258. *Studies in the Polyene Series. Part XLII.* Some Reactions of* cyclo*Hexenyl-lithium with Polyene Aldehydes.*

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The application of *cyclo*hexenyl-lithium to the preparation of some intermediates for the synthesis of vitamin A analogues has been examined.

*cyclo*Hexenyl-lithium reacts with sorbaldehyde, octatrienal, and 3-methyloctatrienal to give the carbinols (III; $n = 2$ and 3) and (VIII) respectively. Anionotropic rearrangement of (III; $n = 2$ and 3) and oxidation of the resulting isomers give the triene ketone (VI; $n = 2$) and a tetraene ketone, probably (VI; $n = 3$), respectively. Attempts to convert (VIII) into the ketone (VII) were unsuccessful.

In exploring the scope of application of alkenyl-lithium reagents it was demonstrated (Braude and Coles, *J.*, 1950, 2014) that *cyclo*hexenyl-lithium (I) is readily prepared and reacts with acraldehyde and crotonaldehyde, yielding the carbinols (II) and (III; $n = 1$) respectively, and further that these undergo anionotropic rearrangement to (IV) and

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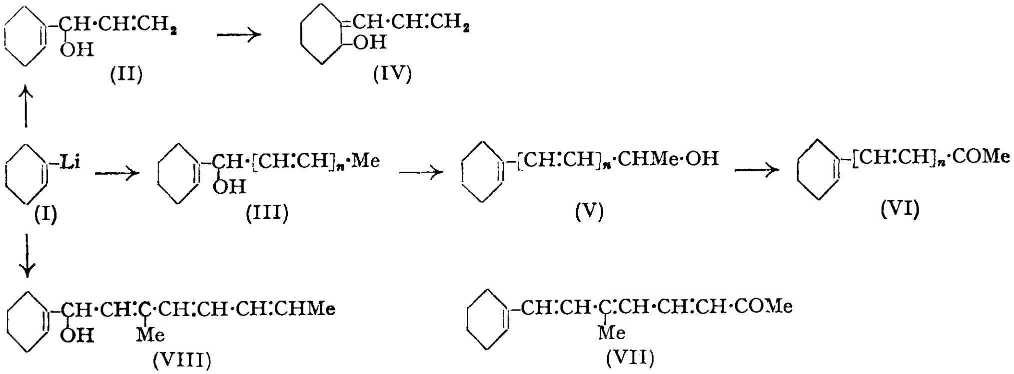
* Part XLI, *J.*, 1952, 1154.

(V; $n = 1$), respectively. The last on oxidation yielded the corresponding ketone (VI; $n = 1$), previously obtained by a number of alternative routes (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737; Chanley and Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4141). To account for the difference in direction of rearrangement of the carbinols (II) and (III; $n = 1$) it was suggested that the hydroxyl group migrates initially to the γ-carbon atom at which electron accession is greatest. Other factors, such as the strain accompanying the formation of an exocyclic double bond, may also be involved, but are of less importance (Braude and Forbes, *J.*, 1951, 1755). These observations suggested that the reaction of *cyclo*hexenyl-lithium (I) with polyene aldehydes, substituted in such a manner as to favour isomerisation of the resulting carbinols to *cyclo*hexenyl rather than to *cyclo*hexylidene derivatives, might furnish routes to polyene ketones of use for the synthesis of compounds related to vitamin A. This paper reports an investigation of these possibilities by using the polyene aldehydes, sorbaldehyde, octatrienal, and 3-methyloctatrienal.

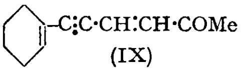


Addition of sorbaldehyde to an ethereal solution of (I) furnished the carbinol (III; $n = 2$), in yields up to 67% (based on aldehyde). The carbinol was characterised by oxidation to the corresponding ketone (2 : 4-dinitrophenylhydrazone), and by catalytic hydrogenation and subsequent oxidation to 1-*cyclo*hexylhexan-1-one. Dilute hydrochloric acid rearranged (III; $n = 2$) to a product which was similarly converted into the known 6-*cyclo*hexylhexan-2-one (semicarbazone) by hydrogenation and subsequent oxidation. None of the isomeric 2-*n*-hexyl*cyclo*hexanone (a sample of which was prepared by alkylation of *cyclo*hexanone) could be detected, and it was therefore concluded that isomerisation of (III; $n = 2$) gives mainly, if not exclusively, (V; $n = 2$) by migration of the hydroxyl group along the side chain as in the case of the carbinol from crotonaldehyde. Oxidation of the rearranged product with aluminium *tert.*-butoxide and acetone yielded the triene ketone (VI; $n = 2$), the structure of which was confirmed by hydrogenation to 6-*cyclo*hexylhexan-2-one.

