626. *The Synthesis and Prototropic Rearrangement of 4-Hydroxyhept-5-en-3-one.*

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4-Hydroxyhept-5-en-3-one, $\mathrm{CHMe{:}CH{\cdot}CH(OH){\cdot}COEt}$, has been synthesised from crotonaldehyde cyanohydrin and ethylmagnesium bromide and found to undergo double prototropic rearrangement with great ease to heptane-3 : 4-dione, $\mathrm{Me{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}COEt}$. The reaction of crotonaldehyde cyanohydrin with other ethyl- or with methyl-magnesium halides results predominantly in replacement of, rather than addition to, the cyano-group, giving the alcohols $\mathrm{CHMe{:}CH{\cdot}CHR{\cdot}OH}$ (R = Me or Et).

The ultra-violet light absorption properties of α-keto-alcohols and their derivatives are briefly discussed and appreciable spectral interaction is noted between the unconjugated ethylenic and carbonyl chromophores in the $\mathrm{C{=}C{-}C{-}C{=}O}$ system.

The work of Heilbron, Jones, Smith, and Weedon (*J.*, 1946, 54; cf. Braude and Timmons, *J.*, 1953, 3131) leads to the conclusion that βγ-ethylenic α-hydroxy-ketones containing the system $\mathrm{C{=}C{\cdot}CH(OH){\cdot}C{=}O}$ (*e.g.*, I) are converted with great ease into α-diketones (*e.g.*, II) by double prototropic rearrangement. As systems of this type have only been postulated as probable intermediates, but have not actually been isolated, it was of interest to synthesise a keto-alcohol such as (I) and confirm the occurrence of the expected reaction.

An obvious route to (I) is by the reaction of Grignard reagents with crotonaldehyde cyanohydrin. The addition of Grignard reagents to the cyano-group of aldehyde cyanohydrins has been described in a number of cases (cf. Gauthier, *Compt. rend.*, 1911, **152**, 1100; Tiffeneau and Levy, *Bull. Soc. chim.*, 1925, **37**, 1247; Willstaedt, *Svensk Kem. Tidskr.*, 1941, **53**, 416; Ruggli and Hegedüs, *Helv. Chim. Acta*, 1942, **25**, 1285). On the other hand, ketone cyanohydrins, originally claimed to react in an analogous manner (Gauthier, *Compt. rend.*, 1911, **152**, 1259), were later shown to yield tertiary alcohols by replacement of, instead of addition to, the cyano-group (Geurden, *Bull. Soc. chim. Belg.*, 1926, **35**, 253; Khaletskii, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2854). Crotonaldehyde cyanohydrin and alkylmagnesium halides in ether reacted in both ways, and the proportion of replacement and addition was found to depend in a somewhat unexpected manner on the nature of the alkyl and the halide groups (Table 1). With MeMgBr, MeMgI, EtMgCl, and EtMgI replacement predominates, whereas with EtMgBr the keto-alcohol (I; R = Et), formed by addition, is the main isolatable product. In each case, the keto-alcohol was accompanied by some of the corresponding saturated diketone (II), the expected product of double prototropic rearrangement. Higher-boiling materials were also formed, which were not investigated. In contrast to the comparatively low overall yields obtained from crotonaldehyde cyanohydrin, butyraldehyde cyanohydrin and ethylmagnesium bromide gave a 90% yield of the saturated keto-alcohol, 4-hydroxyheptan-3-one (IV; R = Et).

$$\begin{tikzcd}
\text{(III)}\ \mathrm{CHMe{:}CH{\cdot}CHR{\cdot}OH} & \mathrm{CHMe{:}CH{\cdot}CH(OH){\cdot}CN} \arrow[l] \arrow[r] & \mathrm{CHMe{:}CH{\cdot}CH(OH){\cdot}COR}\ \text{(I)} \arrow[d] \\
\underset{\text{(IV)}}{\mathrm{Pr{\cdot}CH(OH){\cdot}COR}} \arrow[r] & \underset{\text{(II)}}{\mathrm{Me{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}COR}} & {[\mathrm{Me{\cdot}CH_2{\cdot}CH{:}C(OH){\cdot}COR}]} \arrow[l]
\end{tikzcd}$$

