99. *Researches on Acetylenic Compounds. Part V. αβ-Acetylenic Hydroxy-acids.*

By L. J. Haynes and E. R. H. Jones.

Carboxylation of ethynylcarbinols [*e.g.*, $-\mathrm{CH(OH){\cdot}C{\vdots}CH}$], by treating the Grignard complexes with solid carbon dioxide in an autoclave, gives excellent yields of the *αβ*-acetylenic hydroxy-acids (*e.g.*, I—IV). The choice of solvent is important as the solubility of the initial Grignard complex has considerable influence upon the yield of acid. Decarboxylation and esterification as well as the ultraviolet light absorption properties of the acids have been studied.

When the above procedure is applied to the vinylacetylenic carbinol, hex-3-en-5-yn-2-ol, a furanacetic acid is formed together with the expected carboxylation product. This intramolecular hydration is analogous to that observed when the carbinol itself is treated with acids in the presence of mercuric salts.

αβ-Acetylenic carboxylic acids can generally be obtained readily by reaction of the Grignard complexes or sodio-derivatives of acetylenic hydrocarbons with carbon dioxide, ethyl carbonate, or ethyl chloroformate. The carboxylation of ethynylcarbinols, however, appears to have presented considerable difficulty to previous workers. Lespieau and Viguier (*Compt. rend.*, 1908, **146**, 295; see also Lespieau, *Ann. Chim.*, 1912, **27**, 178, 184) described carboxylations of the Grignard complexes from propargyl alcohol and ethylethynylcarbinol, but no yields were stated, and the authors noted that absorption of carbon dioxide was very slow and recommended the passage of gas for periods of up to a fortnight. Salkind and Michantjev (*J. Gen. Chem. Russia*,

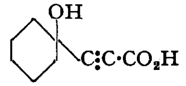
$$\mathrm{R{\cdot}C{\vdots}CH \longrightarrow R{\cdot}C{\vdots}C{\cdot}CO_2H}$$

1941, **11**, 92) obtained only a 1·25% yield of the acid (I; $R_1 = R_2 = Me$) on carboxylation of the Grignard complex from dimethylethynylcarbinol and state that this can be improved somewhat by passing in carbon dioxide for five days. In connection with the synthesis of the selective growth inhibitor, δ-hexenolactone (Haynes and Jones, *Nature*, 1945, **155**, 730), and related substances, a detailed study of the carboxylation of ethynylcarbinols has been undertaken.

In the above mentioned investigations the reactions were presumably attempted in ethereal solutions. It has now been found that the choice of solvent for these carboxylations is extremely important, as the Grignard complexes from simple ethynylcarbinols are only very sparingly soluble in ether. Benzene has proved to be a useful solvent for this purpose and, by carboxylating under pressure in the presence of an excess of solid carbon dioxide at ordinary temperatures for twenty-four hours, excellent conversions (up to 70%) of the carbinols and yields (usually 80—90%) of the acetylenic hydroxy-acids (I—IV) have been obtained. (The comparatively simple experimental procedure is described in detail below.) By this means methyl-, propyl-, and dimethyl-ethynylcarbinols have been converted into the *acids* (I; $R_1 = H$; $R_2 = Me$), (I; $R_1 = H$; $R_2 = Pr$), and (I; $R_1 = R_2 = Me$); pent-1-yn-4-ol gave (II) (Haynes and Jones, *loc. cit.*), and

(I.) $CR_1R_2(OH)\cdot C\vdots C\cdot CO_2H$ $CHMe(OH)\cdot CH_2\cdot C\vdots C\cdot CO_2H$ (II.)

(III.)

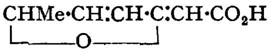


$CHMe(OH)\cdot CH{:}CH\cdot C\vdots C\cdot CO_2H$ (IV.)

ethynyl*cyclo*hexanol gave the highly crystalline *acid* (III) in excellent yield.* From hex-3-en-5-yn-2-ol (Jones and McCombie, *J.*, 1943, 261) two isomeric acids were obtained, that produced in greater yield being proved to be *hex-3-en-1-yn-5-ol-1-carboxylic acid* (IV) by its light absorption properties and conversion into 4-aceto-*n*-valeric acid.