Attempts were next made to carry out similar series of reactions with the triene aldehydes, octa-2 : 4 : 6-trien-1-al and 3-methylocta-2 : 4 : 6-trien-1-al. The expected product (VII) from the latter would be of particular interest as a possible intermediate for the synthesis of a compound possessing the polyene side chain of vitamin A but a modified ring system (cf. Weedon and Woods, *J.*, 1951, 2687). The carbinols (III; $n = 3$) and (VIII) were obtained in good yields, the latter being characterised by oxidation to the corresponding ketone (2 : 4-dinitrophenylhydrazone) and catalytic reduction to 1-*cyclo*hexyl-3-methyloctan-1-ol. The unstable product formed on rearrangement of (III; $n = 3$) with dilute acid was estimated by light-absorption measurements to contain a high proportion of a fully conjugated tetraene. This, by analogy, with the carbinols similarly obtained from crotonaldehyde and sorbaldehyde, is formulated as (V; $n = 3$); it yielded a ketone, probably (VI; $n = 3$), which was isolated as its 2 : 4-dinitrophenylhydrazone, the light-absorption properties of the ketone and of its derivative being in agreement with this structure. Treatment of (VIII) with acids, however, gave a mixture of products which, on oxidation, yielded an unidentified carbonyl compound (semicarbazone and

2 : 4-dinitrophenylsemicarbazone) but none of the required tetraene ketone (VII). Since alternative routes to (VII) have now been developed (Bharucha and Weedon, forthcoming publication), investigations along these lines have for the present been discontinued.

Light-absorption data for the majority of the compounds referred to above are collected in the Table. The *cyclo*hexenylcarbinols (III; *n* = 2 and 3), (VIII), and (V; *n* = 2) exhibit maxima of high intensity at wave-lengths consistent with the conjugated diene or triene structures assigned. The triene ketone (VI; *n* = 2) shows maximal absorption at slightly longer wave-lengths, and of higher intensity, than that of the acetylenic analogue (IX).



(IX)

	$\lambda_{\text{max.}}$, Å	$\varepsilon_{\text{max.}}$		$\lambda_{\text{max.}}$, Å	$\varepsilon_{\text{max.}}$
(III; *n* = 2)	2280	25 000	(VIII)	2690	41 000
	2350 *	23 000		2780	38 500
(V; *n* = 2)	2590 *	25 000	(VI; *n* = 2)	3200	37 500
	2700	33 500	(IX) †	2220	7 500
	2790	27 500		3120	20 000
(III; *n* = 3)	2590 *	32 500			
	2690	44 000			
	2780	34 500			

* Inflexion. † Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742.

EXPERIMENTAL

M. p.s are uncorrected. Light-absorption data were determined in ethanol unless otherwise stated. Wherever possible, operations were carried out in nitrogen. The 2 : 4-dinitrophenylhydrazones were purified by chromatographic adsorption from benzene solution on alumina (Spence, grade H). All other chromatograms were on alumina which had been partly deactivated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 2310).

1-cyclo*Hex*-1'-*enylhexa*-2 : 4-*dien*-1-*ol* (III; *n* = 2).—A solution of sorbaldehyde (15·5 g.) in ether (40 c.c.) was added during 20 minutes to a stirred and cooled (ice–salt) solution of *cyclo*hexenyl-lithium (from 18·8 g. of chloro*cyclo*hexene and 2·3 g. of lithium; cf. Braude and Coles, *J.*, 1950, 2014) in ether (310 c.c.). The mixture was stirred for a further hour at 0° and the temperature then allowed to rise to 20°. Ice and water were added and the product was extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4 and a trace of K_2CO_3), and evaporated. Distillation of the residue from a short-path still was accompanied by extensive polymerisation and gave 1-cyclo*hex*-1'-*enylhexa*-2 : 4-*dien*-1-*ol* (12·5 g., 44%), b. p. 60° (bath-temp.)/10^{-4} mm., $n_{\rm D}^{16}$ 1·5358 (Found : C, 80·8; H, 10·15. $C_{12}H_{18}O$ requires C, 80·9; H, 10·2%). Light absorption : see Table.