The keto-alcohols (I) and diketones (II) were isolated in the pure state only from the reaction with ethylmagnesium bromide, but the proportions of the three main products could be estimated spectrometrically in each case, on the assumption that the characteristic ultra-violet and visible absorptions of the methyl and ethyl homologues are identical. The keto-alcohols (I) exhibit well-defined low-intensity bands at 2810 Å ($\varepsilon \sim 300$) associated with the $\mathrm{C(OH){\cdot}CO}$ grouping, while the diketones (II) exhibit bands near 4300 Å ($\varepsilon \sim 20$) characteristic of the $\mathrm{CO{\cdot}CO}$ grouping. The proportion of the alcohols (III), which are optically transparent in these regions, was obtained by difference. The results are summarised in Table 1.

The alcohols (III) were identified by comparison with authentic specimens, prepared from crotonaldehyde and methyl- or ethyl-magnesium bromide, and by their *p*-nitrobenzoates and α-naphthylurethanes. It was suggested by Geurden and by Khaletskii (*locc. cit.*) that the formation of alcohols in the reaction of cyanohydrins with Grignard reagents involves decomposition of the cyanohydrin to the ketone or aldehyde, followed by normal addition to the carbonyl group. It seems far more probable, however, that a direct nucleophilic replacement of the cyano-group occurs, which has been observed with some other nitriles (cf. Rabe and Pasternack, *Ber.*, 1913, **46**, 1026; Stevens, Cowan, and McKinnon, *J.*, 1931, 2568; Fuson, Emmons, and Tull, *J. Org. Chem.*, 1951, **16**, 648; Schultz, *J. Amer. Chem. Soc.*, 1952, **74**, 5793) and will be favoured by inductively electron-attracting substituents (such as OH).

TABLE 1. *Yields* (%) *of products from crotonaldehyde cyanohydrin and* RMgX.

	MeMgBr	MeMgI	EtMgCl	EtMgBr	EtMgI
Alcohol (III)	18	26	25	3	28
Keto-alcohol (I)	1	3	3	23	8
Diketone (II)	1	1	1	8	5
Total	20	30	29	34	41

Extensive fractionation of the products from the reaction with ethylmagnesium bromide gave the keto-alcohol 4-hydroxyhept-5-en-3-one (I; R = Et) and the diketone, heptane-3 : 4-dione (II; R = Et). Heptane-3 : 4-dione was isolated through the bisulphite derivative and was characterised by the phenylosazone, bis-2 : 4-dinitrophenylhydrazone, and quinoxaline, identical with the derivatives of an authentic sample of the diketone prepared by the oxidation of 3-hydroxyheptan-2-one (IV; R = Et) with lead tetra-acetate. 4-Hydroxyhept-5-en-3-one was characterised by a mono-2 : 4-dinitrophenylhydrazone. On treatment with phenylhydrazine in the presence of acetic acid, it afforded the phenylosazone of heptane-3 : 4-dione, evidently formed by prototropic rearrangement under the mildly acid conditions. The ready occurrence of prototropic rearrangement in systems of the type C=C–CR(OH)–C=O, where R = H, is thus confirmed. It has been shown (Braude and Timmons, *loc. cit.*) that anionotropy in systems of this type can be effected if prototropy is blocked by suitable alkyl substitution and it is highly probable that both types of reaction proceed through the same intermediate oxonium ion C=C–CR(OH_2^+)–X, formed by reversible addition of a proton to the hydroxyl group. If R = Me, anionotropy takes place, though it is greatly retarded when X contains the strongly electron-attracting carbonyl group. If R = H, prototropy becomes possible and separation of R as a proton will be assisted by the adjacent positive change in the oxonium ion. In this case, the mode of rearrangement is controlled by the nature of the substituent X; anionotropy predominates when X is either an electron-donating or even a moderately electron-attracting group such as –C≡CH (Braude, *Quart. Reviews*, 1950, **4**, 404), but only prototropy is observed when X is a very strongly electron-attracting group such as –COMe.

