

Ahmad-Strong synthesis of 8-, 9-, and 10-pentadecynoic acids

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ABSTRACT Three pentadecynoic acids, with the triple bond in the 8-, 9-, and 10-positions, have been synthesized on a gram scale in over-all yield of 65% by refinements of the five-step Ahmad-Strong method; isolation of intermediates was shown to be unnecessary prior to purification of the acetylenic nitriles by column chromatography on silicic acid.

The melting points of the pentadecynoic acids alternate regularly and widely with position of unsaturation, in marked contrast to behavior of the homologous octadecynoic acids described by Huber.

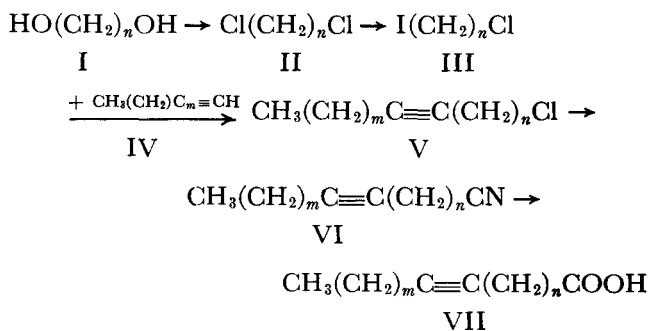
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ALTHOUGH tariric (6-octadecynoic) acid was for over 70 yr the sole known naturally occurring straight-chain acetylenic fatty acid, others (stearolic or 9-octadecynoic [1,2] and 8-heptadecynoic [2]) have recently been discovered in seed fats, and the list is almost certainly destined to grow further. Easy and unequivocal synthesis of such substances is important not only because they occur in nature, but because they are useful intermediates in the preparation of fatty acids with specifically situated functional groups, for example the monoenoic acids obtainable from the acetylenic precursors by stereospecific hydrogenation.

In the 20 yr which have passed since it was described, the general utility of the straight-chain acetylenic

carboxylic acid synthesis of Ahmad and Strong (3) (and minor modifications of it) has been well established (4-6). Preparation by this method and characterization of two previously unknown substances of this type (8- and 10-pentadecynoic acids) is described here, together with that of the recently reported 9-isomer (7).

Starting with commercially available α,ω -alkanediols (I) and 1-alkynes (IV), we obtained these substances by the reaction sequence outlined below ($m + n = 11$, Series A yielding 8-pentadecynoic acid [VIIA]; Series B, the 9-isomer [VIIB]; and Series C, the 10- [VIIC]):



In adapting the procedure to the preparation of small (gram) quantities, we avoided unnecessary isolation of intermediates. The entire sequence can, in fact, be carried out in good over-all yield without resorting to fractional distillation and by purification of but a single intermediate (the acetylenic nitrile, VI) by silicic acid column chromatography.

Treating the diols (I) with thionyl chloride and washing the crude product with concentrated sulfuric acid

yield the dichlorides (*II*) almost quantitatively and in purity adequate for use in the next step.

Periodic gas-chromatographic analysis of the resulting mixtures showed that reaction of the dichlorides with 1 molar equivalent of sodium iodide in refluxing acetone solution required about 24 hr for completion. The mixture of unchanged *II*, iodochloride (*III*), and the corresponding diiodide [$I(CH_2)_nI$, *VIII*] has a composition that agrees well with the 1:2:1 molar ratio expected, assuming that the rate constant for reaction of *II* with NaI is twice that for conversion of *III* to *VIII*. Since the iodides are rather unstable under the conditions required for precise fractional distillation, isolation of the iodochloride (*III*) is impractical (8). The unresolved 1:2:1 mixture of dihalides may, however, be used in the condensation in liquid ammonia with the sodio derivative of the 1-alkyne. Gas-chromatographic analyses of the resulting mixtures of products showed that the dichloride (*II*) remains unchanged, the iodochloride (*III*) is converted to acetylenic chloride (*V*), and the diiodide (*VIII*) yields the analogous acetylenic iodide (*IX*) together with some diacetylenic hydrocarbon, $CH_3(CH_2)_mC\equiv C(CH_2)_nC\equiv C(CH_2)_mCH_3$. Use of unresolved mixtures of dihalides is thus (to the extent that hydrocarbon is produced) somewhat wasteful of 1-alkyne, but it provides a bonus in formation of *IX*, which furnishes additional acetylenic nitrile (*VI*) in the reaction of the crude condensation product with sodium cyanide.

