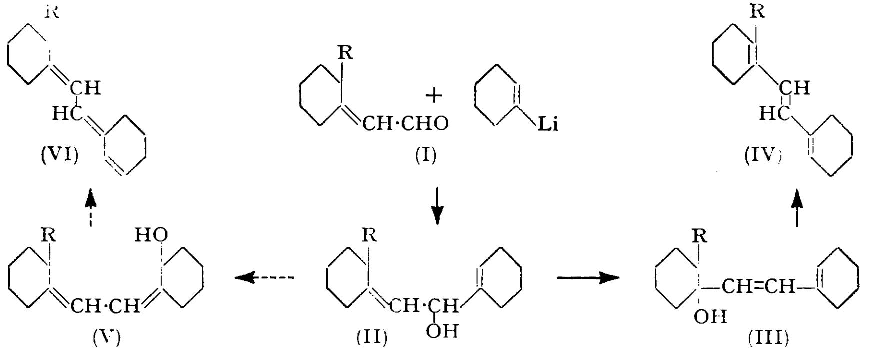
The structures and light-absorption properties of tachysterol and calciferol are discussed.

Although the chemistry of calciferol and its congeners was first elucidated some twenty years ago, the D group of vitamins is exceptional in that no synthesis of practical value of any of its members has yet been effected. In a formal sense, the total synthesis of calciferol has recently been achieved by way of methyl 3-oxo*ætio*cholatrienate and cholestanol (Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223) and by way of *ætioallo*bilianic acid and cholestanol (Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, **361**) but these schemes involve some 50 steps and their significance lies primarily in the methodology of steroid synthesis rather than in the vitamin D field. A few attempts aimed at a direct synthesis of calciferol have been recorded (Burkhardt *et al.*, *J.*, 1938, 545, 987; 1940, 10; Milas and Alderson, *J. Amer. Chem. Soc.*, 1939, **61**, 2534; Dimroth and Jonsson, *Ber.*, 1938, **71**, 1333, 1346, 2658; Dimroth, *Ber.*, 1943, **76**, 634; Raphael and Sondheimer, *J.*, 1950, 3185) but, compared with the enormous efforts expended on other similar problems, the extent of such investigations has been relatively limited. This problem merits further attention, not only in view of the great physiological importance of calciferol, but also because the synthetical difficulties presented by the tricyclic system appear, at least on paper, rather less formidable than those posed by the tetracyclic steroid skeleton. Furthermore, D vitamins are not only generated from steroids, but can also be transformed back into steroids with considerable ease (see Fieser and Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949). In addition, there are still certain stereochemical and other features of vitamin D and its progenitors which have not been completely clarified.

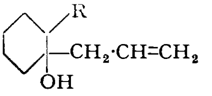
The present series will describe some new approaches to the synthesis of vitamin D and related compounds. Although we are far from having achieved the final goal, an interim report is now submitted since the problem has recently been taken up in several other laboratories, particularly by Inhoffen and his co-workers who have effected a partial synthesis of an isomer of calciferol designated as *iso*tachysterol and of its methyl ether (*Chem. Ber.*, 1954, **87**, 1, 187; cf. Inhoffen and Brückner, *Fortschr. Chem. org. Naturstoffe*, 1954, **11**, 83).

This and the following paper deal with experiments in which new routes to simple analogues containing the chromophoric systems of calciferol and tachysterol, respectively, have been explored. Since tachysterol is believed to be the immediate precursor of calciferol in the photochemical preparation of the latter from ergosterol, methods leading to either of these two systems are equally of interest. In the present work, the tachysterol analogues (IV*a*, *b*) have been synthesised by the addition of *cyclo*hexenyl-lithium (Braude and Coles, *J.*, 1950, 2014; Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1414) to *cyclo*hexylidene- and 2′-methyl*cyclo*hexylidene-acetaldehyde (I*a*, *b*), to give the diallylic alcohols (II*a*, *b*), followed by anionotropic rearrangement to the conjugated isomers (III*a*, *b*) and dehydration.

The aldehyde (I*b*) has not previously been described, but the parent compound (I*a*) has been prepared, though in low yield, by the ozonisation of 1-allyl*cyclo*hexanol (VII*a*) (Burkhardt *et al.*, *locc. cit.*) as well as from 1-ethynyl*cyclo*hexanol (Dimroth, *Ber.*, 1938, **71**, 1333; Chaco and Iyer, *Current Sci.*, 1953, **22**, 240). Attempts to improve the conversion of 1-allyl*cyclo*hexanol into the aldehyde met with little success; for example, hydroxylation with performic acid to give the triol (VIII*a*) followed by fission with periodic acid and dehydration of the resulting hydroxy-aldehyde (IX*a*) with iodine furnished even lower overall yields and the product was contaminated with the unconjugated isomer (X*a*). Fortunately, the direct conversion of 1-allyl-2-methyl*cyclo*hexanol (VII*b*), obtained from 2-methyl*cyclo*hexanone and allylmagnesium chloride, into 2′-methyl*cyclo*hexylideneacetaldehyde (I*b*) by ozonisation proceeds in considerably better yield (70%) than with the lower homologue (35%). The product was again contaminated with the unconjugated isomer (X*b*) as well as with the hydroxy-aldehyde (IX*b*) which could, however, be largely separated by careful fractionation. 2′-Methyl*cyclo*hexylideneacetaldehyde (I*b*), like its lower homologue (I*a*) (cf. Dimroth, *loc. cit.*), is rather unstable and even the best fractions showed an oxygen-content in excess of that calculated. The aldehyde was characterised by a semicarbazone and a 2 : 4-dinitrophenylhydrazone, the light absorption properties of which confirmed the absence of unconjugated components in the purified aldehyde.