Ultra-violet light absorption data for the α-keto-alcohols (I) and (IV) and for some derivatives and related compounds are given in Table 2. The three main generalisations which emerge are: (1) an α-hydroxyl or α-alkoxyl substituent displaces the low-intensity *R*-band near 2800 Å associated with an isolated carbonyl group towards longer wave-lengths by *ca.* 50 Å, (2) an α-hydroxyl substituent has the opposite effect on the long-wave-length bands of the corresponding 2 : 4-dinitrophenylhydrazones which are displaced by *ca.* 50 Å to shorter wave-lengths, and (3) a βγ-ethylenic bond causes a four- to ten-fold increase in the intensity of the 2800-Å band associated with the carbonyl group.

The bathochromic effects of α-hydroxyl as well as other saturated substituents in the R–C–C=O system have been noted previously (cf. Rice, *J. Amer. Chem. Soc.*, 1920, **42**, 725; Herold, *Z. physikal. Chem.*, 1932, **18**, *B*, 265; Lowry and Lishmund, *J.*, 1935, 1313); their interpretation in terms of the forbidden transition of oxygen *p* electrons to the anti-bonding π orbital thought to be responsible (McMurry, *J. Chem. Physics*, 1941, **9**, 231) for the 2800-Å bands is not very clear. The hypsochromic effect of α-hydroxyl groups in hydrazones has also been observed in steroid derivatives (Fleisher and Kendall, *J. Org.*

Chem., 1951, **16**, 566), and similar effects are found with acetoxyl, carboxyl,* and halogeno-substituents (Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331), whereas methyl groups have bathochromic effects (Braude and Jones, *J.*, 1945, 498). The excited state of the electronic transition giving rise to the characteristic band of the 2 : 4-dinitrophenylhydrazones is polarised in the sense $CX{-}C{=}N{-}NH^+{=}C_6H_4{=}N(O){-}O^-$ and the hypsochromic displacements are ascribable to the counter-polarisation $X^- \; C{=}C{-}N^+$ due to hyperconjugative electron attraction which will be effective in an allowed transition. Such interaction is analogous to that observed in allylic ($X{-}C{-}C{=}C$) and similar systems (Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1951, 2085; Armitage and Whiting, *J.*, 1952, 2005), although in these cases the displacements are uniformly bathochromic because the transition will be facilitated by hyperconjugative polarisation in either direction, *e.g.*, $X^- \; C{=}C{-}C^+$ or $X^+ \; C{=}C{-}C^-$.

TABLE 2. *Ultra-violet absorption of α-keto-alcohols and derivatives.*

	Ketone *		2 : 4-Dinitrophenylhydrazone †	
	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
$Pr^n\cdot COMe$	2770	21 [1]	3650	22,000
$Pr^i\cdot COMe$	2800	21 [1]	—	—
$Me_2C(OH)\cdot COMe$	2810 2910	25	3550	23,000
$Pr^n\cdot CH(OH)\cdot COEt$	2820 2910	40	3590	26,000
$Pr^i\cdot CH(OH)\cdot COPr^i$	2880	30	3600	20,000
$Me\cdot C(OMe)_2\cdot COMe$	2960	25 [2]	—	—
CHMe:CH·CH(OH)·COEt	2810 2900	300	3530	31,000
$CMe_2{:}CH\cdot CMe(OH)\cdot COMe$	2810	230 [2]	3580	23,000 [2]
$CH_2{:}CHMe\cdot CH_2\cdot COMe$	2900	80 [3]	—	—
$Ph\cdot CMe_2\cdot COMe$	2900	160 [4]	—	—

* In ethanol. † In chloroform.