Conversion of acetylenic chlorides (e.g., *V*) to the corresponding nitriles by refluxing with NaCN, a very slow process in aqueous ethanol, was found to proceed rapidly in dimethyl sulfoxide (9–11) at 125°C, the reaction being 91% complete in 15 min and complete in 32 min. The crude acetylenic halides thus yield mixtures of hydrocarbons (unchanged diacetylenes, together with small amounts of 1-alkenes), the desired acetylenic nitriles (from both *V* and *IX*), and saturated α,ω -dinitriles (from residual dihalides *II*, *III*, and/or *VIII*). Since these components have widely disparate adsorptivities, the acetylenic nitriles can be freed of contaminants without loss by silicic acid column chromatography (see Fig. 1). In the preparation of 8-pentadecynenitrile (*VIA*), the over-all yield of pure nitrile (quantitatively convertible to acid *VII*) from glycol *I* was 65.5%.

The time required for conversion of the acetylenic nitriles to the corresponding acids (*VII*) by refluxing with aqueous ethanolic NaOH was established (by determination of the ammonia released) as about 7 hr. The acids are obtained in almost quantitative yields and crystallize beautifully from acetone at low temperature. *VII*B melts at 33.8–34.3°C (in good agreement with reported values [5, 7]), while the previously unknown 8- (*VII*A) and 10- (*VII*C) isomers melt at considerably lower tempera-

tures: 21.0–22.0° and 24.8–25.3°C, respectively. The large periodic variation in melting point exhibited by these substances is further borne out by the two other known contiguous isomers, the 6-, mp 25.5–26.3°C (5, 12), and the 7-, mp 36.0–37.5°C (5). This behavior contrasts strikingly with that of the homologous octadecynoic acids prepared by Huber (13), the 7- through 12-isomers of which all melt at very nearly the same temperature.

Triphenylphosphine reduction of the ozonides of the acetylenic acids converts them in good yield (Stein, R. A., to be published) to the corresponding *vic*-dioxopentadecanoic acids, all of which melt within a few degrees of 80°C.

EXPERIMENTAL METHODS

Melting points were obtained in open capillary tubes heated at 1°C/min (at the melting point) in a silicone oil bath or, for material melting below room temperature (only the temperature of disappearance of the solidus is reported for frozen-oil samples), in an acetone bath contained in an unsilvered cylindrical Dewar flask. All melting points are corrected.

Analyses were performed by the Elek Micro Analytical Laboratories, Los Angeles, Calif.

Adsorption chromatography was carried out as previously described (14), on 33 × 83 mm columns of J. T. Baker Chemical Co. (North Phillipsburg, N.J.) silicic acid powder (void space, 50 ml), untreated except for activation after dry packing by sequential washing with acetone, ether, and *n*-pentane (Phillips Petroleum Co., Bartlesville, Okla.; "Pure Grade"). Chromatograms were developed with *n*-pentane mixed with regularly increased amounts of diethyl ether. 100 ml of each of a standard series of mixtures (see abscissa, Fig. 1) were used, and 25-ml fractions were collected.

Gas-liquid chromatography (GLC) was done in a Barber-Colman model 10 apparatus containing a packed 6 mm × 100 cm column of Apiezon L on Gas-Chrom Q (Applied Science Laboratories Inc., State College, Pa.). The effluent was monitored by argon or hydrogen-flame ionization detectors. Peak areas were assumed to be proportional to the product of peak height times emergence time or, when peaks exhibited appreciable skewness, measured by planimeter or by use of an electronic integrator (Infotronics Company, River Forest, Ill., Model CRS-11 HSB). Because many of the mixtures included components with widely differing functional groups, specific responses were determined and internal standards were used in the conversion of peak areas to percentage composition. Specific-response corrections for substances containing iodine are particularly large

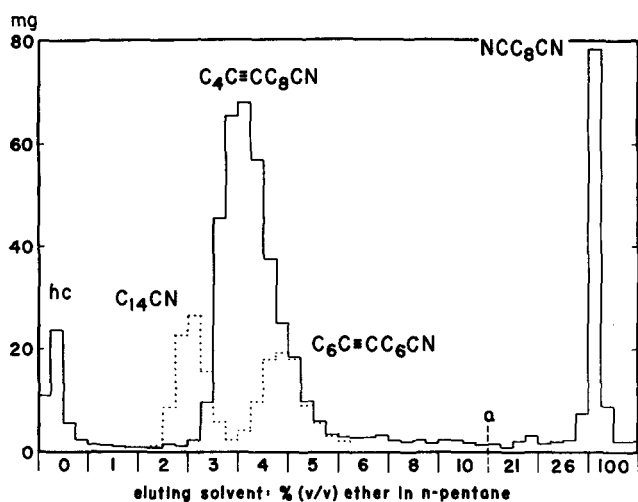


FIG. 1. Isolation of 10-pentadecynenitrile ($C_4C\equiv CC_8CN$; VIC) from contaminating hydrocarbons (hc) and sebaconitrile (NCC_8CN) by silicic acid column chromatography. Weights of nonvolatile solute eluted per 25 ml (one-half column-volume) of eluate are plotted: yield of VI, 67.7% of charge (495 mg). Negligible amounts of material eluted by 13 and 17% solvent mixtures (see a) are not shown. For comparison, chromatographic resolution under the same conditions of an artificial mixture of about 90 mg each of the saturated pentadecanenitrile ($C_{14}CN$) and of VIA ($C_6C\equiv CC_8CN$) is shown superimposed (dotted-line histogram).