(*a*, R = H; *b*. R = Me; throughout this paper



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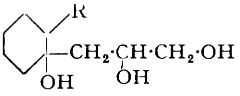

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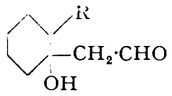

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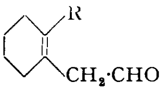
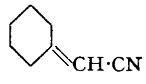


(X)

Some possible alternative methods for the preparation of the aldehydes (I) were also investigated. The first envisaged the partial reduction of *cyclo*hexylideneacetonitrile (XI) which is readily accessible from *cyclo*hexylideneacetic acid (Kandiah and Linstead, *J.*, 1929, 2139; Cope *et al.*, *Org. Synth.*, 1951, **31**, 25), to the imine (XII), followed by hydrolysis. Partial reductions of this type have been successfully effected with several aliphatic nitriles by means of lithium aluminium hydride (Henne, Pelley, and Alm, *J. Amer. Chem. Soc.*, 1950, **72**, 3370; Yandik and Larsen, *ibid.*, 1951, **73**, 3534; Smith and Rogier, *ibid.*, p. 4048; Lowy, *ibid.*, 1952, **74**, 1354) as well as with aromatic nitriles (Braude and Gore, unpublished work). In the present case, however, reduction of the ethylenic bond occurred in preference to that of the cyano-group and *cyclo*hexylacetonitrile (XIII) was obtained, identified by hydrolysis to *cyclo*hexylacetic acid. Presumably, 1 : 4-addition to the C=C–C≡N system is involved, analogous to that which has been observed with ethylenic ketones (Lutz and Hinkley, *ibid.*, 1950, **72**, 4091; cf. Hochstein and Brown, *ibid.*, 1948, **70**, 3484), vinylacetylenes (Bharucha and Weedon, *J.*, 1953, 1584; Bates, Jones, and Whiting, *J.*, 1954, 1854), and other conjugated systems. 1 : 4-Reduction of conjugated ethylenic nitriles by lithium aluminium hydride appears to be the rule when a deficiency of hydride is employed; thus, 1-cyano*cyclo*hexene gave 1-cyano*cyclo*hexane. By contrast, *cyclo*hexenylacetonitrile in which the two unsaturated groups are not conjugated, is reduced to the ethylenic amine in good yield (Schnider and Hellerbach, *Helv. Chim. Acta*, 1950, **33**, 1437).

A second method, which is more successful, is based on 1-ethoxyethynyl*cyclo*hexanol

(XIV) and is analogous to that previously used for other ethylenic aldehydes (Arens and van Dorp, *Rec. Trav. chim.*, 1948, **67**, 973; 1951, **70**, 289; Heilbron, Jones, *et al.*, *J.*, 1949, 1823; Petrov *et al.*, *J.*, 1950, 2393; 1952, 161, 3358; Plattner *et al.*, *Helv. Chim. Acta*, 1950, **33**, 370, 1088; Schinz *et al.*, *ibid.*, 1951, **34**, 2009; 1952, **35**, 1469; Bohlmann, *Chem. Ber.*, 1951, **84**, 545; Sarrett *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 1715). The acetylenic alcohol (XIV) was obtained in good yield by the addition of ethoxyethynylmagnesium bromide to *cyclo*hexanone. Partial catalytic reduction in dioxan furnished the ethylenic alcohol (XV) which, without isolation, was treated with sulphuric acid and readily underwent anionotropic rearrangement and loss of ethanol to give *cyclo*hexylideneacetaldehyde (I*a*). When the acetylenic alcohol (XIV) was dissolved in methanol instead of dioxan, an exothermic reaction occurred and methyl *cyclo*hexylideneacetate (XVII; R = Me) was formed. This undoubtedly involves initial addition of methanol to the triple bond to give (XVI), followed by (allylic) rearrangement and elimination of ethanol; direct (propargylic) rearrangement of (XIV) to the ethyl ester (XVII; R = Et) takes place only under quite strongly acid conditions (cf. Braude, *Quart. Reviews*, 1950, **4**, 404).



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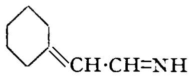

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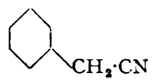

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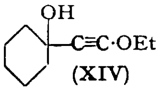

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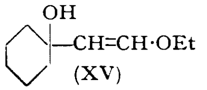

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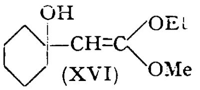

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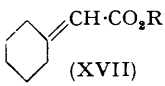
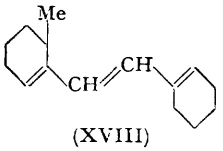


(XVII)

Addition of *cyclo*hexenyl-lithium to *cyclo*hexylideneacetaldehyde gave the alcohol (II*a*) in good yield. Anionotropic rearrangement was readily effected by dilute hydrochloric acid; by analogy with earlier work (Braude and Coles, *loc. cit.*; Braude and Timmons, *J.*, 1950, 2006) the isomerisation was expected to yield the conjugated tertiary alcohol (III*a*) rather than the secondary isomer (V*a*). This was confirmed by the ultra-violet light absorption properties ($\lambda_{max.}$ 2360 Å, ε 18,000) which correspond to those of tri- rather than of a tetra-alkylated diene and by the formation of a well-crystallised adduct with maleic anhydride; the diene system in (V*a*) would be sterically prevented from undergoing a Diels–Alder reaction. Dehydration of the alcohol by distillation from potassium hydrogen sulphate afforded 1 : 2-di*cyclo*hexenylethylene (IV*a*) as a liquid showing characteristic triple-peak absorption in the 2700-Å region (see Table). Like other hydrocarbons of this type (for references, see p. 320) and like tachysterol itself (Grundmann, *Z. physiol. Chem.*, 1938, **252**, 151), the triene (IV*a*) avidly absorbs oxygen and was not obtained analytically pure, but its light-absorption properties are in good agreement, when allowance is made for the oxygen content, with those recorded by Burkhardt and Hindley (*J.*, 1938, 987). These workers prepared the triene by the pyrolysis of 1 : 2-di-1′-acetoxy*cyclo*hexylethylene, which they obtained in turn by partial catalytic hydrogenation and acetylation of di-1′-hydroxy*cyclo*hexylacetylene. This method might be expected to lead to a triene with *cis*-configuration at the central double bond, but it must be presumed that inversion took place during pyrolysis since the high intensity of the ultra-violet absorption indicates a *trans*-configuration (Koch, *Chem. and Ind.*, 1942, **61**, 273; cf. Braude and Waight, " Progress in Stereochemistry," Vol. 1, Chapter 4, Butterworths, London, 1954). The *trans*-configuration is also to be expected for the product obtained in the present work, since anionotropic rearrangement is known to lead normally to the less sterically hindered arrangement at the new double bond (Braude and Coles, *J.*, 1951, 2085).