[1] Rice, *loc. cit.* [2] Braude and Timmons, *J.*, 1953, 3131. [3] Gray, Rasmussen, and Tunnicliff, *J. Amer. Chem. Soc.*, 1947, **69**, 1630 (octane solution). [4] Kumler *et al.*, *loc. cit.*

The effect of a βγ-ethylenic bond in the $C{=}C{-}C{-}C{=}O$ systems provides an interesting example of interaction between unconjugated chromophores (Braude, *J.*, 1949, 1902) and is reminiscent of the strong intensification of the carbonyl band observed in the α-phenyl ketone system $Ph{-}C{-}C{=}O$ (Kumler, Strait, and Alpen, *J. Amer. Chem. Soc.*, 1950, **72**, 1463, 4558). It may be represented as a hyperconjugative interaction of the type $C{=}C{-}C{-}C{=}O \longleftrightarrow C{=}C{-}C^+ \; C{\equiv}O^- \longleftrightarrow C^+{-}C{=}C \; C{\equiv}O^-$.

EXPERIMENTAL

M. p.s marked (K) were determined on a Kofler block and are corrected. Other m. p.s are uncorrected (sealed capillary). Light absorption data are only given when not included in Table 2.

4-Hydroxyhept-5-en-3-one (I; R = Et).—Crotonaldehyde cyanohydrin (97 g.; b. p. 95°/5 mm.; cf. Moureu, Murat, and Tampier, *Bull. Soc. chim.*, 1921, **29**, 29) in ether (300 ml.) was added during 2 hr. to a stirred solution of ethylmagnesium bromide (from Mg, 72 g.) in ether (1 l.) under nitrogen. After 15 hr., saturated aqueous ammonium chloride (700 g.) was added, and the ethereal layer was separated, dried (Na_2SO_4), and distilled. A total of 40 g. (31%) of products boiling in the range 50—85°/18 mm. was obtained, which had n_D^{23} 1·425—1·442, $\lambda_{max.}$ 2600 ($E^{1\%}_{1\,cm.}$ 20) and 4300 Å ($E^{1\%}_{1\,cm.}$ 0·6), and consisted of a mixture of (i) 4-hydroxyhept-5-en-3-one (*ca.* 70%), (ii) heptane-3 : 4-dione (*ca.* 20%), and (iii) hex-4-en-3-ol (*ca.* 10%), which were separated as follows :

(i) Extensive fractionation afforded pure *4-hydroxyhept-5-en-3-one* as a colourless oil, b. p. 58—59°/0·7 mm., 78—79°/12 mm., n_D^{16} 1·4532 (Found : C, 65·7; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). The *2 : 4-dinitrophenylhydrazone* separated from aqueous methanol in yellow needles, m. p. 93—94° (Found : C, 50·9; H, 5·0; N, 18·2. $C_{13}H_{16}O_5N_4$ requires C, 50·7; H, 5·2; N, 18·2%).

Treatment of the keto-alcohol (1 g.) with phenylhydrazine hydrochloride (3·6 g.) and sodium

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* Thus, pyruvic acid 2 : 4-dinitrophenylhydrazone shows $\lambda_{max.}$ 3510 Å (ε 24,000) in $CHCl_3$. The value 3600 Å given earlier (Braude and Jones, *loc. cit.*) is incorrect; we are indebted to Professor H. Reich (Utah) for drawing our attention to this error.

acetate (2·7 g.) in 50% aqueous ethanol at 80° (2 hr.) gave heptane-3 : 4-dione phenylosazone, m. p. 106—107°, undepressed on admixture with the sample described below.

(ii) The lower-boiling fractions were extracted with aqueous sodium hydrogen sulphite, and the aqueous extract was concentrated, acidified with hydrochloric acid, and steam-distilled, giving heptane-3 : 4-dione, b. p. 92°/102 mm., n_D^{19} 1·4118 (Found : C, 65·3; H, 9·6. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%) (Favorskii and Venus-Danilova, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 369, give b. p. 58—61°/25 mm.). It formed a bis-2 : 4-dinitrophenylhydrazone, m. p. 263—264° and a phenylosazone, m. p. 106—107°, undepressed on admixture with the authentic specimens described below.

