[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Synthesis of Unsaturated Fatty Acids: Linoleic Acid

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The 1,4-diyne system may be formed in satisfactory yield by the cuprous chloride catalyzed coupling of propargyl bromides with acetylenic Grignard reagents. Observations in this process as well as on the alkali-catalyzed isomerization and on the hydrogenation of the 1,4-diyne system are reported. Linoleic acid has been synthesized.

Recent reports of the synthesis of linoleic acid by Raphael and Sondheimer[1] and by Walborsky, Davis and Howton[2] prompt us to record the progress of similar work which has resulted in the successful synthesis of the same acid. Although the course followed in our independently initiated synthesis (see formulation I–V) is practically the same as that employed by Raphael and Sondheimer, a number of findings are new. It is these findings, the results of work on the reaction of propargyl bromides with acetylenic Grignard reagents, the isomerization of the 1,4-diyne system, and the hydrogenation of octadecadiyn-9,12-oic acid (IV), which constitute the subject of the present paper. Further investigations into these types of reactions are planned.

Coupling of Propargyl Bromides and Acetylenic Grignard Reagents.—In experiments directed to the formation of the 1,4-diyne system

$$\underset{\text{I}}{CH_3(CH_2)_4C{\equiv}CCH_2Br} + \underset{\text{II}}{HC{\equiv}C(CH_2)_6Cl} \longrightarrow$$

$$CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_6Cl \xrightarrow[2.\ \text{malonic ester, etc.}]{1.\ \text{potassium iodide}}$$

$$\underset{\text{III}}{CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_6Cl} \longrightarrow$$

$$\underset{\text{IV}}{CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH} \longrightarrow$$

$$\underset{\text{V}}{CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH}$$

(*e.g.*, as in compound III) it was found that acetylenic Grignard reagents fail to react with propargyl bromides.[3] This observation stands in sharp contrast to the facile coupling of ethylmagnesium bromide with 1-bromoöctyne-2[4] but is in agreement with the negative results obtained in other similar reactions.[5] The fact that cuprous halide catalyzes the reaction of allyl bromide and acetylenic Grignard reagents[9] suggested that cuprous salts might be effective in promoting the corresponding propargyl bromide reaction. This indeed proved to be the case. However, the results were found to depend markedly on the amount of ethylmagnesium bromide used in forming the acetylenic Grignard derivative

For example, pentadecadiyne-6,9[4] could be obtained in 70% yield by treating the Grignard derivative prepared from ethylmagnesium bromide and a 10% excess of heptyne-1 first with a small amount of cuprous chloride and then with 1-bromoöctyne-2.[10] On the other hand, when the process was carried out in the same way but with the molar ratio of heptyne-1 to ethyl Grignard reagent somewhat less than unity, a black precipitate formed on addition of cuprous chloride, and the yield of coupling product dropped to 30%. By taking advantage of this experience in the series leading to linoleic acid, it was found possible to combine 8-chloroöctyne-1 (II) with 1-bromoöctyne-2 (I) to obtain 1-chlorohexadecadiyne-7,10 (III) in over 70% yield. 1-Chloropentadecadiyne-7,10 was also prepared in the course of this investigation by coupling 8-chloroöctyne-1 with 1-bromoheptyne-2.[11,12]

As a check on the structures of the pentadecadiyne and the chlorohexadecadiyne the compounds were cleaved by ozonolysis. The expected cleavage products were obtained.

We assume, as a tentative hypothesis concerning this catalysis by cuprous halide, that ethylmagnesium bromide, but not the acetylenic Grignard reagent, converts the catalytically active cuprous halide to catalytically inactive black metallic copper.[13] The cuprous halide may function as the catalyst by acting on the acetylenic Grignard reagent, possibly forming an intermediate copper acetylide.[14] However, we prefer to interpret the process as one involving coördination of electrophylic cuprous chloride with the halogen of the propargyl bromide, and thereby activation of the carbon-to-bromide bond.[15]

(1) Raphael and Sondheimer, *Nature*, **165**, 235 (1950); *J. Chem. Soc.*, 2100 (1950).

(2) Walborsky, Davis and Howton, THIS JOURNAL, **73**, 2590 (1951).

(3) The English workers circumvent this difficulty in the coupling reaction leading to compound III by utilizing not the propargyl bromide, I, but the corresponding propargyl methanesulfonate.