Addition of *cyclo*hexenyl-lithium to 2′-methyl*cyclo*hexylideneacetaldehyde and the rearrangement of the alcohol (II*b*) proceeded readily and in a similar manner. In contrast to the lower homologue (III*a*), however, the isomerisation product (III*b*) did not form a Diels–Alder adduct with maleic anhydride. Dehydration of the alcohol (III*b*) furnished a triene which again could not be obtained free from oxygen-containing material. The ultra-violet absorption of the triene component (main maximum at 2710 Å, ε 40,000; see Table) was somewhat less well resolved. but otherwise closely resembled that of the lower homologue (IV*a*) (main maximum at 2690 Å, ε 42,600) and the triene is assigned the structure (IV*b*). The small bathochromic displacement of 20 Å due to the additional methyl substituent in (IV*b*) is not unusual for triene systems (see Table) in contrast to the shifts of about 50 Å normally observed in dienes (Booker, Evans, and Gillam, *J.*, 1940, **1453**; Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72). Dehydration of (III*b*) would be expected to give (IV*b*) in preference to the less highly hyperconjugated 6′-methyldi*cyclo*hex-1′-enylethylene (XVIII), though the latter is not excluded. The maximal absorption of (IV*b*) lies at slightly shorter wave-lengths than that of the similarly (penta)substituted triene (XIX) ($\lambda_{max.}$ 2820 Å) first prepared by Dimroth (*loc. cit.*); the difference may be ascribed to the presence in (XIX) of two double bonds in exocyclic positions, known to have a small bathochromic effect (Woodward, *loc. cit.*).



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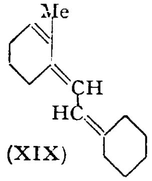


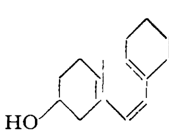
(XIX)

Ultra-violet light absorption of conjugated trienes.

	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$
Hexatriene [1]	2475 2575 2675	68 79 56
2-Methylhexatriene [2]	2480 2570 2670	>21 >28 >22
2 : 5-Dimethylhexatriene [2]	2510 2610 2710	37 46 34
2-Methylhepta-1 : 3 : 5-triene [3]	2510 2610 2710	>29 >41 >31
1-*cyclo*Hexenylbutadiene [4]	2550 2650 2750	32 43 34
(IV*a*) [5, 6]	2595 2690 2810	35 42 37
(IV*b*) [6]	2710 2810	34 34
(XIX) [6]	2820	20
Tachysterol [7]	2640 2800 2940	18 23 20
" *iso*Tachysterol " [8]	2800 2900 3020	31 41 31

[1] Woods and Schwartzman, *J. Amer. Chem. Soc.*, 1948, **70**, 3394 (in *cyclo*hexane). [2] Braude and Timmons, *J.*, 1950, 2006 (in EtOH). [3] Kharasch, Nudenberg, and Sternfeld, *J. Amer. Chem. Soc.*, 1940, **62**, 2034 (solvent not stated). [4] Bates, Jones, and Whiting, *J.*, 1954, 1854. [5] Burkhardt and Hindley, *J.*, 1938, 987 (in EtOH). [6] Present work (in EtOH); cf. Dimroth, *Ber.*, 1938, **71**, 1333. [7] Windaus, Werder, and Lüttringhaus, *Annalen*, 1932, **499**, 188 (in C_6H_6). [8] Inhoffen, Brückner, and Gründel, *Chem. Ber.*, 1954, **87**, 1 (in Et_2O).

The method employed here for the preparation of the triene (IV*b*) adumbrates a synthetical route to tachysterol derivatives, provided analogous reactions can be carried out with 5′-hydroxy-2′-methyl*cyclo*hexylideneacetaldehyde and the appropriate ring CD components. Tachysterol has generally been formulated as containing a *cis*-ethylenic bond (XX), but most of the degradative evidence (Windaus, Werder, and Lüttringhaus, *Annalen*, 1932, **499**, 188; Grundmann, *loc. cit.*; von Werder, *Z. physiol. Chem.*, 1939, **260**, 119) is equally compatible with a *cis*- or a *trans*-structure (XXI). Actually there are two items of evidence which strongly favour a *trans*-configuration; first, the ready Diels–Alder reaction with citraconic anhydride, which is characteristic of tachysterol, and, secondly, the reported conversion of calciferol into tachysterol (Meunier and Thibaudet, *Compt. rend.*, 1946, **223**, 173; cf. Velluz, Petit, and Amiard, *Bull. Soc. chim.*, 1948, 1115) by successive iodination and de-iodination under conditions unlikely to lead to a *cis*-bond. Against these must be considered the relatively low intensity of the triene absorption reported for tachysterol ($\lambda_{max.}$ 2640 Å, ε 18,000; $\lambda_{max.}$ 2800, ε 23,000, $\lambda_{infl.}$ 2940 Å, ε 20,000; Windaus *et al.*, *loc. cit.*) which has, in fact, been adduced in support of the *cis*-configuration (Koch, *loc. cit.*). The spectral data were, however, obtained with a non-crystalline material for which no analytical figures were given, and in view of the exceptional ease of oxidation of tachysterol the low intensity might be due to the presence of less-absorbing products; as it happens, the ε value is almost identical with that obtained here for the partly oxidised triene (IV*b*) (see p. 323).