(iii) Treatment of the residual low-boiling fractions from (ii) with *p*-nitrobenzoyl chloride in pyridine gave the *p*-nitrobenzoate, m. p. and mixed m. p. 41—43°, of hex-2-en-4-ol. An authentic sample of the alcohol was prepared from crotonaldehyde and ethylmagnesium bromide and had b. p. 62°/30 mm., n_D^{17} 1·4368 (von Auwers and Westermann, *Ber.*, 1921, **54**, 2996, give b. p. 59°/27 mm., n_D^{23} 1·4329). The p-*nitrobenzoate* crystallised from aqueous methanol in plates, m. p. 42—44° (Found : C, 62·3; H, 6·2; N, 5·7. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·1; N, 5·6%).

Seven similar runs with some variations in the conditions of the Grignard addition gave total yields of 20—40% and some differences in the composition of the products, but no definite correlation was established.

4-*Hydroxyheptan*-3-*one* (IV; R = Et).—Butyraldehyde cyanohydrin (38 g.; b. p. 92°/1 mm., n_D^{16} 1·4225; Ultée, *Rec. Trav. chim.*, 1909, **28**, 252) was added to ethylmagnesium bromide (from Mg, 29 g.), and the product isolated as above, giving 4-hydroxyheptan-3-one as a colourless liquid (44 g., 91%), b. p. 71°/11 mm., n_D^{19} 1·4297 (Found : C, 64·8; H, 10·6%; *M*, in camphor, 135; active H, 1·01 atoms. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%; *M*, 130). The semicarbazone separated from water in plates, m. p. 115° (Found : C, 51·6; H, 9·2; N, 22·5. Calc. for $C_8H_{17}O_2N_3$: C, 51·3; H, 9·2; N, 22·5%) (Favorskii and Venus-Danilova, *loc. cit.*, give b. p. 74—75°/18 mm. for the keto-alcohol and m. p. 121—122° for the semicarbazone). The 2 : 4-*dinitrophenylhydrazone* separated from aqueous methanol in yellow needles, m. p. 96° (Found : C, 50·6; H, 6·1; N, 18·3. $C_{13}H_{18}O_5N_4$ requires C, 50·3; H, 5·9; N, 18·1%). Treatment of the keto-alcohol with phenylhydrazine acetate gave the phenylosazone, m. p. 107°, of heptane-3 : 4-dione, undepressed on admixture with the sample described below.

Heptane-3 : 4-*dione* (II; R = Et).—(*a*) 4-Hydroxyheptan-3-one (3·9 g.), lead tetra-acetate (13·4 g.), and anhydrous ether (90 ml.) were heated under reflux for 5 hr. Isolation of the product by means of sodium hydrogen sulphite as above gave the dione (2 g.), b. p. 98—99°/105 mm., $\lambda_{max.}$ 2640 and 4300 Å (ε 35 and 21) in hexane, $\lambda_{max.}$ 2670 and 4210 Å (ε 35 and 16) in EtOH (Found : C, 65·3; H, 9·6. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%) (Favorskii and Venus-Danilova, *loc. cit.*, give b. p. 58—61°/25 mm.). The *phenylosazone* separated from aqueous methanol in yellow plates, m. p. 107°, $\lambda_{max.}$ 3530 Å (ε 51,000) in EtOH (Found : C, 73·9; H, 7·8; N, 18·3. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8; N, 18·2%). The *bis*-2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene–methanol or aqueous dioxan in red needles, m. p. 264° (K), $\lambda_{max.}$ 2600, 2800, and 3980, $\lambda_{infl.}$ 4350 Å (ε 38,000, 28,000, 52,000, and 45,000) in $CHCl_3$ (Found : C, 47·1; H, 4·4; N, 22·9. $C_{19}H_{20}O_8N_8$ requires C, 46·7; H, 4·1; N, 22·9%). The *quinoxaline* derivative separated from aqueous methanol in buff crystals, m. p. 44° (K) (Found : N, 14·0. $C_{13}H_{16}N_2$ requires N, 14·0%).