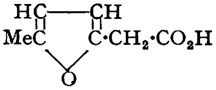
The by-product formed during the carboxylation of hex-3-en-5-yn-2-ol, and accompanying the vinyl-acetylenic hydroxy-acid (IV), is 5-methylfuran-2-acetic acid (VI). This is proved by its m. p., its light absorption properties, and the formation of 2 : 5-dimethylfuran on decarboxylation. The intramolecular hydration by which this acid is formed is exactly analogous to that leading to 2 : 5-dimethylfuran on hydration of hex-3-en-5-yn-2-ol with dilute acids in the presence of mercuric salts (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54), an intermediate stage such as (V) probably being involved. Whether this hydration occurs during the actual carboxylation reaction or on the subsequent treatment of the magnesium complex with acids has yet to be determined. It may well be that the difficulty we have experienced in isolating any homogeneous product from the carboxylation of propenylethynylcarbinol is associated with complications due to simultaneous hydration and rearrangement reactions.

(V.)



$CHMe\cdot CH{:}CH\cdot C{:}CH\cdot CO_2H$

(VI.)



A comparison, using hexynylmagnesium bromide, of the yields accruing with the carbon dioxide, ethyl carbonate, and ethyl chloroformate processes for the introduction of the carboxylic acid group, reveals the superiority, in this respect, of the straightforward carboxylation reaction.

The αβ-acetylenic hydroxy-acids are crystalline solids which are stable, but decompose above their melting points. With traces of copper bronze at about 200° quantitative decarboxylation into the parent ethynylcarbinols takes place. The acids can be characterised very conveniently as their *S-benzyl*iso*thiouronium* salts, and the *ethyl* esters are readily produced in excellent yields by refluxing with alcoholic sulphuric acid. Treatment of the resulting esters [except the ester of (III)] with aqueous ammonia gives non-crystalline products, doubtless due to addition to the acetylenic bond (cf. Feist, *Annalen*, 1906, **345**, 100).

Light absorption data for the acids and their esters in alcoholic solutions are given in the accompanying table. As in the corresponding αβ-ethylenic acids, the maximal absorption is just beyond the limit of the usual ultraviolet range, and consequently only the intensities at convenient wavelengths are recorded.

	Acid.		Ethyl ester.	
	λ, A.	ε.	λ, A.	ε.
(I; $R_1 = H$; $R_2 = Me$)	2110	4,500	—	—
(I; $R_1 = H$; $R_2 = Pr$)...	2150	4,500	2140‡	5,000
(I; $R_1 = R_2 = Me$)	2150	4,000	2150	4,500
(II)	2150	4,000	2160	6,000
(III)	2150	4,500	2160	7,000
$Bu\cdot C\vdots C\cdot CO_2H$	2140	6,500	2150	5,000
Cf. Crotonic acid [1]	2040*	11,500	—	—
(IV)	2455*	12,000	—	—
	2560†	9,500	2480*	14,000
Cf. Sorbic acid	2540*	24,800	—	—

* Maximum. † Inflexion. ‡ Methyl ester. [1] Smakula, *Angew. Chem.*, 1934, **47**, 657.

EXPERIMENTAL.

(Light absorption data obtained with alcoholic solutions.)

Hex-1-yn-1-carboxylic Acid.—A solution of 1-hexyne (24 g.) in ether (25 c.c.) was added to an ethereal solution of ethylmagnesium bromide (from 6 g. of magnesium) and the mixture refluxed for 4 hours. The solution of the Grignard

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* Hydrogenation of the acid (III) to the *spiro*-lactone, followed by dehydration and cyclisation of the acid chloride, appears to furnish a convenient route to 1-hydrindenone and related substances (cf. Chuang, Tien, and Ma, *Ber.*, 1936, **69**, 1494; Haberland and Heinrich, *ibid.*, 1939, **72**, 1222).

