432. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part III. The Synthesis of Linoleic Acid.*

By R. A. Raphael and Franz Sondheimer.

A flexible method for the preparation of the hitherto inaccessible 1 : 4-diacetylenes has been evolved. By this procedure heptadeca-8 : 11-diyne-1-carboxylic acid (V) has been obtained; catalytic partial hydrogenation of this acid furnished a product containing 63% of linoleic acid. A preliminary account of the work has already been given (*Nature*, 1950, **165**, 235).

Long-chain unsaturated acids with an unbranched carbon skeleton occur abundantly in Nature, most commonly in the form of their glycerides (Hilditch, " The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1947; Ralston, " Fatty Acids and their Derivatives," John Wiley, New York, 1948; Markley, " Fatty Acids," Interscience Publishers, New York, 1947). Usually the acids possess the *cis*-configuration about the double bonds. Synthetic investigations of these acids have been confined almost exclusively to the monoethylenic compounds and, until recently, the routes employed could be classified as variants of four procedures, *i.e.* the Robinson–Robinson keto-ester method (Robinson and Robinson, *J.*, 1925, 175; 1926, 2204; 1930, 745; Kapp and Knoll, *J. Amer. Chem. Soc.*, 1943, **65**, 2062), the Noller bromo-aldehyde method (Noller and Bannerot, *J. Amer. Chem. Soc.*, 1934, **56**, 1563; Baudart, *Compt. rend.*, 1943, **217**, 399), the Baudart acyloin method (*Compt. rend.*, 1945, **220**, 404), and the recent Bowman method (*J.*, 1950, 177). None of these schemes is of general application, and mixtures of *cis–trans*-isomers are always obtained.

The only general reaction available which produces nearly pure *cis*-ethylenic compounds is the catalytic partial hydrogenation of the corresponding acetylenic compounds (for references and discussion, see Raphael and Sondheimer, *J.*, 1950, 115; Sondheimer, *J.*, 1950, 877), and this reaction is obviously capable of being widely utilised for the synthesis of the natural ethylenic acids. Although an isolated example of the synthesis of one of the requisite acetylenic acids has been recorded (Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678) it is only recently that an elegant general method has been developed by Strong and his collaborators (*J. Amer. Chem. Soc.*, 1948, **70**, 1699, 3391; cf. Newman and Wotiz, *ibid.*, 1949, **71**, 1292), which provides a ready synthesis of long-chain acetylenic acids of the general formula (I):

$$\mathrm{CH_3\cdot[CH_2]_{\mathit{m}}\cdot C{\equiv}CH + I\cdot[CH_2]_{\mathit{n}}\cdot Cl \xrightarrow{NaNH_2} CH_3\cdot[CH_2]_{\mathit{m}}\cdot C{\equiv}C\cdot[CH_2]_{\mathit{n}}\cdot Cl \xrightarrow[\text{hydrolysis}]{NaCN} CH_3\cdot[CH_2]_{\mathit{m}}\cdot C{\equiv}C\cdot[CH_2]_{\mathit{n}}\cdot CO_2H}$$

(I.)

Catalytic partial hydrogenation of (I) readily furnishes the corresponding *cis*-ethylenic acid.

