10. *Studies in the Polyene Series. Part XXII. Condensations between Methyl Propargyl Ether and αβ-Unsaturated Carbonyl Compounds.*

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Condensations of the Grignard complex from methyl propargyl ether and αβ-unsaturated carbonyl compounds (crotonaldehyde, mesityl oxide, and ethylideneacetone) proceed normally. The methoxy-carbinols (II) thus obtained undergo the expected anionotropic rearrangements in acidic media yielding the isomerides (III), which exhibit light absorption properties corresponding to previous values for conjugated vinylacetylene systems.

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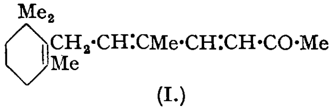
* If it be assumed that conversion to α-phenylethyl *iso*cyanate is complete, then this benzene solution contained 1·5 g. in 20 c.c. It had $[\alpha]_D^{15^\circ}$ + 6·19° (*l*, 2; *c*, 7·5); and therefore $[\alpha]_D^{15^\circ}$ + 41·3° is an approximate value of the specific rotatory power of (+)-α-phenylethyl *iso*cyanate.

A similar condensation and isomerisation can be effected by employing the C_{17}-ketone (I), but dehydration of the rearranged product (V) fails to yield materials containing the 5-conjugated system, comparable with that of vitamin A. Migration of the cyclic ethylenic linkage or cyclisation reactions presumably accompany dehydration.

In Part V of this series (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727) the preparation of the C_{17}-ketone (I) was described, and its possible employment for the synthesis of compounds related to vitamin A by condensations with propargyl alcohol or its derivatives was considered. Some preliminary work employing propargyl acetal has already been described (Heilbron, Jones, and Koch, *J.*, 1942, 735), and this paper contains an account of work carried out using methyl propargyl ether. The preparation of the latter from 2 : 3-dibromo-1-methoxypropane has been improved by carrying out the dehydrobromination with potassium hydroxide in glycol solution.

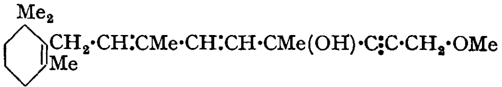


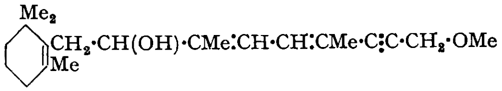
(I.)

$$\underset{\text{(II.)}}{\mathrm{Me{\cdot}CR_1{:}CH{\cdot}CR(OH){\cdot}C{\vdots}C{\cdot}CH_2{\cdot}OMe}} \xrightarrow{\text{acids}} \underset{\text{(III.)}}{\mathrm{Me{\cdot}CR_1(OH){\cdot}CH{:}CR{\cdot}C{\vdots}C{\cdot}CH_2{\cdot}OMe}}$$

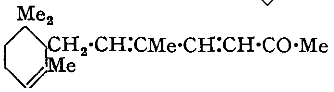
A Grignard condensation between methyl propargyl ether and butaldehyde proceeded satisfactorily (40% yield) and with crotonaldehyde, mesityl oxide, and ethylideneacetone the expected methoxycarbinols (II; $R = R_1 = H$, $R = R_1 = Me$, and $R_1 = H$, $R = Me$ respectively) were obtained in 60, 50, and 25% yields respectively. The last two condensations were effected in cold ethereal solution, a necessary condition in order to prevent undesirable side reactions (Cymerman, Heilbron, and Jones, *J.*, 1944, 145). The various carbinols (II) were all converted into the corresponding rearranged carbinols (III) by keeping them in aqueous acetone containing dilute sulphuric acid, the acid concentration being adjusted in accordance with earlier experience with similar anionotropic rearrangements (Cymerman, Heilbron, and Jones, *loc. cit.*; *J.*, 1945, 90). These carbinols all exhibited light absorption typical of the conjugated vinylacetylene chromophore, described in detail in previous papers in this series.

(IV.)





(V.)



(VI.)