complex was cooled and poured on to a large excess (*ca.* 200 g.) of solid carbon dioxide in a steel autoclave of capacity *ca.* 1 l. The autoclave was sealed, shaken at room temperature for 24 hours, and then allowed to stand for 48 hours. Excess pressure was then released and the white powdery complex transferred to a beaker and treated with ice and 2N-sulphuric acid (*ca.* 500 c.c.). After the initial vigorous effervescence had subsided, isolation with ether in the usual manner gave hex-1-yn-1-carboxylic acid (24·9 g.; 72%), b. p. 128°/12 mm., 93°/3 mm., $n_{\text{D}}^{16^\circ}$ 1·4633 (Zoss and Hennion, *J. Amer. Chem. Soc.*, 1941, **63**, 1152, give b. p. 122°/10 mm., $n_{\text{D}}^{20^\circ}$ 1·4619).

*Ethyl Hex-*1-*yn-*1-*carboxylate.*—(a) A solution of 1-hexynylmagnesium bromide (prepared as above, from 6 g. of magnesium) in benzene–ether (300 c.c.; 1 : 1) was added dropwise during 6 hours to a vigorously stirred, gently refluxing, solution of ethyl carbonate (40 g.) in ether (150 c.c.) in nitrogen. As the addition proceeded, a white crystalline solid separated and the solution assumed a dark brown colour. The reaction mixture was stirred overnight at 20° and the unreacted Grignard complex decomposed with ammonium chloride solution (ice). Isolation by the normal procedure gave ethyl hex-1-yn-1-carboxylate (14·6 g.), b. p. 105—106°/16 mm., $n_{\text{D}}^{14^\circ}$ 1·4491 (Moureau and Delange, *Bull. Soc. chim.*, 1903, **29**, 653 give b. p. 106—108°/24 mm.).

(b) A solution of 1-hexynylmagnesium bromide (from 6 g. of magnesium) in benzene–ether (300 c.c.; 1 : 1) was added dropwise during 3½ hours to a vigorously stirred solution of ethyl chloroformate (35 g.) in ether (*ca.* 200 c.c.) at 20° in nitrogen. A white precipitate formed as the addition proceeded. The unreacted Grignard complex was decomposed with ammonium chloride solution (ice); isolation with ether gave ethyl hex-1-yn-1-carboxylate (10·1 g.), b. p. 103—105°/18 mm., $n_{\text{D}}^{15^\circ}$ 1·4483, and *ca.* 2 g. of ethyl carbamate, b. p. 85°/18 mm., m. p. 49—50°, undepressed on admixture with an authentic specimen.

Identical amides were obtained from each specimen of ester on shaking overnight at 20° with ammonia (*d* 0·88). They separated from light petroleum (b. p. 60—80°) in leaflets, m. p. 68—69°, undepressed on admixture with each other (Zoss and Hennion, *loc. cit.*, give m. p. 68—69°).

Carboxylation of Ethynylcarbinols. General Method.—Ethylmagnesium bromide (from 1 g.-mol. of magnesium) was prepared in ethereal solution in the usual way, and the excess of ether evaporated during the addition of sodium dried AnalaR benzene (200 c.c.). The ethynylcarbinol (½ g.-mol.) in benzene (100 c.c.) was added to the ice-cooled solution during 1½ hours and the mixture refluxed for 2 hours. The solution of the Grignard complex was poured on to a large excess (*ca.* 200 g.) of solid carbon dioxide in a steel autoclave, capacity *ca.* 1 l., which was then sealed and shaken at room temperature for 24 hours. The resulting complex was hydrolysed with ice and a 20% excess of the calculated quantity of 15% sulphuric acid at 0°. After the initial vigorous effervescence had subsided, the aqueous solution was saturated with salt and extracted with ether. The ethereal extract was washed thoroughly with saturated sodium bicarbonate solution. After extraction of any non-acid material with ether, the bicarbonate washings were acidified with 15% sulphuric acid, saturated with salt, and extracted with ether. Owing to the great solubility of the lower molecular weight acids in water, extractions in these cases were carried out in a continuous extraction apparatus. Evaporation of the ethereal solution after drying (sodium sulphate), gave the acetylenic hydroxy-acid, generally as a syrupy liquid which solidified completely on standing at 0° for some hours. Unchanged carbinol was recovered on distillation of the residue remaining after evaporation (through a 12 inch Dufton column) of the residual ethereal solution from the sodium bicarbonate washing.