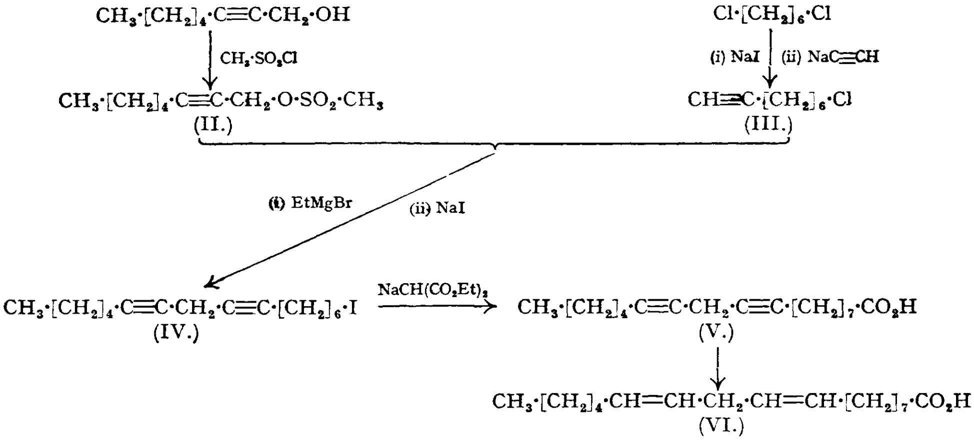
A great many natural polyethylenic acids contain the grouping *cis* : *cis*-$\mathrm{CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot}$. One of the most important members of this class is linoleic acid (heptadeca-8 : 11-diene-1-carboxylic acid) (VI), the characteristic acid constituent of the semi-drying oils; the substance derives added interest as an essential food factor (Rosenberg, " Chemistry and Physiology of the Vitamins," Interscience Publishers, New York, 1932, p. 531), and an antibiotic (Riley and Miller, *Arch. Biochem.*, 1948, **18**, 13). Although attempts have been made to synthesise this acid by classical methods, the results have not been encouraging (Noller and Girvin, *J. Amer. Chem. Soc.*, 1937, **59**, 606; Baudart, *Bull. Soc. chim.*, 1944, **11**, 336).

The problem of the acetylenic approach resolves itself into the synthesis of the 1 : 4-diacetylenic acid (V). The scanty literature on 1 : 4-diacetylenes reveals their comparative inaccessibility. A few hydrocarbons of this type had been made by the reaction of substituted propargyl bromides with sodium acetylides at 140°; the yields were poor, however, since the reactivity of the methylene group situated between the two triple bonds resulted in further alkylation of the 1 : 4-diyne produced (Tchao Yin Lai, *Bull. Soc. Chim.*, 1933, **53**, 1533, 1537; Grignard and Lapayre, *ibid.*, 1928, **43**, 141; *Compt. rend.*, 1931, **192**, 250).

It was therefore decided to utilise the ready alkylation of an acetylenic Grignard reagent by means of an alkyl sulphonate (Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839; Truchet, *Ann. Chim.*, 1931, **16**, 309; Johnson, Schwartz, and Jacobs, *J. Amer. Chem. Soc.*, 1938, **60**, 1882, 1885).

An ethereal solution of the Grignard complex of 8-chloro-oct-1-yne (III) (prepared by the action of sodium acetylide on 1-chloro-6-iodohexane) was very slowly added to a boiling ethereal solution of oct-2-yn-1-yl methanesulphonate (II). This procedure ensured that no excess of

Grignard reagent was present at any time to attack the central, activated methylene group of the product, 16-chlorohexadeca-6 : 9-diyne. This reaction constitutes an efficient and flexible



method of obtaining the hitherto little-studied 1 : 4-diacetylenes. Conversion of the diacetylenic chloride into the corresponding iodide (IV) followed by condensation with sodiomalonic ester, hydrolysis, and decarboxylation, finally gave the required heptadeca-8 : 11-diyne-1-carboxylic acid (V) as a white crystalline solid, m. p. 42—43°. Catalytic partial hydrogenation of (V) employing a palladium–calcium carbonate catalyst gave a pale yellow oil; analysis of this oil by the bromination procedure of Brown and Frankel (*J. Amer. Chem. Soc.*, 1938, **60**, 54) showed it to contain 63% of linoleic acid. The resulting tetrabromostearic acid exhibited no depression in melting point on admixture with a sample prepared from natural linoleic acid. Complete hydrogenation of the diacetylenic acid (V) furnished stearic acid, identified as such by comparison with an authentic sample. As the above tetrabromostearic acid has been shown to furnish substantially pure linoleic acid on debromination (Frankel and Brown, *ibid.*, 1943, **65**, 415) the above series of reactions constitutes a complete synthesis of linoleic acid.