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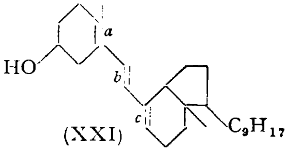

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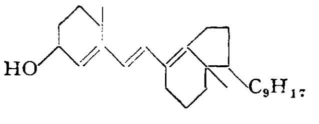

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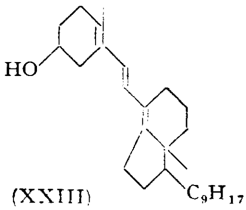
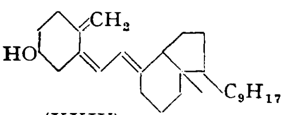


(XXIII)

Nevertheless, structure (XXI) also seems unsatisfactory, for two reasons. First, it has recently been shown by Stork, Wagle, and Mukherji (*J. Amer. Chem. Soc.*, 1953, **75**, 3197) that the diene system in 1-methyl-2-vinyl*cyclo*hexene, unlike that in 1-vinyl*cyclo*hexene, is unreactive towards maleic anhydride. If the analogy with 1-methyl-2-vinyl*cyclo*hexene is sound, the diene system *ab* in (XXI) should be unreactive in Diels–Alder addition, and certainly less reactive than the diene system *bc*, contrary to fact. Secondly, structure (XXI) does not explain the small, but definite, bathochromic shift of the maxima of tachysterol with respect to those shown by the synthetic trienes (IV*a*) and (IV*b*). (The long-wave-length inflection of 2940 Å recorded for tachysterol *in benzene* is very faint and part of the bathochromic shift may be apparent rather than real, arising simply from a change in the relative heights of the subsidiary peaks which undoubtedly represent partly resolved vibrational structure of the same electronic band.) All the facts appear, however, to be accommodated by structure (XXII) which contains a diene system analogous to that of 6-methyl-1-vinyl*cyclo*hexene, known to be highly reactive towards dienophiles (Stork *et al.*, *loc. cit.*), and a double bond in a bridgehead position, known to produce a small bathochromic shift. Structure (XXII) is also acceptable in relation to that (XXIII) assigned by Inhoffen *et al.* (*loc. cit.*) to " *iso*tachysterol " ($\lambda_{max.}$ 2900 Å), the further bathochromic shift being ascribed to the movement of the double bond in ring A to the more highly alkylated (and hyperconjugated) position.

The considerable difference in the wave-lengths of the characteristic absorption of tachysterol-type and calciferol-type systems also deserves brief comment. Inhoffen *et al.* (*loc. cit.*) have ascribed this to " strong steric hindrance " in the latter. The *X*-ray diffraction work of Crowfoot and Dunitz (*Nature*, 1948, **162**, 608) makes it probable, however, that calciferol exists in the extended *s-trans*-configuration (XXIV) rather than in the *s-cis*-configuration, and comparison with simpler systems (cf. Braude and Waight, *loc. cit.*, and references there cited) suggests that the deviation of the triene chromophore in (XXIV) from uniplanarity, though sufficient to decrease ε, would not result in a marked hypsochromic shift. The location of the maximum of calciferol at shorter wave-length ($\lambda_{max.}$ 2650 Å, ε 18,000) may be explained, however, at least in part, by the presence of a *cisoid* diene grouping and the consequent reduction in chromophore length (cf. Braude and Waight, *loc. cit.*); a similar, though, as would be expected, smaller displacement is found in



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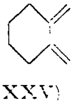

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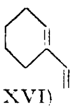

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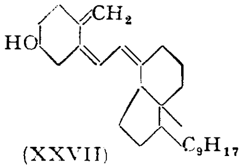

(XXVII)

comparing the *cisoid* diene (XXV) ($\lambda_{\text{max.}}$ 2200 Å; Bailey and Golden, *J. Amer. Chem. Soc.*, 1953, **75**, 4780) and the *transoid* diene (XXVI) ($\lambda_{\text{max.}}$ 2300 Å; Gillam *et al., loc. cit.*). The calciferol isomer " precalciferol " discovered by Velluz, Amiard, and Petit (*Bull. Soc. chim.*, 1948, 1115; 1949, 501), which is reported to show absorption of identical wavelength location with, but lower absorption intensity ($\lambda_{\text{max.}}$ 2650 Å, ε 9000) than, calciferol, may be the less stable stereoisomer (XXVII); the lower ε can be ascribed to steric hindrance between the hydrogen atoms attached to $C_{(6)}$ and $C_{(15)}$.

EXPERIMENTAL

Analytical data were determined in the microanalytical (Mr. F. H. Oliver and staff) and spectrographic (Mrs. I. A. Boston) laboratories of this Department. Oxygen determinations were carried out by Unterzaucher's method (*Ber.*, 1940, **73**, 391).

cyclo*Hexylideneacetaldehyde* (I*a*).—*First method* (cf. Aldersley *et al.*, *J.*, 1940, 10). *cyclo*Hexanone (100 g.) and allyl chloride (80 g.) in ether (500 ml.) were added during 3 hr. to finely divided magnesium (24 g.) and iodine (0·1 g.) in ether, with rapid stirring and external cooling so as to maintain gentle refluxing. After a further hour, excess of ice-cold 2N-sulphuric acid was added, the ether layer was separated, and the aqueous layer extracted with ether. The combined ethereal solutions were washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and fractionated, giving some unchanged *cyclo*hexanone and 1-allyl*cyclo*hexanol (69·5 g., 49%), b. p. 62—64°/3 mm., n_{D}^{24} 1·4730.