β-(1′-*Hydroxy-*1′-cyclo*hexyl*)*propiolic Acid* (III).—From 1-ethynyl*cyclo*hexanol (¼ g.-mol.; prepared by the method detailed by Heilbron, Jones, and Weedon, *J.*, 1945, 81, for propenylethynylcarbinol). The Grignard complex was prepared in ether (250 c.c.) in which it was completely soluble. The *acid* (30 g.; 72% conversion; 9 g. of carbinol recovered) readily solidified on cooling and crystallised from benzene–ethyl acetate in plates, m. p. 125° (Found : C, 64·35; H, 7·25. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). A mixture of the acid (1 g.) and copper bronze (10 mg.) was heated at 200°/20 mm. Ethynyl*cyclo*hexanol (0·5 g.) distilled, having $n_{\text{D}}^{19^\circ}$ 1·4818 and m. p. 28°, undepressed on admixture with an authentic specimen. The acid (5 g.) was refluxed for 16 hours with alcoholic sulphuric acid (1%; 25 c.c.); isolation by the usual procedure gave *ethyl β-*(1′-*hydroxy-*1′-cyclo*hexyl*)*propiolate* (5 g.), as a viscous odourless liquid, b. p. 93°/2 mm., $n_{\text{D}}^{20^\circ}$ 1·4910 (Found : C, 67·35; H, 8·45. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). The ester (0·5 g.) was hydrolysed on standing with alcoholic potassium hydroxide (50 c.c.; 2%) for 28 hours. Isolation by the usual procedure gave the acid (0·3 g.) which did not depress the m. p. of an authentic sample. The ester (1 g.) was shaken overnight at 20° with ammonia (*d* 0·88; *ca.* 10 c.c.); it dissolved completely and, on scratching, the solution deposited needles of the *amide* (0·8 g.), m. p. 157°, after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) or water (Found : C, 64·75; H, 7·95. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·85%). Light absorption : Maximum, 2150 A.; $\varepsilon = 7{,}500$.

*Pent-*1-*yn-*4-*ol-*1-*carboxylic Acid* (II).—Pent-1-yn-4-ol (42 g.; Kreimeier, U.S.P. 2,106,182) was carboxylated by the general method to give *pent-*1-*yn-*4-*ol-*1-*carboxylic acid* (40 g.; 62·5% conversion, 6·7 g. carbinol recovered) as a very hygroscopic, crystalline solid. The acid, sublimed at 50° (bath temp.)/10^{-4} mm., had m. p. 59° (Found : C, 56·55; H, 6·2. $C_6H_8O_3$ requires C, 56·25; H, 6·3%). The p-*bromophenacyl* ester separated from aqueous alcohol as lustrous plates, m. p. 78—80° (Found : C, 51·6; H, 4·0. $C_{14}H_{13}O_4Br$ requires C, 51·7; H, 4·05%). The S-*benzyl*iso*thiouronium* salt crystallised from alcohol in micro-laths, m. p. 157° (decomp.) (Found : C, 57·4; H, 6·35. $C_{14}H_{18}O_3N_2S$ requires C, 57·1; H, 6·15%). The *ethyl* ester prepared as above had b. p. 90°/0·2 mm., $n_{\text{D}}^{19^\circ}$ 1·4660 (Found: C, 61·7; H, 8·1. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%). A solution of the acid (1 g.) in methyl acetate (35 c.c.) was shaken with hydrogen in presence of platinic oxide until absorption of hydrogen was complete. The δ-hexolactone obtained on removal of catalyst and solvent had $n_{\text{D}}^{18.5^\circ}$ 1·4448 (Linstead and Rydon, *J.*, 1934, 2000, give $n_{\text{D}}^{20^\circ}$ 1·4451). The S-*benzyl*iso*thiouronium* salt of the corresponding hydroxy-acid separated from acetone in leaflets, m. p. 128—129° (Found : C, 56·4; H, 7·65. $C_{14}H_{22}O_3N_2S$ requires C, 56·35; H, 7·45%).