Repetition of the preceding experiment with twice the quantity of *cyclo*hexenyl-lithium and distillation of the crude product in batches of about 10 g. raised the yield of carbinol to 67%.

1-cyclo*Hexylhexan*-1-*ol and* 1-cyclo*Hexylhexan*-1-*one*.—A solution of the preceding carbinol (900 mg.) in methanol (25 c.c.) was shaken in hydrogen in the presence of platinic oxide (90 mg.) until absorption was complete (2·8 mols.). After removal of catalyst and solvent, the residue was distilled, giving the saturated *carbinol* (600 mg.), b. p. 40—50° (bath-temp.)/10^{-4} mm., $n_{\rm D}^{16}$ 1·4740 (Found : C, 78·4; H, 13·0. $C_{12}H_{24}O$ requires C, 78·2; H, 13·15%).

This product (785 mg.) in acetone (1·1 c.c.) was oxidised with a solution of chromium trioxide (332 mg.) and concentrated sulphuric acid (0·3 c.c.) in water (1·1 c.c.). The crude product (770 mg.) was isolated in the usual way. One portion (25 mg.) was converted into the 2 : 4-*dinitrophenylsemicarbazone* (32 mg.), which crystallised for alcohol–chloroform in yellow leaflets, m. p. 189° (Found : C, 56·3; H, 6·65; N, 17·4. $C_{19}H_{27}O_5N_5$ requires C, 56·25; H, 6·7; N, 17·25%). A second portion (740 mg.) was heated on the steam-bath for 1½ hours with an excess of methanolic semicarbazide acetate and gave the *semicarbazone* (126 mg.), which crystallised from methanol in laths, m. p. 136° (Found : C, 65·25; H, 10·6; N, 17·7. $C_{13}H_{25}ON_3$ requires C, 65·25; H, 10·55; N, 17·55%). Light absorption : maximum, 2280 Å; ε, 15 000.

1-cyclo*Hex*-1'-*enylhexa*-2 : 4-*dien*-1-*one*.—A solution of 1-*cyclo*hex-1'-enylhexa-2 : 4-dien-1-ol 1·53 g.) and aluminium *tert.*-butoxide (5 g.) in acetone (83 c.c.) and benzene (124 c.c.) was heated under reflux for 48 hours. The mixture was cooled and then shaken with dilute sulphuric acid (670 c.c.; 2·5% w/v). The benzene layer was separated, washed with water, dried, and evaporated. Distillation of the residue gave the crude ketone (1·1 g.), b. p. 50° (bath-temp.)/10^{-4} mm., $n_{\rm D}^{21}$ 1·5584. Light absorption : maximum, 2940 Å; $E^{1\%}_{1\,\text{cm.}}$, 820. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 232° (Found : N, 15·6.

$C_{18}H_{20}O_4N_4$ requires N, 15·7%). Light absorption in chloroform (main band only): maximum, 3980 Å; ε, 37 500.

A portion (0·8 g.) of the crude ketone in light petroleum (b. p. 40—60°) was poured on to a column of alumina. Elution of the main band with the same solvent and distillation gave 1-cyclo*Hex-1′-enylhexa-2 : 4-dien-1-one* (600 mg.), b. p. 60° (bath-temp.)/10^{-3} mm., n_D^{21} 1·5632, which solidified when kept at 0° but melted again on warming to 20° (Found: C, 81·9; H, 9·25. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%). Light absorption: maximum, 2930 Å; ε, 19 500.

A solution of the preceding ketone (500 mg.) in ethyl acetate (10 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete (2·8 mols.). After removal of catalyst and solvent, the residue was converted into the semicarbazone which had m. p. 136°, undepressed on admixture with the specimen described above.