EXPERIMENTAL.

(All operations involving acetylenic compounds were carried out under nitrogen.)

Oct-2-yn-1-ol (cf. Tchao Yin Lai, *Bull. Soc. chim.*, 1933, **53**, 682).—To a stirred solution of ethylmagnesium bromide [from magnesium (16·2 g.), ethyl bromide (98 g.), and ether (400 c.c.)] was added rapidly a solution of hept-1-yne (54 g.) in ether (50 c.c.), and the mixture was heated under reflux for 2 hours. Dry gaseous formaldehyde, prepared by heating dry paraformaldehyde (60 g.) to 200°, was then introduced into the cooled solution of heptynylmagnesium bromide by means of a slow current of nitrogen. After the addition the reaction mixture was heated under reflux for a further 30 minutes, and was then decomposed with ice and dilute sulphuric acid. The ethereal layer was separated, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$), and the solvent removed. Distillation of the residue gave oct-2-yn-1-ol (40 g., 57%), b. p. 98—100°/15 mm., n_D^{26} 1·4559 (Tchao Yin Lai, *loc. cit.*, gives b. p. 98—99°/15 mm., n_D^{17} 1·4585). The high-boiling residue (*ca.* 25 g.) presumably consisted of higher-condensation products of the general formula, $C_5H_{11}\cdot C\equiv C\cdot CH_2\cdot[OCH_2]_n\cdot OH$.

Oct-2-yn-1-yl Methanesulphonate (II).—A well-stirred mixture of oct-2-yn-1-ol (36 g.) and methanesulphonyl chloride (40 g., 1 mol.) was cooled to −10° and aqueous sodium hydroxide (25%) added dropwise at such a rate that the temperature did not rise above 5°. When the mixture became alkaline (about 100 c.c. of the alkali solution was needed) it was thoroughly extracted with ether. Evaporation of the washed (water) and dried ($MgSO_4$) ethereal extract followed by fractionation of the residue gave unchanged carbinol (20·5 g.) and *oct-2-yn-1-yl methanesulphonate* (22·1 g.; conversion, 45%; yield, 85%), b. p. 110—112°/0·2 mm., n_D^{26} 1·4610. The employment of two moles of the acid chloride surprisingly occasioned no improvement in conversion (Found: C, 52·5; H, 7·6; S, 14·8. $C_9H_{16}O_3S$ requires C, 52·9; H, 7·9; S, 15·7%).

This reaction could not be carried out by the more usual procedure employing pyridine. When this was attempted the only product obtained, in small yield, was 1-*chloro-oct-2-yne*, b. p. 40—41°/0·5 mm., n_D^{26} 1·4590 (Found: C, 66·65; H, 9·05; Cl, 24·3. $C_8H_{13}Cl$ requires C, 66·45; H, 9·05; Cl, 24·5%).

1 : 6-*Dichlorohexane*.—Hexamethylene glycol (59 g.) and dry pyridine (7 c.c.) were melted together and thionyl chloride (20 g.) then added to lower the melting point. To the cooled, stirred mixture thionyl chloride (218 g.) was added at such a rate that the temperature remained at about 25°. After the addition the flask and contents were heated by steam for 2 hours. Ice and water were then carefully added, and the dense, precipitated oil taken up in light petroleum (b. p. 40—60°); this extract

was washed twice with concentrated sulphuric acid and once with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The residue on distillation furnished 1 : 6-dichlorohexane (72 g.; 92%), b. p. 99°/28 mm., n_D^{25} 1·4576.