(4) Tchao Yin Lai, *Bull. soc. chim.*, [4] **53**, 1537 (1933).

(5) Tchao Yin Lai (ref. 4) reported no reaction between substituted propargyl bromides and acetylenic Grignard derivatives, even after boiling a toluene solution of the two components for 6 hours. Taylor and Strong (ref. 6) found that 1-bromoöctyne-2 and the Grignard derivative of 7-chloroheptyne-1 do not couple. Grignard and Lapayre (refs. 7 and 8) found thay they could obtain 1,5-diphenylpentadiyne-1,4 on treating phenylacetylenemagnesium bromide with methylene iodide, although in very low yield.

(6) Taylor and Strong, THIS JOURNAL, **72**, 4263 (1950).

(7) Grignard and Lapayre, *Compt. rend.*, **192**, 250 (1931).

(8) Grignard and Lapayre, *Bull. soc. chim.*, [4] **43**, 141 (1928).

(9) Danehy, Killian and Nieuwland, THIS JOURNAL, **58**, 611 (1936).

(10) Tchao Yin Lai, *Bull. soc. chim.*, [4] **53**, 1533 (1933).

(11) Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949).

(12) While this manuscript was in preparation, two reports appeared on related cuprous halide catalyzed reactions. Taylor and Strong (ref. 6) described the synthesis of 1-chloropentadecadiyne-6,9 from 1-bromooctyne-2 and 7-chloroheptyne-1 in 25% yield; and Walborsky, Davis and Howton (ref. 2) reported the coupling of the same bromoöctyne with the Grignard compound derived from the ethylene glycol acetal of decyn-8-al in approximately 50% yield. In the light of our experience, it is quite possible that slight modifications in the procedures employed in these two preparations would significantly improve the yield. We are indebted to Dr. Howton for making the experimental details on the latter coupling reaction available to us prior to publication.

(13) Konduirov and Fomin, *C. A.*, **9**, 1473 (1915); Linn and Noller, THIS JOURNAL, **58**, 816 (1936).

(14) Gilman and Straley, *Rec. trav. chim.*, **55**, 821 (1936); see also Coates, *Quarterly Rev.*, **4**, 221 (1950).

(15) Apparently the acetylenic coupling process is not related to other salt-catalyzed Grignard reactions for which Kharasch has proposed free radical mechanisms. [For some examples of such radical reactions see Paper VI in a series of articles by Kharasch and co-workers entitled "Factors Determining the Course and Mechanism of Grignard Reactions," THIS JOURNAL, **65**, 491 (1943).]

Isomerization of the 1,4-Diyne System.—Conversion of 1-chlorohexadecadiyne-7,11 (III) to the corresponding iodo compound, followed by application of the malonic ester synthesis furnished octadecadiyn-9,12-oic acid (IV), identical with the compound obtained in the same way by Raphael and Sondheimer.[1,16] The expected cleavage products were obtained on ozonolysis of the diynoic acid.

However, when the chloro compound, III, was used directly in the malonic ester process, different results were obtained. The conditions for the reaction were the same as those used with the iodo compound except that the reflux period with the chloro compound was much longer than with the iodo compound (fifteen *vs.* two hours). On saponifying the product from the chlorohexadecadiyne alkylation, and decarboxylating the resulting malonic acid, a low-melting acid, isomeric with octadecadiyn-9,12-oic acid (IV) was obtained. The isomeric acid absorbed 3.95 moles of hydrogen and gave rise thereby to pure stearic acid. Ozonolysis, on the other hand, furnished mixtures in both the dibasic and the monobasic acid fractions from which no pure product was obtained. These observations are consistent with an interpretation involving isomerization of the 1,4-diyne system under the influence of boiling alcoholic sodium ethoxide. Possible changes not only in the position of the unsaturation but also in the nature of the unsaturation[17] must be considered.

Hydrogenation of Octadecadiyn-9,12-oic Acid (IV).—In experiments on the hydrogenation of octadecadiyn-9,12-oic acid over a palladium-on-strontium carbonate catalyst, it was observed that the rates of hydrogenation in the acetylene-to-olefin stage and in the olefin-to-saturate stage change by different degrees with change in reaction conditions. For example, doubling the diynoic acid concentration while maintaining roughly the same ratio of catalyst to acid resulted in an increase of less than fourfold in the rate of the first stage of hydrogenation, but resulted in an increase of over 25-fold in the rate of the second stage.