6-cyclo*Hex-1′-enylhexa-3 : 5-dien-2-ol* (V; *n* = 2).—A solution of 1-*cyclo*hex-1′-enylhexa-2 : 4-dien-1-ol (10 g.) and concentrated hydrochloric acid (0·21 c.c.) in a mixture of water (63 c.c.) and acetone (145 c.c.) was kept at 20° for 18 hours and then diluted with water. The crude product (9 g.) was isolated by means of ether. Light absorption: maxima, 2690 and 2800 Å; $E^{1\%}_{1\,\text{cm.}}$, 1680 and 1410 respectively.

Distillation of a small portion of the crude product gave 6-cyclo*hex-1′-enylhexa-3 : 5-dien-2-ol*, b. p. 70° (bath-temp.)/10^{-4} mm., n_D^{18} 1·5668 (Found: C, 81·0; H, 10·0. $C_{12}H_{18}O$ requires C, 80·9; H, 10·2%). Light absorption: see Table.

6-cyclo*Hexylhexan-2-ol and* 6-cyclo*Hexylhexan-2-one.*—A solution of the preceding carbinol (1·3 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete. After removal of catalyst and solvent, the residue was distilled, giving the saturated carbinol (290 mg.), b. p. 70° (bath-temp.)/10^{-4} mm.

A portion (240 mg.) of the carbinol in acetone (0·35 c.c.) was oxidised with a solution of chromium trioxide (102 mg.) and concentrated sulphuric acid (0·1 c.c.) in water (0·35 c.c.). The crude ketone was isolated in the usual way and treated with an excess of semicarbazide acetate in methanol. The crude derivative was crystallised once from methanol and had m. p. 148—150° (100 mg.). One further crystallisation from the same solvent gave 6-*cyclo*hexylhexan-2-one semicarbazone as plates, m. p. 154°, undepressed on admixture of the sample with an authentic specimen (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742, give m. p. 154°).

2-n-*Hexyl*cyclo*hexanone* (with K. R. Bharucha).—A mixture of *cyclo*hexanone (4·9 g.) and *n*-hexyl bromide (8·4 g.) was poured into a boiling solution of potassium *tert.*-butoxide (from 2·2 g. of potassium) in *tert.*-butanol (25 c.c.) (cf. Braude and Coles, *J.*, 1950, 2014). The mixture was heated under reflux for 20 minutes, then cooled and treated with excess of cold (0°) 2N-hydrochloric acid. Isolation of the crude product (9·5 g.) with ether in the usual manner and distillation gave 2-n-*hexyl*cyclo*hexanone* (2·9 g.), b. p. 80—91°/0·5 mm., n_D^{24} 1·4570 (Found: C, 79·05; H, 12·15. $C_{12}H_{22}O$ requires C, 78·65; H, 12·25%). The *semicarbazone* crystallised from methanol in needles, m. p. 128—129° (Found: N, 17·55. $C_{13}H_{25}ON_3$ requires N, 17·85%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange needles, m. p. 130° (Found: N, 15·3. $C_{18}H_{26}O_4N_4$ requires N, 15·45%).

6-cyclo*Hex-1′-enylhexa-3 : 5-dien-2-one* (VI; *n* = 2).—A solution of 6-*cyclo*hex-1′-enylhexa-3 : 5-dien-2-ol (9·1 g.) and aluminium *tert.*-butoxide (30 g.) in a mixture of acetone (500 c.c.) and benzene (750 c.c.) was heated under reflux for 48 hours. The mixture was then cooled and shaken with dilute sulphuric acid (4 l.; 2·5% w/v). The benzene layer was separated, washed with water, dried, and evaporated, giving the crude product (9 g.). Light absorption: maxima, 2800 and 3240 Å; $E^{1\%}_{1\,\text{cm.}}$, 580 and 600 respectively.

A portion (7·5 g.) of the crude product in light petroleum (b. p. 40—60°) was poured on to a column of alumina (235 g.; grade IV). The chromatogram was developed with the same solvent and the main yellow band eluted, yielding the crude ketone as an oil (3·4 g.), n_D^{23} 1·5995. Light absoprtion: maximum, 3240 Å; $E^{1\%}_{1\,\text{cm.}}$, 1580. The 2 : 4-*dinitrophenylhydrazone* was purified by chromatographic absorption on alumina (only one band being observed) and crystallised from ethyl acetate, giving red leaflets, m. p. 205° (Found: N, 16·0. $C_{18}H_{20}O_4N_4$ requires N, 15·7%). Light absorption in chloroform (main band only): maximum 4120 Å; ε, 38 000.