When the ketone (I), regenerated from its semicarbazone, was treated with an ethereal suspension of the Grignard complex from methyl propargyl ether, a product was obtained which, although too unstable to be purified by high vacuum distillation, must be the expected carbinol (IV). It showed intense light absorption at 2390 A., practically identical with that observed with the ethylcarbinol prepared by condensation of (I) with ethylmagnesium bromide (Part V, *loc. cit.*), and with 0·5% sulphuric acid in an aqueous acetone medium it underwent rearrangement to the more stable *carbinol* (V). Such a 5-carbon anionotropic migration has previously been observed in the case of the ethynylcarbinol from sorbaldehyde (Heilbron, Jones, and McCombie, *J.*, 1944, 134) and the light absorption of (V) ($\lambda_{max.}$ 2810 A.) corresponded with that anticipated for a conjugated dien-yne system. Although the rearranged carbinol (V) can easily be dehydrated, the product, instead of being the desired conjugated tetraen-yne ether contains, according to light absorption indications, at most a trien-yne system. It thus appears that dehydration ensues in such a manner that the double bond in the cyclic system is not brought into conjugation and either rearrangement of this ethylenic linkage into the so-called α-position or cyclisation reactions may be involved. This point will be discussed further in a subsequent communication, where other examples of this behaviour will be described (Part XXIII; in the press).

In the hope of determining the possible fate of the isolated double bond during dehydration reactions the α-C_{17}-*ketone* (VI) has been prepared from the corresponding aldehyde. Its condensation with ethylmagnesium bromide, however, is anomalous and the Zerewitinoff value (0·85 atom of active hydrogen), the light absorption data, and a positive reaction with ketonic reagents indicate that the product is a mixture of carbinols and ketone resulting from 1 : 2-, 1 : 4-, and (possibly) 1 : 6-addition to the conjugated system.

EXPERIMENTAL.

Light absorption data were determined in alcohol.

Methyl Propargyl Ether.—To a solution of sodium (40 g.) in dry methanol (400 c.c.), allyl bromide (200 g.) was added with stirring at such a rate that gentle refluxing occurred, the reaction being completed by heating on the steam-bath. Bromine (270 g.) was then added to the cooled stirred mixture during 2 hours, water was added and on isolation of the product in the usual manner, two fractions were obtained on distillation: (i) b. p. 78—82°/16 mm., $n_D^{20^\circ}$ ranging from 1·49 to 1·51 (120 g.) and (ii) 2 : 3-dibromo-1-methoxypropane (200 g.), b. p. 82—83°/16 mm., $n_D^{20^\circ}$ 1·5123 (Irvine, Macdonald, and Suter, *J.*, 1915, 348, give b. p. 83—84°/17 mm., n_D 1·5143).

The dibromo-ether (200 g.) was slowly added (1·5 hours) to a solution of potassium hydroxide (150 g.) in ethylene glycol (1 litre) contained in a three-necked copper flask, the liquid temperature of the well agitated mixture being kept at 90—100°. After the addition the temperature was raised to 130° and all material with b. p. below 90° was distilled over. The upper layer was separated and dried and, on redistillation through a short column, gave methyl propargyl ether (36 g.), b. p. 63—64°, $n_D^{19^\circ}$ 1·3975 (Bourguel, *Compt. rend.*, 1923, **176**, 752, gives b. p. 63°).

1-*Methoxyhept*-2-*yn*-4-*ol*.—To a solution of ethylmagnesium bromide (from 5·15 g. Mg) in ether, dry benzene (200 c.c.) was added and the ether removed by distillation. Methyl propargyl ether (15 g.) in benzene (40 c.c.) was added to the cooled, stirred Grignard reagent during 30 minutes and the mixture gently warmed on the steam-bath for 2 hours by which time the complex had separated as a fine granular white solid. Butaldehyde (16 g.) was added to the cooled, stirred mixture during 20 minutes and the reaction was completed by heating for 2 hours on the steam-bath. The complex was decomposed with saturated ammonium chloride solution and isolation in the usual way gave 1-*methoxyhept*-2-*yn*-4-*ol* (11·5 g.), b. p. 76°/4 mm., $n_{\rm D}^{19^\circ}$ 1·4565 (Found : C, 67·9; H, 9·8. $C_8H_{14}O_2$ requires C, 67·55; H, 9·9%. Active hydrogen (Zerewitinoff) : The carbinol (100 mg.) gave 17·6 c.c. of methane at 19°/758 mm., *i.e.*, 1·05 atoms of active hydrogen per mol.). The *a-naphthylurethane* crystallised from ligroin (b. p. 40—60°) in needles, m. p. 66—67° (Found : N, 4·65. $C_{19}H_{21}O_3N$ requires N, 4·5%).