1-Allyl*cyclo*hexanol (50 g.) in acetic acid (50 ml.) was treated with ozone at 0° until absorption ceased (15 hr.). After addition of zinc dust (5 g.), the mixture was heated on the steam-bath for 20 min. and then poured into water (100 ml.) and extracted with ether. The ethereal solution was washed with sodium carbonate solution and water until nearly neutral, dried (Na_2SO_4), and fractionated, giving two main products. The first (b. p. 90°/10 mm.) was *cyclo*hexylideneacetaldehyde (14 g., 32%), n_{D}^{20} 1·5005, $\lambda_{\text{max.}}$ 2310 Å, ε 15,000 in hexane. It was characterised by the semicarbazone, m. p. 207—208° (from ethanol), $\lambda_{\text{max.}}$ 2740 Å, ε 28,000 in EtOH (Aldersley *et al., loc. cit.*, give m. p. 205°, $\lambda_{\text{max.}}$ 2720 Å, ε 28,000; Dimroth, *Ber.*, 1938, **71**, 1333, gives m. p. 210°, $\lambda_{\text{max.}}$ 2720 Å, ε 32,000), and by the 2 : 4-*dinitrophenylhydrazone*, which was chromatographed on alumina in benzene and after crystallisation from ethyl acetate had m. p. 200°, $\lambda_{\text{max.}}$ 3870 Å, ε 27,400 in $CHCl_3$ (Found : C, 55·5; H, 5·5; N, 18·2. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3; N, 18·4%). The second product was 1-*hydroxy*cyclo*hexylacetaldehyde* (5 g., 18%), a viscous oil, b. p. 100°/0·5 mm., n_{D}^{20} 1·4828 (Found : C, 67·1; H, 10·1. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). It was characterised by a *semicarbazone*, prepared in, and crystallised from, aqueous solution, and having m. p. 165° (Found : N, 21·3. $C_9H_{17}O_2N_3$ requires N, 21·1%).

When the decomposition of the ozonide was conducted by addition of the acetic acid solution to boiling water (100 ml.) and zinc dust (4 g.), instead of as above, mainly the hydroxy-aldehyde was obtained.

Second method. 1-Allyl*cyclo*hexanol (14 g.) was added to formic acid (98%; 60 ml.) and hydrogen peroxide (30%; 12 ml.), the temperature being kept at 25—30° by external cooling. After being kept overnight at room temperature, the solution was concentrated under reduced pressure and the residue was treated with sodium hydroxide (8 g.) in water (20 ml.) for 15 min. at 50°. The resulting solution was saturated with sodium chloride and extracted with chloroform (6 × 50 ml.). After drying (Na_2SO_4), the chloroform was evaporated and the residue was distilled at 100° (bath-temp.)/10^{-3} mm., giving 1-(2 : 3-*dihydroxypropyl*)cyclo*hexanol* as a viscous oil (11·3 g.), n_{D}^{20} 1·4980, which solidified on being kept and crystallised from ethyl acetate in plates, m. p. 72° (Found : C, 62·2; H, 10·4. $C_9H_{18}O_3$ requires C, 62·0; H, 10·4%). Distillation at a higher temperature, or from a trace of potassium hydrogen sulphate resulted in dehydration to 1-(2 : 3-*dihydroxypropyl*)cyclo*hexene*, a viscous oil, b. p. 120° (bath-temp.)/10^{-3} mm., n_{D}^{23} 1·4900 (Found : C, 69·3; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

1-(2 : 3-Dihydroxypropyl)*cyclo*hexanol (10 g.) in 50% aqueous methanol (40 ml.) was treated with periodic acid (10 g.) in water (10 ml.). The temperature rose to *ca.* 50°. After 10 min., water was added and the solution was extracted with chloroform. The extract was washed with water and aqueous sodium carbonate, dried (Na_2SO_4), and distilled, giving 1-hydroxy*cyclo*hexylacetaldehyde (4·5 g., 55%), b. p. 88—90°/0·1 mm. This was dehydrated by distillation from iodine (50 mg.), giving *cyclo*hexylideneacetaldehyde (2·1 g.), b. p. 93°/12 mm., n_{D}^{21} 1·4920, $\lambda_{\text{max.}}$ 2320 Å, ε 11,000 (in hexane), which contained some of the unconjugated isomer, 1-*cyclo*hexenylacetaldehyde, but formed a 2 : 4-dinitrophenylhydrazone, m. p. 202°, undepressed on admixture with the specimen described above.

Similar oxidation of 1-(2 : 3-dihydroxypropyl)*cyclo*hexene (1·7 g.) with periodic acid (2·1 g.) gave 1-*cyclo*hexenylacetaldehyde (1·1 g.), b. p. 100°/24 mm., n_D^{22} 1·4788, ε <500 at 2300 Å.

Treatment of 1-allyl*cyclo*hexanol (7·0 g.) in benzene (70 ml.) with lead tetra-acetate (22 g.) resulted in an unexpected rise in temperature (to 40°), and lead dioxide was precipitated. The solution was heated at 60° for ½ hr. and then cooled, washed with water and aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and distilled, giving *cyclo*hexanone (4·0 g., 80%), b. p. 48—50°/20 mm., identified by the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 158°.

Third method. Ethoxyacetylene was prepared by the following method adapted from Eglington, Jones, Shaw, and Whiting (*J.*, 1954, 1860).* Diethylchloroacetal (48 g.), prepared in 75% yield from vinyl acetate by Filachione's method (*J. Amer. Chem. Soc.*, 1939, **61**, 1705), was added during 1 hr. to a stirred solution of sodamide (from Na, 24 g.) in liquid ammonia (1 l.). The ammonia was allowed to evaporate under oxygen-free nitrogen, the last traces being cautiously removed at 50° (water-bath). Sodium chloride (65 g.) in water (200 ml.) was then added carefully to the solution at −40° and the ethoxyacetylene liberated was distilled off into a trap at −10°. The crude product (14·5 g., 66%) was washed with water and saturated aqueous sodium dihydrogen phosphate, dried (Na_2SO_4), and used without further purification.