Half-hydrogenation of the diynoic acid gave rise to a mixture from which, after addition of bromine, linoleic acid tetrabromide was isolated.

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Experimental[18]

1-Bromoöctyne-2 (I).—Heptyne-1 (b.p. 97–100°, $n^{25}D$ 1.4081; obtained in 65–83% from *n*-amyl bromide and sodium acetylide) was converted to octyn-2-ol-1, b.p. 97–99° (19 mm.), $n^{25}D$ 1.4538 in 60–80% yield by allowing the Grignard derivative to react with depolymerized *dry* paraformaldehyde.[19] 1-Bromoöctyne-2, b.p. 89–92° (12 mm.), $n^{25}D$ 1.4845, was formed in 73–78% yield by adding phosphorus tribromide to an ethereal solution of the octynol in the presence of catalytic amounts of pyridine.[10]

1-Bromoheptyne-2.—By reactions analogous to those above, heptyne-2-ol-1 b.p. 92–94° (22 mm.), prepared in 60% yield from hexyne-1, was converted (67%) to 1-bromoheptyne-2, b.p. 76–80° (15 mm.), n_D 1.491.

8-Chloroöctyne-1 (II).—1,6-Dichlorohexane, b.p. 98–100° (20 mm.), was prepared in 87–95% yield by adding hexamethylene glycol to boiling thionyl chloride containing a small amount of pyridine. Heating the dichlorohexane in acetone containing 10% water with an equimolar amount of potassium iodide afforded a mixture from which were isolated dichlorohexane (26% recovery), 1,6-diiodohexane, b.p. 140–145° (12 mm.), $n^{25}D$ 1.5819, in 23% yield, and the desired 1-chloro-6-iodohexane, b.p. 112–116° (12 mm.), $n^{25}D$ 1.5220 in 43% yield. The use of potassium iodide in one-half the stoichiometric amount, in an effort to decrease the amount of diiodohexane formed, offered no advantage. Stirring a mixture of equimolar amounts of 1-chloro-6-iodohexane and sodium acetylide in liquid ammonia for five hours resulted in the formation of 8-chloroöctyne-1, b.p. 73–76° (11 mm.), $n^{25}D$ 1.4548, in 86–88% yield.

Experiments on the Preparation of Pentadecadiyne-6,9 from Heptyne-1 and 1-Bromoöctyne-2.—A stock solution of the Grignard derivative of heptyne-1 was prepared by adding 53 g. (0.55 mole) of heptyne-1 in 100 ml. of absolute ether to 450 ml. of 1.11 N^{20} filtered ethylmagnesium bromide solution (0.50 mole), and boiling the mixture for one hour. Analysis of an aliquot from this solution after lapse of a short time showed it to be 0.93 *N* in Grignard reagent. The same value (0.94) was obtained after the solution had been allowed to stand for 40 hours.

When 17 g. of 1-bromoöctyne-2 (0.093 mole) in ether (combined volume of bromo compound and ether, 37 ml.) was added to 100 ml. of the freshly prepared stock solution of acetylenic Grignard reagent (0.093 mole) and the mixture boiled under nitrogen for 19 hours, no coupling occurred. This was indicated by the fact that a 2-ml. aliquot of the reaction mixture neutralized approximately the same amount of acid at the beginning and at the end of the reaction period. Hydrolysis was effected by pouring the ethereal reaction mixture into iced water containing enough acid to combine with the alkali generated. The ether layer was washed first with sodium bicarbonate solution and then with water and dried over magnesium sulfate. Distillation afforded a small amount of heptyne-1, b.p. 97–100°, and practically the entire amount of unchanged 1-bromoöctyne-2, b.p. 100–105° (18 mm.). The indices of refraction of the recovered materials agreed with the respective values recorded above.