The crude ketone was treated with a methanolic solution of semicarbazide acetate (from 3·8 g. of semicarbazide hydrochloride), and the mixture kept for 24 hours at 20° and then for 24 hours at 0°. The solid (1·3 g.) which separated was removed and crystallised from methanol, yielding the *semicarbazone* (800 mg.) as yellow leaflets, m. p. 202° (decomp.) (Found: C, 67·0; H, 8·35. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·2%). Light absorption: maxima, 3170 and 3320 Å; ε, 58 000 and 49 000 respectively.

A mixture of the finely powdered semicarbazone (500 mg.), light petroleum (b. p. 40—60°; 25 c.c.), and dilute sulphuric acid (25 c.c.; 10% w/v) was stirred vigorously and heated under reflux until nearly all the solid had disappeared. The mixture was cooled and the upper layer was removed, washed with water, dried, and evaporated. Distillation of the residue gave 6-cyclo*hex-1'-enylhexa-3 : 5-dien-2-one* (221 mg.), n_D^{28} 1·62 (Found : C, 81·35; H, 9·2. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%). Light absorption : see Table.

6-cyclo*Hexylhexan-2-one.*—A solution of the preceding regenerated ketone (172 mg.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of platinic oxide (30 mg.) until absorption was complete (hydrogen absorbed: 68 c.c. at 24°/768 mm., equiv. to 2·9 double bonds). The catalyst and solvent were removed and the residue was treated with semicarbazide acetate (270 mg.) in methanol. The crude product (218 mg.) which separated yielded, from methanol, the semicarbazone (115 mg.) of 6-*cyclo*hexylhexan-2-one as plates, m. p. 154°, undepressed on admixture with an authentic specimen.

1-cyclo*Hex-1'-enylocta-2 : 4 : 6-trien-1-ol* (III; *n* = 3).—A solution of octatrienal (7·7 g.; crystalline, freshly prepared) in ether (30 c.c.) was added slowly to a cooled (ice–salt) solution of *cyclo*hexenyl-lithium (from 20 g. of chloro*cyclo*hexene and 2·4 g. of lithium), and the mixture stirred and cooled for 2 hours. The mixture was added to ice and the product isolated with ether in the usual way, giving an oil (10 g.) which exhibited light absorption maxima at 2680 and 2800 Å ($E_{1\,cm.}^{1\%}$, 1450 and 980 respectively). Distillation of a small portion of the crude product gave the *carbinol*, b. p. 90—100° (bath-temp.)/10^{-4} mm., n_D^{18} 1·572 (Found : C, 81·8; H, 10·15. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). Light absorption : see Table. When kept at 0°, the carbinol partly solidified and after recrystallisation from pentane had m. p. *ca.* 60°. Light absorption : maxima, 2580, 2680, and 2800 Å; ε, 36,500, 41 000, and 36 500 respectively.

Treatment of the crude carbinol (9·0 g.) for 17 hours at 20° with a 0·01M-solution of hydrochloric acid in a mixture of acetone (170 c.c.) and water (40 c.c.) gave a product which exhibited light absorption maxima at 3040 and 3150 Å ($E_{1\,cm.}^{1\%}$, 1100 and 1020 respectively) and an inflexion at 2800 and 2900 Å ($E_{1\,cm.}^{1\%}$, 580 and 670 respectively), indicating an appreciable content of the rearranged carbinol. Distillation of a small portion gave an oil, b. p. 90—100° (bath-temp.)/10^{-4} mm., n_D^{24} 1·6015, which exhibited light absorption maxima at 3020 and 3160 Å ($E_{1\,cm.}^{1\%}$, 1550 and 1350 respectively). Oppenauer oxidation of the crude, unstable, rearranged carbinol, and separation of the products by chromatography, yielded (*ca.* 20—25%) a ketonic fraction which exhibited a light absorption maximum at 3480 Å ($E_{1\,cm.}^{1\%}$, 1100). Distillation gave an oil, light absorption maximum, 3510 Å ($E_{1\,cm.}^{1\%}$, 1580). The 2 : *4-dinitrophenylhydrazone* crystallised from ethyl acetate in needles, m. p. 220° (Found : N, 15·15. $C_{20}H_{20}O_4N_4$ requires N, 14·65%). Light absorption in chloroform (main band only) : maximum, 4200 Å; ε, 49 000.