1-*Methoxyhept*-5-*en*-2-*yn*-4-*ol* (II; R = R$_1$ = H).—Methyl propargyl ether (20 g.) in benzene (40 c.c.) was treated with ethylmagnesium bromide (from 6·8 g. Mg) in benzene (200 c.c.) as above. Crotonaldehyde (20 g.) in benzene (40 c.c.) was added during 15 minutes to the ice-cold stirred reagent and the vigorously stirred mixture was heated to *ca*. 50° for one hour. Isolation in the usual manner gave the *methoxy-carbinol* (23 g.), b. p. 72°/4 mm., $n_{\rm D}^{20^\circ}$ 1·4795 (Found : C, 68·4; H, 8·5. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%. Active hydrogen (Zerewitinoff) : The carbinol (83 mg.) gave 14·6 c.c. of methane at 27°/765 mm., *i.e.*, 1·0 atom of active hydrogen per mol.). The *a-naphthylurethane* crystallised from ligroin (b. p. 60—80°) in needles, m. p. 75—76° (Found : C, 73·9; H, 6·4. $C_{19}H_{19}O_3N$ requires C, 73·75; H, 6·2%). Light absorption : Maximum, 2230 A.; $\varepsilon = 66,500$.

1-*Methoxyhept*-4-*en*-2-*yn*-6-*ol* (III; R = R$_1$ = H).—The above methoxy-carbinol (4 g.) was dissolved in the minimum volume of an acetone–dilute sulphuric acid solution (40% acetone, 5% sulphuric acid) and, after the mixture had been kept for 48 hours at 20°, 1-*methoxyhept*-4-*en*-2-*yn*-6-*ol* (3 g.), b. p. 71°/3 mm., $n_{\rm D}^{19^\circ}$ 1·4976 was obtained (Found : C, 68·8; H, 8·75. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%. Active hydrogen (Zerewitinoff) : The carbinol (95 mg.) gave 14·7 c.c. of methane at 26°/769 mm., *i.e.*, 0·9 atom of active hydrogen per mol.). Light absorption : Maximum, 2280 A.; $\varepsilon = 13,000$. Inflexion, 2340 A.; $\varepsilon = 10,000$. The *a-naphthylurethane* crystallised from ether–ligroin (b. p. 40—60°) in micro-needles, m. p. 65° (Found : N, 4·65. $C_{19}H_{19}O_3N$ requires N, 4·55%). Light absorption : Maximum, 2230 A.; $\varepsilon = 74,000$.

1-*Methoxy*-4 : 6-*dimethylhept*-5-*en*-2-*yn*-4-*ol* (II; R = R$_1$ = Me).—Methyl propargyl ether (12·5 g.) in ether (100 c.c.) was added to a stirred solution of ethylmagnesium bromide (from 4·2 g. Mg) in ether (200 c.c.) during 20 minutes. After gentle refluxing with vigorous stirring for 2 hours, the mixture was cooled (ice) and treated with mesityl oxide (18 g.) in ether (150 c.c.) and then stirred at 20° for 18 hours. This procedure yielded 1-*methoxy*-4 : 6-*dimethylhept*-5-*en*-2-*yn*-4-*ol* (14 g.), b. p. 76°/3 mm., $n_{\rm D}^{19^\circ}$ 1·4770 (Found : C, 71·55; H, 9·75. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%. Active hydrogen (Zerewitinoff) : The carbinol (102 mg.) gave 15·5 c.c. of methane at 26°/771 mm., *i.e.*, 1·05 atoms of active hydrogen per mol.).

1-*Methoxy*-4 : 6-*dimethylhept*-4-*en*-2-*yn*-6-*ol* (III; R = R$_1$ = Me).—The above methoxy-carbinol (4·5 g.) was dissolved in the minimum volume of an acetone–dilute sulphuric acid solution (50% acetone, 0·5% sulphuric acid). After 20 hours at 20°, the deep red solution was diluted and extracted with ether from which was obtained 1-*methoxy*-4 : 6-*dimethylhept*-4-*en*-2-*yn*-6-*ol* (4 g.), b. p. 73—74°/3 mm., $n_{\rm D}^{21^\circ}$ 1·4813 (Found : C, 71·4; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%. Active hydrogen (Zerewitinoff): The carbinol (97 mg.) gave 14·2 c.c. of methane at 25°/765 mm., *i.e.*, 1·0 atom of active hydrogen per mol.). Light absorption : Maximum, 2280 A.; $\varepsilon = 13,000$.