On the other hand, when 150 ml. of stock solution of heptyne Grignard derivative (0.139 mole) was boiled for 15 minutes with 0.25 g. of cuprous chloride[21] before adding the ethereal solution of 1-bromoöctyne (25.5 g. or 0.139 mole in a combined volume of 55 ml.) the desired reaction did occur. Titration of aliquots indicated that after 16 hours of reaction under nitrogen at reflux temperature the total Grignard content had decreased from the original value of 0.139 mole to 0.007 mole.[22]

After hydrolysis of the ethereal mixture in iced water containing acid, the mixture was filtered to remove solid material, and the two-phase filtrate treated as described above. Distillation under dry oxygen-free nitrogen using a short Vigreux column afforded 21.5 g. (75%) of pentadecadiyne-6,9, b.p. 85–95° (0.08 mm.), $n^{25}D$ 1.4625, and on redistillation, 19.0 g. (66%) of product, b.p. 90–93° (0.08 mm.), $n^{25}D$ 1.4620. The same compound was previously reported with b.p. 134–136° (4 mm.) and $n^{20}D$ 1.4693.[4]

Pentadecadiyne-6,9, initially water-white, turns dark on exposure to air, but can be stored for long periods at room temperature when kept under nitrogen.

Ozonolysis of Pentadecadiyne-6,9.[4]—Using the apparatus already described[23] ozonized oxygen was bubbled through 35

(16) We are indebted to Dr. Sondheimer for his kindness in furnishing the sample of octadecadiyn-9,12-oic acid used in the mixed melting point determination.

(17) Jacobs, Akawie and Cooper, THIS JOURNAL, **73**, 1273 (1951).

(18) Details of some of the reactions reported here only in outline may be found in the publication of Raphael and Sondheimer.[1]

(19) Tchao Yiu Lai, *Bull. soc. chim.*, [4] **53**, 682 (1933).

(20) Acid–base titration according to Gilman, *et al.*, THIS JOURNAL, **45**, 150 (1923).

(21) Practically the same results were obtained with carefully dried Merck cuprous chloride as with cuprous chloride prepared according to Marvel and McElvain, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 163.

(22) It should be noted that no black precipitate was observed at any time during the reaction. Toward the end of the reaction period a yellow-green solid separated from the ether solution. The fact that this solid did contain copper, but very little if any ionic halogen, suggests that it is the copper acetylide. Formation of a similar solid when the reaction was near completion was observed in other successful couplings.

(23) Smith, Greenwood and Hudrlik, *Org. Syntheses*, **26**, 63 (1946).

ml. of carbon tetrachloride containing 1.01 g. (0.0048 mole) of pentadecadiyne-6,9 at the rate of 0.54 millimole ozone per minute. The reaction vessel soon became warm to the touch, but then gradually returned to room temperature. At the end of 30 minutes, 9.5 millimoles of the 16.2 millimoles of ozone passed into the solution had reacted; and after a total of 55 minutes, a total of 12.5 millimoles of the 29.7 millimoles of ozone passed in the solution was absorbed.

The reaction mixture was distilled at slightly reduced pressures until the volume was 10 ml. Hydrogen peroxide (20 ml. of a 30% solution) was added, and the mixture was allowed to stand overnight. After dilution with water to a volume of approximately 100 ml., the mixture was made alkaline with potassium hydroxide and extracted with petroleum ether. Acidic material was collected by acidifying the aqueous solution, extracting several times with petroleum ether, washing the petroleum ether extract with water until the washings showed *p*H 6, drying over magnesium sulfate, and removing the solvent. Titration of an alcoholic solution of the residue with standard alcoholic sodium ethoxide showed the presence of 0.0061 equivalent of acid. If the acid were the expected caproic acid, the yield from the diyne would be 63%. When the *p*-bromophenacyl derivative was prepared using this alcoholic solution, *p*-bromophenacyl caproate, m.p. and m.m.p. 70–71°, was obtained in 63% yield calculated from the titration value. In a separate experiment caproic acid was isolated by distilling the petroleum ether extract. The neutralization equivalent was found to be 115.4 (calculated, 116).

The correct neutralization equivalent together with the sharp melting point of the *p*-bromophenacyl derivative indicated that very little if any acid other than caproic acid was formed in the ozonolysis reaction, and consequently that there is unsaturation in the pentadecadiyne at the 6- and 9-positions.