1-*Chloro*-6-*iodohexane*.—1 : 6-Dichlorohexane (65 g.) was added to a solution of sodium iodide (65 g.) in dry acetone (400 c.c.), and the solution heated by steam for 4 hours (violent bumping occurred as the precipitate of sodium chloride formed). Water (600 c.c.) was then added and the precipitated oil was taken up in light petroleum (b. p. 40—60°). After being washed (water) and dried ($MgSO_4$) the extract was evaporated, and the residue distilled through a Dufton column to give (i) unchanged dichloride (18 g.), b. p. 51—53°/0·6 mm., (ii) crude 1-chloro-6-iodohexane (50·3 g.), b. p. 74—79°/0·6 mm., and (iii) 1 : 6-di-iodohexane (28 g.). Fraction (ii) was redistilled slowly through a vacuum-jacketed column packed with glass helices to give pure 1-*chloro*-6-*iodohexane* (41·6 g., 50%), b. p. 73—74°/0·7 mm., n_D^{24} 1·5248 (Found: C, 29·4; H, 5·45; total halogen, 65·8. $C_6H_{12}ClI$ requires C, 29·25; H, 4·9; total halogen, 65·85%).

8-*Chloro-oct*-1-*yne* (III).—To a stirred suspension of sodium acetylide [prepared from Na (4·1 g.), by the usual ferric nitrate-catalysed reaction] in liquid ammonia (400 c.c.) was rapidly added a solution of 1-chloro-6-iodohexane (44 g.) in ether (25 c.c.). The reaction vessel was not cooled but was well lagged with cotton wool. After 4 hours' stirring, the lagging was removed, solid ammonium chloride (15 g.) added, and the ammonia allowed to evaporate. Water and ether were added to the residue, and the ethereal layer washed successively with dilute sulphuric acid and sodium hydrogen carbonate solution. Drying ($MgSO_4$) and evaporation followed by distillation furnished 8-*chloro-oct*-1-*yne* (19·4 g., 75%), b. p. 73—76°/10 mm., n_D^{12} 1·4590 (Found: C, 66·2; H, 9·1; Cl, 24·75. $C_8H_{13}Cl$ requires C, 66·45; H, 9·05; Cl, 24·5%).

16-*Iodohexadeca*-6 : 9-*diyne* (IV).—To a stirred solution of ethylmagnesium bromide [from magnesium (1·25 g.), ethyl bromide (7·5 g.), and ether (150 c.c.)] was added rapidly a solution of 8-chloro-oct-1-yne (7·5 g.) in ether (10 c.c.). After being stirred for a further 2 hours the resulting solution was transferred to a dropping-funnel and added dropwise during 4 hours to a stirred, vigorously boiling solution of oct-2-yn-1-yl methanesulphonate (22 g.) in ether (100 c.c.). A white solid formed as the reaction proceeded. The resulting suspension was heated under reflux for a further 14 hours, and the cooled reaction mixture was then decomposed by the addition of 2N-sulphuric acid (100 c.c.). Evaporation of the washed (sodium hydrogen carbonate solution) and dried ($MgSO_4$) ethereal layer, and distillation of the residue, gave (i) 1-bromo-oct-2-yne (9·1 g.), b. p. 45—47°/10^{-3} mm., 85°/12 mm., n_D^{17} 1·4830 (Tchao Yin Lai, *Bull. Soc. chim.*, 1933, **53**, 1533, gives b. p. 92—93°/15 mm., n_D^{16} 1·4927) and (ii) crude 16-chlorohexadeca-6 : 9-diyne (7·3 g.), b. p. 103—115°/10^{-3} mm., n_D^{17} 1·4760. A Lassaigne test indicated that the second fraction contained sulphur as well as chlorine, thus showing that some unchanged methanesulphonate was present. As fractional distillation was impracticable the following procedure was adopted. The crude chlorodiyne, sodium iodide (10 g.), and dry acetone (100 c.c.) were heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue treated with water and ether; the ethereal layer after being dried, evaporated, and distilled gave (i) 1-*iodo-oct*-2-*yne* (1·2 g.), b. p. 53°/10^{-4} mm., n_D^{16} 1·5330 (Found: I, 53·4. $C_8H_{13}I$ requires I, 53·75), and (ii) 16-*iodohexadeca*-6 : 9-*diyne* (5·3 g.), b. p. 120—124°/10^{-4} mm., n_D^{16} 1·4958 (Found: C, 55·4; H, 7·2. $C_{16}H_{25}I$ requires C, 55·8; H, 7·3%).