1-*Methoxy*-4-*methylhept*-5-*en*-2-*yn*-4-*ol* (II; R$_1$ = H, R = Me).—Methyl propargyl ether (30 g.) in ether (200 c.c.) was added to a stirred solution of ethylmagnesium bromide (from 10·2 g. Mg) in ether (500 c.c.) during 30 minutes, the reaction being completed by gently refluxing for 2 hours. Ethylideneacetone (38 g.) in ether (200 c.c.) was then added to the cooled (ice) stirred mixture (30 minutes) which was then stirred at 20° for 20 hours. This procedure gave the *methoxy-carbinol* (15 g.), b. p. 72°/3 mm., $n_{\rm D}^{16^\circ}$ 1·4738 (Found : C, 70·2; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%. Active hydrogen (Zerewitinoff) : The carbinol (162 mg.) gave 27·0 c.c. of methane at 21°/755 mm., *i.e.*, 1·05 atoms of active hydrogen per mol.).

1-*Methoxy*-4-*methylhept*-4-*en*-2-*yn*-6-*ol* (III; R$_1$ = H, R = Me).—This was prepared by isomerising the preceding carbinol (5·5 g.) in acetone–dilute sulphuric acid (50% acetone, 1% sulphuric acid) at 20° for 48 hours. The rearranged *methoxy-carbinol* (3 g.) had b. p. 73°/4 mm., $n_{\rm D}^{19^\circ}$ 1·4889 (Found : C, 69·85; H, 9·0. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%. Active hydrogen (Zerewitinoff) : The carbinol (157 mg.) gave 21·6 c.c. of methane at 20°/760 mm., *i.e.*, 0·9 atom of active hydrogen per mol.). Light absorption : Maximum, 2260 A.; $\varepsilon = 11,500$. Inflexion, 2330 A.; $\varepsilon = 10,500$.

7-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexenyl*)-5-*methylhepta*-3 : 5-*dien*-2-*one* (I).—The finely powdered semicarbazone (3 g., Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 733) was suspended in a mixture of ligroin (250 c.c.; b. p. 60—80°) and 2N-sulphuric acid (70 c.c.) and heated under reflux with stirring for 12 hours. This gave the ketone (2·35 g.), b. p. 75—80°(bath temp.)/10^{-4} mm., $n_{\rm D}^{18\cdot5^\circ}$ 1·5475. Light absorption : Maximum, 2825 A.; $\varepsilon = 25,500$ (previous values, $n_{\rm D}^{19^\circ}$ 1·5412 and $\varepsilon = 22,500$).

Condensation of the β-C_{17}-*Ketone* (I) *with Methyl Propargyl Ether*.—Methyl propargyl ether (5 g.) in ether (100 c.c.) was dropped into a cold stirred solution of ethylmagnesium bromide (from 1·35 g. Mg) and the mixture refluxed for 2 hours. The suspension, diluted to about 700 c.c. with ether, was cooled and treated during 20 minutes with a solution of the ketone (2·8 g; constants as above) in ether (50 c.c.), after which the mixture was vigorously stirred and refluxed for 3—4 hours. The product, a viscous orange-coloured oil, had $n_{\rm D}^{19^\circ}$ 1·5204 (Max. 2380 A.; $E_{1\,\rm cm.}^{1\%}$ 660). The product usually underwent dehydration and/or rearrangement on distillation, but on one occasion it distilled at 85—90° (bath temp.)/10^{-4} mm., as a pale yellow viscous liquid with $n_{\rm D}^{17^\circ}$ 1·5280 (Max. 2390 A.; $E_{1\,\rm cm.}^{1\%}$ 750, *i.e.*, $\varepsilon = 24,000$ on assumed composition, IV). On other occasions products with much higher *n* values and entirely different light absorption resulted on attempted distillation, *e.g.*, b. p. 90—110° (bath temp.)/10^{-4} mm., $n_{\rm D}^{14^\circ}$ 1·5570 (Maxima, 2280, 2410, and 3230 A.; $E_{1\,\rm cm.}^{1\%}$ 580, 580, and 480 respectively).