1-cyclo*Hex-1'-enyl-3-methylocta-2 : 4 : 6-trien-1-ol* (VIII) *and* 1-cyclo*Hexyl-3-methyloctan-1-ol.*—A solution of 2-methylhepta-1 : 3 : 5-trien-1-al (20 g.) (Weedon and Woods, *J.*, 1951, 2687) in ether (100 c.c.) was added during 45 minutes to a cooled (0°) solution of *cyclo*hexenyl-lithium (from 21·6 g. of chloro*cyclo*hexene and 2·6 g. of lithium) in ether (500 c.c.). The mixture was stirred overnight at 20°, a saturated aqueous ammonium chloride solution (250 c.c.) was then added, and the product was isolated with ether in the usual manner. Distillation yielded the carbinol (18·2 g., 57%), b. p. 70—75° (bath-temp.)/10^{-4} mm., n_D^{19} 1·5830, which gave erratic analytical results. Light absorption : see Table. To characterise the carbinol a portion (1·0 g.) was oxidised by shaking its solution in light petroleum (b. p. 40—60°; 70 c.c.) with manganese dioxide (5 g.) at 20° for 15 hours (cf. *idem, loc. cit.*) and the resulting ketone (0·7 g.), b. p. 75° (bath-temp.)/10^{-4} mm., n_D^{25} 1·6020, was converted into the 2 : *4-dinitrophenylhydrazone.* This crystallised from ethyl acetate and had m. p. 184° (Found : N, 14·15. $C_{21}H_{24}O_4N_4$ requires N, 14·15%). Light absorption in chloroform (main band only) : maximum, 4130 Å; ε, 43 500.

A solution of the preceding carbinol (3·5 g.) in methanol (25 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete (hydrogen absorbed, 1440 c.c. at 23°/765 mm., equiv. to 3·6 double bonds). Removal of the catalyst and solvent and distillation of the residue gave 1-cyclo*hexyl-3-methyloctan-1-ol* (2·2 g.), b. p. 95° (bath-temp.)/10^{-4} mm., n_D^{25} 1·4708 (Found : C, 79·55; H, 13·2. $C_{15}H_{30}O$ requires C, 79·55; H, 13·35%).

Treatment of the unsaturated carbinol (VIII) for 4 hours at 20° with a 0·002M-solution of sulphuric acid in a mixture of water (180 c.c.) and acetone (420 c.c.) and chromatographic separation of the products gave an oil (40%), n_D^{19} 1·5725, which exhibited light absorption maxima at 3140 and 3220 Å ($E_{1\,cm.}^{1\%}$, 1210 and 1270 respectively). It decomposed on attempted distillation, the distillate showing light absorption of lower intensity than the starting material. Oxidation of the undistilled material in light petroleum (b. p. 40—60°) with manganese dioxide and chromatographic separation of the products gave an oil (60%), b. p. 70° (bath-temp.)/10^{-4}

mm., n_D^{24} 1·6047; light absorption: maxima, 2680, 2790, and 3220 Å; $E_{1\,\text{cm.}}^{1\%}$, 1320, 1320, and 1700 respectively. A portion (200 mg.) of the oil was converted into the *semicarbazone* (235 mg.) which crystallised from aqueous methanol in pale yellow needles, m. p. 203° (decomp.) (Found: N, 21·5, 21·45%). Light absorption: maximum, 3300 Å; $E_{1\,\text{cm.}}^{1\%}$, 2900. The 2 : 4-*dinitrophenylsemicarbazone* crystallised from aqueous pyridine and had m. p. 218° (decomp.) (Found: N, 19·5%). Light absorption in chloroform: maximum, 3380 Å; $E_{1\,\text{cm.}}^{1\%}$, 1450. An attempt to oxidise the crude rearranged carbinol by the Oppenauer method was unsuccessful. Treatment of (VIII) with acids under more vigorous conditions than those described above led to extensive dehydration and decomposition of the product.

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