1-Chlorohexadecadiyne-7,10 (III) from 8-Chloroöctyne-1 and 1-Bromoöctyne-2 (I).—To a stirred and boiling solution of 500 ml. of 0.584 *N* ethylmagnesium bromide (0.292 mole, filtered before titration) was added 45 g. (0.31 mole) of 8-chloroöctyne-1. After Grignard exchange had been allowed to proceed for one hour, 0.6 g. of dry cuprous chloride was added and the heating continued for another 15 minutes. 1-Bromoöctyne-2 in slight deficiency (52.5 g. or 0.28 mole) was added,[24] and the coupling mixture boiled under nitrogen for 15 to 24 hours, or until analysis of an aliquot showed that the Grignard content was small. Again the formation of a yellow-green precipitate served as a convenient index for the end of the reaction. The reaction mixture was hydrolyzed and treated as described above in the pentadecadiyne-6,9 experiment. Distillate boiling at 134–136° (0.7 mm.) was collected as the desired coupling product (51 g. or 72.5% based on 1-bromoöctyne-2). A sample prepared for analysis boiled at 119–120° (0.05 mm.) and showed $n^{25}D$ 1.4796.

Anal.[25] Calcd. for $C_{16}H_{25}Cl$: C, 75.9; H, 9.98. Found: C, 75.9; H, 10.1.

1-Chlorohexadecadiyne-7,10, obtained as a water-white distillate, is stable on standing at room temperature under nitrogen, and may be distilled at low pressure with little loss. This behavior is in contrast with the instability on distillation which was reported for the homologous 1-chloropentadecadiyne-6,9.[6] 1-Chlorohexadecadiyne-7,10 is unstable in the presence of air and rapidly acquires a yellow color. A small sample of the pure diyne ($n^{25}D$ 1.4796) after exposure to air for one day became red-brown in color and quite viscous ($n^{25}D$ 1.4920).

Ozonolysis of 1-Chlorohexadecadiyne-7,10.—Ozonolysis of 5.0 g. (0.02 mole) of 1-chlorohexadecadiyne-7,10 was carried out by passing a stream of ozone (0.5 mmole of ozone per minute) into a carbon tetrachloride solution of the diyne for a total of four hours. Oxidative decomposition of the ozonide was accomplished in the manner described for the ozonolysis of pentadecadiyne. Distillation of the crude acids obtained from the petroleum–ether solution permitted separation of the mixture into three fractions: (a) 1.4 g., b.p. 90–100° (18 mm.), (b) 1.0 g., b.p. 100–140° (18 mm.) to 85° (0.05 mm.), and (c) 1.5 g., b.p. 85–90° (0.05 mm.).

The material in the low-boiling fraction was shown to be caproic acid by its neutralization equivalent (120) and by the melting point of the *p*-bromophenacyl derivative (m.p. 70–71° after one crystallization from alcohol; no depression when mixed with an authentic sample).

The acid in the third fraction was taken as 7-chloroheptanoic acid on the basis of its neutralization equivalent. Calcd. for $C_7H_{13}O_2Cl$: neut. equiv., 164. Found: neut. equiv., 164.

1-Chloropentadecadiyne-7,10 from 8-Chloroöctyne-1 and 1-Bromoheptyne-2.—This preparation was carried out in a manner similar to that described for chlorohexadecadiyne, but before the preferred procedure had been developed.

After 0.0504 mole of ethylmagnesium bromide had been allowed to react for one hour with 0.05 mole of 8-chlorooctyne-1, addition of cuprous chloride resulted in the formation of a black precipitate. It was noted that addition of 1-bromoheptyne-2 (0.05 mole) was accompanied by a vigorous boil during approximately the first third of the addition, but by no heat evolution afterwards. After a two-hour reaction period, the mixture was treated as before to obtain the product.

In another experiment 0.0504 mole of ethylmagnesium bromide was taken with 0.058 mole of 8-chloroöctyne-1. Evidently the Grignard exchange was not complete (20-minute reaction period) for, on addition of cuprous chloride a black precipitate was again formed, and again the ether was observed to boil only during addition of the first third of the 1-bromoheptyne-2. The reaction mixture was boiled several hours and finally allowed to stand at room temperature for 36 hours. Isolation of product was carried out as before.

The two experiments gave similar results. Distillate was collected in two fractions: 8.1 g. of material with b.p. 40–80° (15 mm.) and 3.3 g. (28%) with b.p. 125–130° (1 mm.). Fractionation of the higher-boiling material afforded pure 1-chloropentadecadiyne-7,10, b.p. 124–127° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{23}Cl$: C, 75.4; H, 9.6. Found: C, 75.4; H, 9.6.