3-*Methylbut-*1-*yn-*3-*ol-*1-*carboxylic Acid* (I; $R_1 = R_2 = Me$).—This was prepared from dimethylethynylcarbinol (42 g.; Macullum, U.S.P. 2,125,384) by the general method. 3-*Methylbut-*1-*yn-*3-*ol-*1-*carboxylic acid* (28·7 g.; 45% conversion) was obtained as a hygroscopic solid; sublimed at 50° (bath temp.)/10^{-4} mm., it had m. p. 90° (Found : C, 56·1; H, 6·1. $C_6H_8O_3$ requires C, 56·25; H, 6·3%). (Salkind and Michantjev, *loc. cit.*, describe this acid as a yellow oil.) The S-*benzyl*iso*thiouronium* salt crystallised from alcohol–light petroleum (b. p. 60—80°) in prisms, m. p. 167° (decomp.) (Found : C, 57·35; H, 6·25. $C_{14}H_{18}O_3N_2S$ requires C, 57·15; H, 6·15%). The *ethyl* ester prepared as above had b. p. 82°/0·5 mm., $n_{\text{D}}^{19^\circ}$ 1·4560 (Found : C, 61·3; H, 7·8. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%).

*But-*1-*yn-*3-*ol-*1-*carboxylic Acid* (I; $R_1 = H$; $R_2 = Me$).—Prepared from methylethynylcarbinol (35 g.; Macullum, *loc. cit.*) by the general method, the Grignard complex separating from the benzene solution as a sticky solid. *But-*1-*yn-*3-*ol-*1-*carboxylic acid* (23 g.; 40% conversion) was obtained as a crystalline solid, subliming at 55° (bath temp.)/10^{-4} mm., m. p. 66—67° (Found : C, 52·5; H, 5·35. $C_5H_6O_3$ requires C, 52·65; H, 5·3%). The S-*benzyl*iso*thiouronium* salt separated from alcohol–light petroleum (b. p. 60—80°) in needle-like plates, m. p. 136·5° (decomp.) (Found : C, 55·8; H, 5·9. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·75%).

*Hex-*1-*yn-*3-*ol-*1-*carboxylic Acid* (I; $R_1 = H$; $R_2 = Pr$).—Prepared from propylethynylcarbinol (24·5 g.; Bowden, Heilbron, Jones, and Weedon, this vol., p. 39) by the general method. The *acid* (17 g.; 48% conversion, 9·5 g. carbinol recovered) was obtained as a crystalline solid, subliming at 55° (bath temp.)/10^{-4} mm., m. p. 64° (Found : C, 59·45. H, 7·1. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). By carboxylating for 72 hours the conversion is increased to 66%.

The acid (1 g.) was heated to 170° in the presence of copper bronze (*ca.* 10 mg.). Propylethynylcarbinol (0·6 g.), $n_{\mathrm{D}}^{19^\circ}$ 1·4347 distilled rapidly. Its *a-naphthylurethane* separated from light petroleum (b. p. 60—80°) in prisms, m. p. 76°, undepressed on admixture with a specimen prepared from authentic carbinol (Found : N, 5·2. $C_{17}H_{17}O_2N$ requires N, 5·25%). The acid (10 g.) was refluxed with methyl-alcoholic sulphuric acid (100 c.c., 1%) for 24 hours in nitrogen. The resulting *methyl* ester (8·1 g.) had b. p. 135°/13 mm., 73°/0·2 mm., $n_{\mathrm{D}}^{18\cdot5^\circ}$ 1·4618 (Found : C, 61·4; H, 8·05. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%).