Ethoxyacetylene (8 g.) in ether (30 ml.) was added at 0° to ethylmagnesium bromide (from Mg, 2·8 g., and ethyl bromide, 12·7 g.) in ether (70 ml.) and benzene (50 ml.). The solution was stirred for ½ hr. at 0° and then heated under reflux for ½ hr. *cyclo*Hexanone (12 g.) in ether (30 ml.) was added at 0°, and the mixture stirred for ½ hr. at room temperature and then under reflux for 1 hr. Excess of saturated aqueous ammonium chloride was added next at 0°, and the product worked up in the usual manner. Distillation of the ethereal solution gave 1-2′-*ethoxyethynyl*cyclo*hexanol* (13·4 g., 67%), b. p. 63—64°/0·1 mm., n_D^{21} 1·4820 (Found: C, 70·85; H, 9·75. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Omission of the benzene, or of either period of refluxing, led to much reduced yields. A poor yield was also obtained on reaction of sodioethoxyacetylene (prepared *in situ*) and *cyclo*hexanone in liquid ammonia.

1-2′-Ethoxyethynyl*cyclo*hexanol (10 g.) in dioxan (100 ml.) was hydrogenated in the presence of a palladium catalyst (1 g.; Isler *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1911; Lindlar, *ibid.*, 1952, **35**, 446), 1120 ml. (0·80 mol.) of hydrogen being absorbed during 10 hr. Sulphuric acid (2·5 ml.) was carefully added and the solution kept under nitrogen for 3 hr. at room temperature. Ice was then added and the product isolated with ether, giving *cyclo*hexylideneacetaldehyde (3 g.), b. p. 92°/12 mm., identified by the 2 : 4-dinitrophenylhydrazone (isolated in 90% yield), m. p. 202°, undepressed on admixture with the specimen described above. This derivative was also obtained on treating the solution of the hydrogenation product directly with Brady's reagent.

Use of a 0·3% palladium–calcium carbonate catalyst resulted in excessively slow and incomplete hydrogenation, while a similar 3% catalyst gave unselective reduction. Also, an attempted isolation of the vinyl ether gave a highly unstable product, b. p. 60—62°/0·3 mm., which rapidly darkened and polymerised on exposure to air, and afforded only a low yield of aldehyde on acid treatment.

Dissolution of 1-2′-ethoxyethynyl*cyclo*hexanol (3·7 g.) in methanol (35 ml.) gave, exothermally, *methyl* cyclo*hexylideneacetate* (3·2 g.), b. p. 50°/0·2 mm., n_D^{20} 1·4805, $\lambda_{\text{max.}}$ 2220 Å, ε 14,000 in EtOH (Found: C, 70·4; H, 9·4. $C_9H_{14}O_2$ requires C, 70·1; H, 9·2%). Shaking the *cyclo*hexanol (2·5 g.) with 5% aqueous sulphuric acid (25 ml.) for 1 hr. under nitrogen converted it into ethyl *cyclo*hexylideneacetate (1·9 g.) which was isolated with ether and had b. p. 104—106°/10 mm., n_D^{25} 1·4765, $\lambda_{\text{max.}}$ 2200 Å, ε 13,500 in EtOH (Kon and Linstead, *J.*, 1929, 1269, give b. p. 115°/14 mm., n_D^{18} 1·4799). The ester was hydrolysed by refluxing 10% aqueous sulphuric acid for 3 hr. under nitrogen, to the acid, m. p. and mixed m. p. 90°.

Reduction of cyclo*Hexylideneacetonitrile.*—α-Cyano-α-*cyclo*hexylideneacetic acid (m. p. 109°, $\lambda_{\text{max.}}$ 2340 Å, ε 11,600 in EtOH; Cope *et al.*, *Org. Synth.*, 1951, **31**, 25) was converted by heating with copper powder and either pyridine or collidine into *cyclo*hexenylacetonitrile (88%), b. p. 96—98°/10 mm., n_D^{22} 1·4775, $\lambda_{\text{max.}}$ <2100 Å, which was isomerised by 0·1N-sodium ethoxide in ethanol at room temperature into *cyclo*hexylideneacetonitrile (83%), b. p. 98—100°/12 mm., n_D^{23} 1·4890, $\lambda_{\text{max.}}$ 2170 Å, ε 13,700 in EtOH (cf. Kandiah and Linstead, *J.*, 1929, 2139).

To a stirred solution of the nitrile (10 g.) in ether (100 ml.) was added lithium aluminium hydride (1·0 g.) in ether (50 ml.) at −50° under nitrogen. After 20 min., ice-cold 2N-sulphuric acid was added. Isolation of the ether-soluble products (which did not give a precipitate with Brady's reagent) and fractionation furnished a mixture (7·5 g.) of *cyclo*hexylacetonitrile and unchanged starting material, b. p. 94—97°/10 mm., n_D^{25} 1·4710, $\lambda_{\text{max.}}$ 2150 Å, ε 9000 in EtOH

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* We are much indebted to Professor E. R. H. Jones, F.R.S., for communicating this method to us in advance of publication.

(Found: C, 78·7; H, 10·6; N, 11·6. Calc. for $C_8H_{13}N$: C, 78·0; H, 10·6; N, 11·4. Calc. for $C_8H_{11}N$: C, 79·3; H, 9·2; N, 11·6%). Reduction at −20° for 3 hr. gave a lower yield (3·8 g.) of products of similar composition, together with much polymeric material.

The nitrile mixture (4·5 g.) was hydrolysed at 130—140° with 90% phosphoric acid (20 ml.) for 5 hr. Extraction of the products with ether gave crude *cyclo*hexylacetic acid (1·1 g.) which was converted into the amide, m. p. 169—170°, undepressed on admixture with an authentic specimen (Wallach, *Annalen*, 1907, **353**, 297, gives m. p. 168°).