Octadecadiyn-9,12-oic Acid (IV).—The product formed in the 12-hour reaction (nitrogen atmosphere) of 42 g. (0.165 mole) of 1-chlorohexadecadiyne-7,11 with 105 g. of potassium iodide (0.6 mole) in boiling acetone containing a small amount of water was distilled once (b.p. 115–120° (0.005 mm.)). The 1-iodohexadecadiyne-7,11 (39 g. or 0.113 mole) so obtained was used directly in the malonic ester condensation.

A solution of 0.12 gram-atom of sodium in 90 ml. of absolute alcohol was added dropwise over a period of one hour to a stirred and boiling solution of the iodide and diethyl malonate (0.2 mole) in 150 ml. of alcohol. An atmosphere of dry oxygen-free nitrogen was maintained over the reaction mixture. Heating was continued for one hour. Subsequent treatment of the reaction mixture followed essentially the procedure of Raphael and Sondheimer.[1]

After two distillations and several crystallizations from methanol at −30°, pure octadecadiyn-9,12-oic acid (2.8 g., 5.5%), melting at 42–43°, was obtained. The melting point on admixture with the same acid (m.p. 42–43°), prepared by Raphael and Sondheimer,[1] was 42–43°.[16]

Ozonolysis followed by peroxide oxidation was carried out essentially according to the procedure described for the ozonolysis of pentadecadiyne-6,9. The monobasic acids

(24) Raphael and Sondheimer (ref. 1) are careful to add the Grignard derivative slowly to the methanesulfonate of octyn-2-ol-1 in an effort to ensure that no excess of Grignard is present at any time. This was done in order to preclude involvement of the central methylene group of the 1,4-diyne grouping in Grignard interchange. Walborsky, Davis and Howton (ref. 2) use an apparatus which permits them to add their acetylenic Grignard reagent slowly to the 1-bromoöctyne-2, presumably for the same reason. Our results suggest that these precautions may be unnecessary. Actually the acetylenic Grignard interchange process involves the equilibrium between the salt of a relatively strong acid (the terminal acetylene) and the acidic central methylene group of the 1,4-diyne system. Evidently the acetylenic hydrogen is more acidic than the hydrogen of the methylene group, and consequently the equilibrium lies well to the side of the "true" acetylenic Grignard derivative. On the other hand, it is well established (refs. 4 and 7) that ethane is evolved when ethylmagnesium bromide is allowed to react with 1,4-diynes. In such cases formation of the very weak acid, ethane, would be favored, and the interchange does occur. It should be pointed out that, if the interchange equilibrium involves an acetylenic Grignard reagent derived from a low-boiling acetylene (*e.g.*, from acetylene itself), removal of the acetylene from the reaction mixture by volatilization would eventually result in complete interchange.

(25) Analyses by Carol K. Fitz, Needham Heights, Mass.

were easily separated from the dibasic acids by extracting the former with petroleum ether. From 200 mg. of diynoic acid there was isolated 30 mg. (23%) of pure azelaic acid, m.p. and m.m.p. 104–105°. Titration of the monobasic acid fraction with standard alkali indicated the presence of 0.243 mmole of acid. The *p*-bromophenacyl derivative of this acid melted at 67–69°; mixed with *p*-bromophenacyl caproate (m.p. 70–71°), the material showed m.p. 69°.

Attempted Preparation of Octadecadiyne-9,12-oic Acid from 1-Chlorohexadecadiyne-7,11.—A mixture of 23.7 g. (0.094 mole) of 1-chlorohexadecadiyne-7,11, 19 g. (0.12 mole) of diethyl malonate, 0.108 gram atom of sodium, 2 g. of potassium iodide and 300 ml. of absolute ethanol was boiled under nitrogen for 15 hours. (In a separate experiment it was determined that 93% of the theoretical amount of sodium ethoxide was consumed after 18 hours). The isolation procedure was the same as that described for the reaction with iodohexadecadiyne. Decarboxylation of the crude malonic acid in portions afford a total of 6.2 g. of monocarboxylic acid which on redistillation furnished 5.2 g. of product, m.p. 32–33°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.0; H, 10.2.