Hex-3-*en*-1-*yn*-5-*ol*-1-*carboxylic Acid* (IV).—Prepared from hex-3-en-5-yn-2-ol (24 g.; Heilbron, Jones, Smith, and Weedon, *loc. cit.*) by the general method. The acidic product (19·5 g., 55% conversion), a dark brown oil, solidified completely on standing at 0°. Sublimation at 45—50° (bath temp.)/10^{-4} mm. gave two fractions : (i) 5-Methylfuran-2-acetic acid, more volatile, well formed prisms (*ca.* 4 g.), m. p. 61° (Found : C, 59·85; H, 5·7. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·75%). Light absorption : Maximum, 2210 A.; $\varepsilon = 7{,}500$ (Reichstein and Zschokke, *Helv. Chim. Acta*, 1932, **15**, 249, give m. p. 61—62°; Scott and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 2549, give m. p. 57—58°). The acid (0·25 g.) was heated to 250° in the presence of copper bronze (*ca.* 5 mg.). 2 : 5-Dimethylfuran (0·15 g.) distilled as a colourless liquid, $n_{\mathrm{D}}^{19^\circ}$ 1·4422. Light absorption : Maximum, 2200 A.; $\varepsilon = 8000$ (Heilbron, Jones, Smith, and Weedon, *loc. cit.*, give $n_{\mathrm{D}}^{19^\circ}$ 1·4424). Its maleic anhydride adduct had m. p. 73°, undepressed on admixture with an authentic sample (Heilbron *et al.*, *loc. cit.*, give m. p. 73°). Treatment with 2 : 4-dinitrophenylhydrazine reagent gave the bis-2 : 4-dinitrophenylhydrazone of acetonylacetone, m. p. 257° (decomp.) undepressed on admixture with an authentic specimen. Light absorption : Maxima, 2550, 3560, 3610 A.; $\varepsilon = 18{,}000, 29{,}000, 29{,}000$. Inflexion, 2800 A.; $\varepsilon = 14{,}500$ (cf. Braude and Jones, *J.*, 1945, 500). (ii) *Hex*-3-*en*-1-*yn*-5-*ol*-1-*carboxylic acid* (*ca.* 11 g.) as a less volatile, crystalline solid, m. p. 88° (Found : C, 59·6; H, 5·7. $C_7H_8O_3$ requires C, 60·0; H, 5·75%). When the acid (0·5 g.) was heated to 200° in the presence of copper bronze (*ca.* 10 mg.) hex-3-en-5-yn-2-ol (0·25 g.) distilled as a pale yellow liquid, $n_{\mathrm{D}}^{19^\circ}$ 1·4823 (Heilbron, Jones, Smith, and Weedon, *loc. cit.*, give $n_{\mathrm{D}}^{18\cdot5^\circ}$ 1·4842). The phenylurethane separated from light petroleum (b. p. 60—80°) in plates, m. p. 83—84°, undepressed on admixture with an authentic specimen. Esterification of 2 g. of the acid (ii) with alcoholic sulphuric acid gave the *ethyl* ester (2 g.), b. p. 50° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{15^\circ}$ 1·5076 (Found : C, 64·35; H, 7·6. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%).

4-*Aceto*-n-*valeric Acid.*—A solution of hex-3-en-1-yn-5-ol-1-carboxylic acid (2 g.) in methyl acetate (35 c.c.) was shaken with hydrogen in the presence of platinic oxide (100 mg.) until absorption was complete. The crude hydroxy-acid was oxidised with chromic acid and the semicarbazone of the 4-aceto-*n*-valeric acid so obtained had m. p. 145° (Ciamician and Silber, *Ber.*, 1913, **46**, 3077, give m. p. 147°; Blaise and Kohler, *Bull. Soc. chim.*, 1910, **7**, 222, give m. p. 144°). Hydrogenation of the ethyl ester (0·7 g.) described above, followed by oxidation, gave ethyl 4-aceto-*n*-valerate, the semicarbazone (0·6 g.) of which had m. p. 110° (Found : N, 17·95. Calc. for $C_{10}H_{19}O_3N_3$: N, 18·1%) (Blaise and Kohler, *loc. cit.*, give m. p. 107°).

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