*Reduction of Cyano*cyclo*hexene*.—Cyano*cyclo*hexene (10·7 g.; b. p. 84—85°/15 mm., n_D^{19} 1·4810, $\lambda_{max.}$ 2110 Å, ε 11,200 in EtOH; prepared by dehydration of *cyclo*hexanone cyanohydrin) was reduced with lithium aluminium hydride (1·1 g.) in ether as above. Isolation of the products gave a mixture of cyano*cyclo*hexane and unchanged starting material, b. p. 67—69°/10 mm., n_D^{20} 1·4660, $\lambda_{max.}$ 2130 Å, ε 4000 in EtOH. This was hydrolysed with 90% phosphoric acid at 100° for 12 hr. and the crude acid was converted into the amide which crystallised from water in plates, m. p. 185—186° (Lumsden, *J.*, 1905, 90, gives m. p. 185—186°), undepressed on admixture with an authentic specimen of the derivative of *cyclo*hexanecarboxylic acid, prepared by carboxylation of *cyclo*hexylmagnesium bromide (cf. Gilman and Parker, *Org. Synth.*, 1925, **5**, 75).

*2'-Methyl*cyclo*hexylideneacetaldehyde* (I*b*).—Freshly distilled 2-methyl*cyclo*hexanone (112 g.) and allyl chloride (77 g.) in ether (500 ml.) and benzene (200 ml.) were added during 3 hr. to magnesium (24 g.) and a trace of iodine in ether (100 ml.). After being heated under reflux for an extra ½ hr., the mixture was cooled to 0°, and excess of ice-cold 2N-sulphuric acid was added. Isolation of the ether-soluble products and fractionation gave some unchanged ketone (15 g.) and *1-allyl-2-methyl*cyclo*hexanol* (110 g., 70%), b. p. 70—75°/10 mm., n_D^{20} 1·469—1·478, presumably as a mixture of *cis*- and *trans*-isomers (Found: C, 77·8; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%).

The alcohol, in batches of 10 g., was ozonised in acetic acid (50 ml.) at 0° until absorption ceased (12 hr.). The product was worked up as described on p. 325, giving the crude aldehyde (4·3 g., 60%), b. p. 100—120°/10 mm., $\lambda_{max.}$ 2320 Å, ε 6000 in hexane. Refractionation from powdered potassium hydrogen sulphate (0·4 g.) gave as the main product *2'-methyl*cyclo*hexylideneacetaldehyde*, b. p. 99—100°/10 mm., n_D^{20} 1·4930, $\lambda_{max.}$ 2300 Å, ε 12,000 in hexane (Found: C, 75·9; H, 10·2. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). The *semicarbazone* crystallised from aqueous ethanol in plates, m. p. 204°, $\lambda_{max.}$ 2740 Å, ε 28,000 in EtOH (Found: C, 61·8; H, 8·9; N, 21·2. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·8; N, 21·5%). The *2 : 4-dinitrophenylhydrazone* was chromatographed on alumina in benzene and crystallised from ethanol–ethyl acetate in plates, m. p. 174°, $\lambda_{max.}$ 3840 Å, ε 28,000 in $CHCl_3$ (Found: C, 57·1; H, 5·8; N, 17·5. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%).

From the lower-boiling fractions, b. p. 80—90°/10 mm., n_D^{24} 1·470—1·479, the *semicarbazone* of 2'-methyl*cyclo*hexenylacetaldehyde was obtained and crystallised from ethanol in fine needles, m. p. 204° (mixed m. p. with the semicarbazone of 2'-methyl*cyclo*hexylideneacetaldehehyde, 190°), $\lambda_{max.}$ 2330 Å, ε 15,400 in EtOH (Found: C, 61·3; H, 8·9; N, 21·4. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·8; N, 21·5%).

Redistillation of the higher-boiling fractions gave *1'-hydroxy-2'-methyl*cyclo*hexylacetaldehyde* as a highly viscous oil, b. p. 98—100°/0·5 mm. (Found: C, 69·3; H, 9·8. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). On treatment with Brady's reagent it formed the 2 : 4-dinitrophenylhydrazone of 2'-methyl*cyclo*hexylideneacetaldehyde, m. p. 174°, undepressed on admixture with the specimen described above.

1-cyclo*Hex-1'-enyl-2-*cyclo*hexylidene-ethanol* (II*a*).—*cyclo*Hexylideneacetaldehyde (6 g.) in ether (60 ml.) was added during 30 min. to *cyclo*hexenyl-lithium (from 1-chloro*cyclo*hexene, 6·4 g., and lithium, 0·7 g.; cf. *J.*, 1950, 2014) in ether (100 ml.) under nitrogen at room temperature. Stirring was continued for a further 30 min. and then excess of ice-cold saturated aqueous ammonium chloride was added at 0°. The ether layer was separated, dried (Na_2SO_4–K_2CO_3) and distilled from a trace of potassium carbonate, giving 1-cyclo*hex-1'-enyl-2-*cyclo*hexylidene-ethanol* (3·6 g., 36%), b. p. 100° (bath-temp.)/10^{-4} mm., n_D^{20} 1·5225 (Found: C, 81·3; H, 10·6. $C_{14}H_{22}O$ requires C, 81·5; H, 10·8%).

1-(2-cyclo*Hex-1'-enylvinyl*)cyclo*hexanol* (III*a*).—The above alcohol (3 g.) was dissolved in a 0·001M-solution of hydrogen chloride in 75% aqueous acetone (200 ml.), and the mixture kept at room temperature under nitrogen for 15 min. Excess of aqueous potassium carbonate was then added, the acetone was removed under reduced pressure, and the aqueous residue extracted with ether. The ether layer was separated, washed with water, dried (K_2CO_3), and distilled, giving 1-(2-cyclo*hex-1'-enylvinyl*)cyclo*hexanol* (2·3 g.), b. p. 80° (bath-temp.)/10^{-4} mm., n_D^{19}

1·5360, $\lambda_{max.}$ 2360 Å, ε 18,000 in EtOH (Found: C, 81·4; H, 11·0. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%). When the alcohol (300 mg.) was kept with maleic anhydride (160 mg.) in benzene (1·5 ml.) overnight at room temperature, the *adduct* (80 mg.) was precipitated; it crystallised from benzene in plates, m. p. 198° (Found: C, 71·5; H, 7·9. $C_{18}H_{24}O_4$ requires C, 71·0; H, 8·0%).