Quantitative hydrogenation of 0.216 g. of this material over palladium-on-barium sulfate catalyst in alcohol solvent indicated an absorption of 0.00308 mole of hydrogen. The value calculated for two triple bonds is 0.00312 mole. Two low-temperature crystallizations of the hydrogenation product afforded 0.20 g. (91%) of stearic acid, melting alone or admixed with an authentic sample at 70–71°.

Ozonolysis according to the procedure described for the ozonolysis of octadecadiyn-9,12-oic acid led to a mixture of dibasic acids, m.p. 110–128°, and a *p*-bromophenacylate of the monobasic acids melting at 40–62°. Isolation of a pure compound from either fraction failed.

In contrast to the 42–43° diynoic acid, the 32–33° acid could not be crystallized satisfactorily from methanol or from acetone. On contact with air the material immediately acquired a purple color. No linoleic acid tetrabromide could be isolated after adding bromine to the half-hydrogenation product of this low-melting acid.

Hydrogenation Experiments with Octadecadiyn-9,12-oic Acid (m.p. 42–43°).—The different effect of conditions on the relative rates of the first and second stages of hydrogenation is illustrated by the following experiments:

A.—When the volume of hydrogen absorbed in the hydrogenation of 96 mg. of octadecadiyn-9,12-oic acid (0.348 mmole) in 20 ml. of ethanol in the presence of 10 mg. of 5% palladium-on-strontium carbonate is plotted against time, a curve is obtained which is linear (after an induction period) during absorption of the first two moles of hydrogen. Close to the point corresponding to half-hydrogenation the slope changes sharply, and a second straight line is observed. From the graph the rates of hydrogen absorption in the first and second stages of the process were found to be 0.8 ml./min. and 0.025 ml./min., respectively.

B.—When the conditions were changed so that 495 mg. of octadecadiyn-9,12-oic acid (1.8 mmole) in 45 ml. of ethanol was hydrogenated over 45 mg. of catalyst, the hydrogenation curve was again represented by two intersecting lines. However, whereas the rate of hydrogen absorption in the first stage was 3 ml./min.—corresponding to a 3.75-fold change from the first experiment—the rate of hydrogen absorption in the second stage was 0.7 ml./min., corresponding to a 28-fold change.

Linoleic Acid Tetrabromide from Octadecadiyne-9,12-oic Acid (IV).—Hydrogenation of the diynoic acid, m.p. 42–43°, in ethanol over a 5% palladium-on-strontium carbonate catalyst until two moles of hydrogen were absorbed led to an oily product which boiled under a pressure of 0.005 mm. at an external temperature of 160–180°. Bromination of this material in petroleum ether permitted isolation of 35 mg. of white material (m.p. 108–112°), which after two crystallizations from ethanol melted at 113–114°. Mixed with an authentic sample of linoleic acid tetrabromide (m.p. 114–115°), the compound melted at 113–114°.

BOSTON, MASSACHUSETTS RECEIVED FEBRUARY 1, 1951[26]

(26) A summary of the material in the paper was originally submitted for publication (Oct. 13, 1950) as a Communication to the Editor.

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

The Resolution of Amino Acids. III. Methionine[1]

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Methods based on the use of acetyl derivatives[3,4] and α-fenchylamines have been extended with fair success to the resolution of methionine into both active forms. A much more rapid and convenient resolution giving L-methionine has been effected through the salt of (+)-α-bromocamphor-π-sulfonic acid.

The original method of Windus and Marvel[5] using the N-formyl derivative and brucine, with some later modifications,[6,7] remains the only recorded chemical method for resolving methionine. Numerous biochemical methods have been employed recently, including the use of amino acid oxidases,[8,9] yeast fermentation,[10] the papain anilide synthesis[11] and the apparently more convenient selective enzymatic hydrolyses of various N-acyl derivatives[12] and esters.[13,14]

We now report that DL-methionine can be resolved fairly conveniently through the N-acetyl derivatives. N-Acetyl-D- and L-methionines were obtained in 82 and 40% yields, respectively, by successive use of (−)- and (+)-α-fenchylamine[15] and converted to the corresponding amino acids. The method is perhaps as reliable and convenient as that of Windus and Marvel and somewhat more adaptable to large scale use. However, since the racemic and active acetyl derivatives and salts are rather soluble, the procedures at each stage are considerably less convenient and give lower yields than were obtained in the analogous resolu-

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