(*b*) 4-Hydroxyhept-5-en-3-one (1 g.) was added to potassium dichromate (0·4 g.) in sulphuric acid (10%; 20 ml.). After 1 hr., the mixture was extracted with ether. Evaporation gave heptane-3 : 4-dione (0·6 g.) which on treatment with Brady's reagent gave an immediate precipitate of the bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 259°.

Reactions of Alkylmagnesium Halides with Crotonaldehyde Cyanohydrin.—The reactions were performed as in the case of ethylmagnesium bromide, and the compositions of the products were estimated spectrometrically as described above. Only the principal products were isolated.

(*a*) Methylmagnesium bromide gave pent-3-en-2-ol (14 g., 18%), b. p. 75°/180 mm., n_D^{19} 1·4305 (*p*-nitrobenzoate, m. p. and mixed m. p. 54—57°). An authentic sample prepared from crotonaldehyde had b. p. 120°/760 mm., n_D^{15} 1·4311 (Auwers and Westermann, *loc. cit.*, give b. p. 64°/62 mm., n_D^{18} 1·4282). The p-*nitrobenzoate* crystallised from aqueous methanol in plates, m. p. 54—55° (Found : N, 5·5. $C_{12}H_{13}O_4N$ requires N, 5·6%). The α-*naphthylurethane* separated from aqueous methanol in needles, m. p. 110—111° (K) (Found : C, 75·2; H, 6·6; N, 5·8. $C_{16}H_{17}O_2N$ requires C, 75·0; H, 6·7; N, 5·5%).

(*b*) Methylmagnesium iodide gave pent-3-en-2-ol (18 g., 26%), b. p. 65°/80 mm., n_D^{17} 1·4297, identified by the *p*-nitrobenzoate, m. p. 54—55°, and α-naphthylurethane, m. p. 108—110°.

(*c*) Ethylmagnesium chloride gave hex-4-en-3-ol (25 g., 28%), b. p. 135—138°, n_D^{22} 1·4312, identified as the *p*-nitrobenzoate, m. p. and mixed m. p. 42—44°. Heptane-3 : 4-dione was identified in the crude product as the bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 260—263°.

(*d*) Ethylmagnesium iodide gave a mixture of products (total 34 g., 41%; see Table 1) in which hex-4-en-3-ol was identified by the *p*-nitrobenzoate, m. p. 43—44°, and heptane-3 : 4-dione by the bis-2 : 4-dinitrophenylhydrazone, m. p. 260°.

*iso*Butyroin, prepared by the method of Bouveault and Locquin (*Bull. Soc. chim.*, 1906, **35**, 642), had b. p. 82·5°/26 mm., 182°/759 mm., n_D^{28} 1·4232 (Bouveault and Locquin, *loc. cit.*, give b. p. 83°/26 mm.). The *toluene*-p-*sulphonate* crystallised from aqueous methanol in colourless needles, m. p. 49—50° (K) (Found: C, 60·5; H, 7·7; S, 10·6. $C_{15}H_{22}O_4S$ requires C, 60·4; H, 7·4; S, 10·7%). The hydroxy-ketone with 2 : 4-dinitrophenylhydrazine sulphate in aqueous ethanol during 5 days slowly gave a precipitate, which was separated by chromatography on alumina with benzene and chloroform into iso*butyroin* 2 : 4-*dinitrophenylhydrazone* (*α-form*) (10%) which crystallised from aqueous methanol in yellow needles, m. p. 98—101° (K) (Found: C, 52·8; H, 6·4; N, 17·3. $C_{14}H_{20}O_5N_4$ requires C, 51·9; H, 6·2; N, 17·2%), and a *β-form* (50%) which crystallised from aqueous methanol in orange prisms, m. p. 145—147° (K), $\lambda_{max.}$ 3730 Å (ε 22,500) in $CHCl_3$ (Found: C, 52·1; H, 6·4; N, 17·2%).

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