Heptadeca-8 : 11-*diyne*-1-*carboxylic Acid* (V).—Sodium (0·7 g.) was dissolved in dry ethanol (50 c.c.), ethyl malonate (5·1 g.) was added, and the mixture was heated under reflux for 1 hour. 16-Iodohexadeca-6 : 9-diyne (4 g.) in alcohol (10 c.c.) was rapidly added and the solution heated under reflux for 16 hours. The cooled mixture was treated with a solution of potassium hydroxide (10 g.) in aqueous methanol (100 c.c. of methanol + 5 c.c. of water), and after 40 hours at room temperature most of the solvent was evaporated off *in vacuo*, and water and ether were added. The aqueous layer was acidified (Congo-red) with dilute sulphuric acid, and the precipitated oil extracted with ether. Drying ($MgSO_4$) of the solution and evaporation of the solvent gave a viscous orange oil; this was transferred to a small retort and slowly heated to 140°/10^{-4} mm. Considerable effervescence took place and a pale-yellow oil distilled over which rapidly solidified; an orange resin (*ca.* 3 g.) remained in the retort. Crystallisation of the distillate from light petroleum (b. p. 40—60°) at 0° gave prismatic needles, m. p. 42—43°, of *heptadeca*-8 : 11-*diyne*-1-*carboxylic acid* (930 mg., 29%) (Found: C, 78·8, 78·4; H, 9·7, 9·9. $C_{18}H_{28}O_2$ requires C, 78·25; H, 10·2%).

Stearic Acid.—A solution of this diacetylenic acid (53 mg.) in ethyl acetate (30 c.c.) was fully hydrogenated, employing Adams's catalyst (20 mg.). After the reaction was completed (hydrogen absorption, 18 c.c. Theory for 2$\equiv$, 17·2 c.c.) the catalyst and solvent were removed, giving a crystalline residue. Crystallisation of this from methanol gave plates, m. p. 66—67° undepressed on admixture with a sample of authentic stearic acid.

Linoleic Acid (VI).—A solution of the diacetylenic acid (V) (563 mg.) in ethyl acetate (40 c.c.) was stirred in an atmosphere of hydrogen in the presence of palladium–calcium carbonate catalyst (100 mg.; 2%) until hydrogen corresponding to the uptake for two double bonds had been absorbed (96 c.c. at 16°/764 mm.). The catalyst was filtered off and the solvent evaporated *in vacuo* at low temperature. The residue consisted of a pale-yellow oil, n_D^{16} 1·4678, which solidified completely on being cooled to −15° (Matthews, Brode, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 1064, give m. p. −5°, n_D^{20} 1·4699, for pure linoleic acid). The product was dissolved in light petroleum (b. p. 40—60°; 10 c.c.), transferred to a weighed filter beaker, cooled to 0°, and treated with a solution of bromine in light petroleum until a permanent colour resulted. After 16 hours at 0°, the slightly gummy crystalline precipitate was filtered off, washed with a little ice-cold light petroleum, dried *in vacuo*, and weighed. The weight of bromination product (365 mg.) corresponded to a tetrabromide number of 64·8, thus indicating that the product of partial hydrogenation contained 63% of linoleic acid (Matthews, Brode, and Brown, *loc. cit.*, give 102·9 as the tetrabromide number of pure linoleic acid). Crystallisation of the product from ethylene dichloride gave plates, m. p. 113—114° undepressed on admixture with authentic 9 : 10 : 12 : 13-tetrabromostearic acid prepared from naturally occurring linoleic acid.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7.
THE UNIVERSITY, GLASGOW, W.2.

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