The undistilled condensation product (0·5 g.) was dissolved in acetone–dilute sulphuric acid (200 c.c.; 95% acetone, 0·5% sulphuric acid) and after 20 hours at 19° the product was isolated in the usual way. Distillation gave the rearranged carbinol, 1-*methoxy*-9-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-4 : 7-*dimethylnona*-4 : 6-*dien*-2-*yn*-8-*ol* (V) (0·35 g.) as an orange-red viscous oil, b. p. 100—110° (bath temp.)/10^{-4} mm., $n_{\rm D}^{16^\circ}$ 1·5446 (Found : C, 79·8; H, 10·25. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%). Light absorption : Maximum, 2810 A.; $\varepsilon = 25,000$.

7-(2′ : 6′ : 6′-*Trimethyl*-Δ$^{2'}$-cyclo*hexenyl*)-5-*methylhepta*-3 : 5-*dien*-2-*one* (VI).—A solution of the crude α-ionone C_{14}-aldehyde (12 g., $n_{\rm D}^{20^\circ}$ 1·5028; Heilbron, Johnson, Jones, and Spinks, *loc. cit.*) in a mixture of dry pure benzene (600 c.c.) and dry acetone (150 c.c.) together with freshly sublimed aluminium *tert.*-butoxide (18 g.) was refluxed in an atmosphere of nitrogen for 72 hours. The mixture was treated with water (1000 c.c.) and the separated alumina washed with benzene and finally with methanol. The benzene solution was combined with the extracts, washed with water, dried, and evaporated, finally under diminished pressure. Distillation of the residue from an electrically heated retort gave two fractions : (i) bath temp. 40—65°/10^{-4} mm. (2·2 g.), $n_{\rm D}^{19^\circ}$ 1·5172, chiefly unchanged aldehyde, and (ii) bath temp. 75—80°/10^{-4} mm. (5·2 g.), $n_{\rm D}^{20^\circ}$ 1·5306. Fraction (ii) was treated with semicarbazide acetate (4 g.) in methanol and the crude derivative (2·5 g.), m. p. 156—157°, crystallised during some hours. Recrystallisation from aqueous methanol gave the pure *semicarbazone* of (VI) (2·2 g.), as needles, m. p. 162° (Found: N, 14·2. $C_{18}H_{29}ON_3$ requires N, 13·9%). Light absorption: Maximum, 2950 A.; $\varepsilon = 42,500$. Inflexion, 2810 A.; $\varepsilon = 38,000$. The pure semicarbazone (3·3 g.) suspended in ligroin (150 c.c., b. p. 60—80°) was heated on the steam-bath and rapidly stirred in an atmosphere of nitrogen with sulphuric acid (60 c.c., 2N) during 6 hours. The ligroin layer was separated and the aqueous portion extracted three times with ligroin. The combined extracts were washed with sodium bicarbonate solution and water, dried, and evaporated. Distillation of the residue gave the *ketone* (VI) (1·7 g.), b. p. (bath temp.) 75—80°/10^{-4} mm., $n_D^{18°}$ 1·5446 (Found: C, 82·6; H, 10·3. $C_{17}H_{26}O$ requires C, 82·9; H, 10·6%). Light absorption: Maximum, 2825 A.; $\varepsilon = 24,000$. Treatment of the pure ketone with semicarbazide acetate gave the same semicarbazone, m. p. 162°, as that from the crude ketone.

Condensation of the α-C_{17}-*Ketone* (VI) *with Ethylmagnesium Bromide.*—The ketone (450 mg.) regenerated from its semicarbazone was treated with ethylmagnesium bromide (from 100 mg. Mg) in ether (100 c.c.), the reaction being completed by stirring and refluxing for 2 hours in nitrogen. The product (400 mg.) had b. p. 70—80° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·4942 (Found: C, 83·0; H, 11·7. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%. Active hydrogen (Zerewitinoff): The product (98 mg.) gave 7·2 c.c. of methane at 19°/758 mm., *i.e.*, 0·85 atom of active hydrogen per mol.). Light absorption: Maxima, 2190, 2310, 2380 A.; $\varepsilon = 5500$, 6000 and 6000 respectively.

Since this material gave a positive ketonic reaction with 2 : 4-dinitrophenylhydrazine, a similar undistilled preparation (400 mg.) was treated with Girard's reagent P in the normal manner. The non-ketonic portion, purified by chromatography on alumina, had obviously undergone dehydration since it had $n_D^{16°}$ 1·5230 and a maximum light absorption at 2720 A. ($\varepsilon = 13,000$) and an inflexion at 2820 A. ($\varepsilon = 12,000$).

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