1 : 2-*Di*cyclo*hex*-1′-*enylethylene* (IV*a*).—The foregoing alcohol (1·8 g.) was distilled rapidly from powdered potassium hydrogen sulphate (0·8 g.) at 10^{-4} mm. The product was redistilled and had b. p. 100°/10^{-4} mm., n_D^{22} 1·5670, $\lambda_{max.}$ 2590 (ε 22,000), 2680 (ε 27,000), and 2800 Å (ε 24,000) in EtOH (Found: C, 87·3; H, 10·8; O, 3·4. Calc. for $C_{14}H_{20}$: C, 89·3; H, 10·7. Calc. for $C_{14}H_{20}O_2$: C, 76·3; H, 9·2; O, 14·5%). Even on brief exposure to air, the oxygen content increased markedly. If the oxygen is assumed to be bound in the proportions indicated, the analytical results above correspond to a triene content of 75%, and to an ε_{2690} value of 36,000 for the pure triene (Burkhardt and Hindley, *J.*, 1938, 987, report $\lambda_{max.}$ 2690 Å, ε 42,000). No adduct was obtained with maleic anhydride in benzene at room temperature.

1-cyclo*Hex*-1′-*enyl*-2-(2-*methyl*cyclo*hexylidene*)*ethanol* (II*b*).—2′-Methyl*cyclo*hexylideneacetaldehyde (6·2 g.) in ether (50 ml.) was added to *cyclo*hexenyl-lithium (from 1-chloro*cyclo*hexene, 5·8 g., and Li, 1·4 g.) in ether (100 ml.) at 0°. Stirring was continued for 30 min. at room temperature and then excess of ammonium chloride was added at 0°. The product was worked up as above, giving the *alcohol* (3·3 g., 33%), b. p. 100° (bath-temp.)/10^{-4} mm., n_D^{20} 1·5150 (Found: C, 81·4; H, 10·9. $C_{15}H_{24}O$ requires 81·8; H, 11·0%).

1-(2-2′-*Methyl*cyclo*hex*-1′-*enylvinyl*)cyclo*hexanol* (III*b*).—The foregoing alcohol (3 g.) was added to a 0·002M-solution of hydrogen chloride in 80% aqueous acetone (200 ml.) and the mixture kept for 20 min. at room temperature. Excess of potassium carbonate was then added and the product worked up as above, giving the *alcohol* (2·1 g.), b. p. 100° (bath-temp.)/10^{-4} mm., n_D^{24} 1·5230, $\lambda_{max.}$ 2370 Å, ε 15,000 in EtOH (Found: C, 81·1; H, 11·0. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%).

1-cyclo*Hexenyl*-2-(2-*methyl*cyclo*hex*-1-*enyl*)*ethylene* (IV*b*).—The foregoing alcohol (1·7 g.) was distilled from powdered potassium hydrogen sulphate (0·5 g.) at 10^{-4} mm. Redistillation gave a product (1·2 g.), b. p. 105—107°/10^{-4} mm., n_D^{21} 1·5415, $\lambda_{max.}$ 2710 (ε 20,000) and 2810 Å (ε 29,500) in EtOH (Found: C, 84·3; H, 10·9; O, 5·3. Calc. for $C_{15}H_{22}$: C, 89·0; H, 11·0. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·4; O, 13·7%). The analytical data correspond to a triene content of 60% and to an ε_{2710} value of 34,000 for the pure triene. No adduct was obtained with maleic anhydride in benzene at room temperature.

1-cyclo*Hexenylidene*-2-(1-*methyl*cyclo*hex*-1-*enylidene*)*ethane*.—*cyclo*Hexylideneacetaldehyde (2 g.) was added during 3 hr. with vigorous shaking, to *cyclo*hexanone (5 g.) and 0·05N-sodium hydroxide (200 ml.) under nitrogen. The condensation product (2 g.) was isolated with ether, distilled at 10^{-4} mm., and finally crystallised from ethanol as needles, m. p. 65°, $\lambda_{max.}$ 3070 Å, ε 20,000 in EtOH (Dimroth, *Ber.*, 1938, **71**, 1346, gives m. p. 67°, $\lambda_{max.}$ 2970 Å, ε 25,000 in Et_2O). The 2 : 4-*dinitrophenylhydrazone* was chromatographed on alumina in benzene and crystallised from ethyl acetate as dark red needles, m. p. 206°, $\lambda_{max.}$ 3150 (ε 14,000) and 4200 Å (ε 21,000) in $CHCl_3$ (Found: C, 62·3; H, 6·4; N, 14·6. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

The ketone was allowed to react with methylmagnesium bromide (2 mols.) in ether, and the product was hydrolysed with aqueous ammonium chloride, and the resulting tertiary alcohol was isolated from the ether layer. The crude alcohol (0·4 g.; $\lambda_{max.}$ 2480 Å, ε 18,000 in EtOH) was added to pyridine (4 ml.) and toluene-*p*-sulphonyl chloride (200 mg.) and the mixture heated at 80° for 5 min. under nitrogen. After dilution with ice and hydrochloric acid, the product was isolated with ether, giving a triene (0·26 g.), b. p. 100°/10^{-2} mm., $\lambda_{max.}$ 2820 Å, ε 20,000 in EtOH (Dimroth, *loc. cit.*, gives $\lambda_{max.}$ 2760 Å, ε 23,000 in Et_2O). A similar result was obtained with phosphorus oxychloride in pyridine as dehydrating agent.

Grateful acknowledgment is made, with respect to this and the following paper, to the Department of Scientific and Industrial Research for the award of a Maintenance Grant to one of us (O. H. W.) during 1951—1953.

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[*Received, September 15th,* 1954.]