(for both types of detector) and variable; calculation of the composition of mixtures containing appreciable quantities of iodides on the basis of GLC data alone was therefore subject to considerable uncertainty and usually had to be supplemented by uv spectrophotometric determination of primary alkyl iodide content.

UV spectra were determined in 95% ethanol solution by means of a Cary model 14 (Applied Physics Corp., Monrovia, Calif.) spectrophotometer. 1-Iodotetradecane served as a standard for the uv-absorbing properties of the primary alkyl iodide group. Prepared as described for the C_{16} homologue (15) and freed of polar (including highly colored) impurities by silicic acid column chromatography (the desired product travels with the solvent front), the substance (apparently not previously described) melts at 11.7–11.9°C and shows λ_{max} 255 nm (ϵ 503.5) and λ_{min} about 220 nm (ϵ approximately 80), in good agreement with values reported for several primary alkyl iodides by Haszeldine (16).

Polymethylene chlorides (II) were prepared as described by Ahmad, Bumpus, and Strong (17) from the corresponding commercially available glycols (I : $n = 6$, Eastman Chemical Products, Inc., Kingsport, Tenn.; $n = 7$, and 8, Aldrich Chemical Co., Inc., Milwaukee, Wis.). Yields of the sulfuric acid-washed products were about 97%.

Mixed Polymethylene Halides (II, III, and VIII). Conversion of II (about 85 mmoles) to a mixture of unchanged

II, iodochloride (III), and the corresponding diiodide (VIII) by refluxing with 1 molar equivalent of NaI previously dissolved in 140 ml of acetone is slow, requiring (as shown by GLC monitoring) about 24 hr for completion; there is no need to add the NaI solution dropwise (17), but stirring (by magnetically driven bar) is essential to avoid violent bumping (caused by separation of insoluble NaCl). After removal of solvent by rotary evaporation under reduced pressure at about 40°C, the residue was partitioned between water and pentane. (The weight of NaCl in the aqueous phase is a sensitive indication of completeness of the reaction.) The pentane solution was washed with a little aqueous Na_2SO_3 to remove free iodine, was dried over $MgSO_4$, and freed of solvent to yield a lightly colored oil weighing about 97% of theoretical.

Acetylenic Halides (V and IX). The mixed polymethylene halides were coupled with sodio 1-alkynes in liquid ammonia in a 665 ml, 19 cm depth, 7 cm id unsilvered Dewar flask equipped with an efficient stirrer, a reflux condenser cooled with solid CO_2 (with exit protected by a drying tube filled with KOH pellets), and a pressure-compensated addition funnel. Metallic sodium (about 85 mg-atom, 10% in excess of the quantity of iodine in the polymethylene dihalide mixture determined by specific absorption at 255 nm) was dissolved in about 200 ml of liquid ammonia and converted to sodamide, the reaction being assisted by addition of a small amount of freshly-sublimed anhydrous $FeCl_3$. 1-Alkyne (IV; K & K Laboratories Inc., Plainview, N.Y.), equivalent to the quantity of sodium, was then added dropwise, followed by addition of the halide mixture (II, III, and VIII), with vigorous stirring. (Addition of 50 ml of pentane along with the halides markedly improves the completeness of reaction.) After being stirred overnight the mixture was permitted to warm to room temperature and the ammonia to boil off, the dark gray sludge was partitioned between water and pentane, the pentane phase was washed with dilute HCl, dried over $MgSO_4$, and freed of solvent, and the residual oil was analyzed by UV spectrophotometry (for residual alkyl iodides) and by GLC.

Thus, for example, 19.26 g of undistilled II-III-VIII mixture (containing 77.7 meq of iodides by UV absorption analysis) gave 18.20 g of crude product (light-yellow oil) retaining about 20% of unreacted iodide.

Acetylenic nitriles (VI) were prepared by heating the mixtures described above with a small excess of sodium cyanide in dimethyl sulfoxide (9–11), partitioning the resulting mixtures between water and pentane, and isolating the desired acetylenic nitriles by chromatography on a column of silicic acid (see Fig. 1).

Time required for the metathesis was established in the following way. 1-Chlorotetradecane, bp 133–4°C at 0.2

mm, n_D^{20} 1.4467, mp 2.2°C (lit. [18]¹ bp 139–42°C at 4 mm, n_D^{20} 1.4450; the bp of 154–5°C at 15 mm [19] is clearly erroneous), was prepared by the action of thionyl chloride on tetradecyl alcohol. A mixture of 223 mg of the chloride with a 14% excess of NaCN in 0.25 ml of dimethyl sulfoxide, stirred at 125°C, was sampled from time to time and analyzed by GLC; at 2, 5, 10, and 15 min, conversion was found to be 9.2, 31.6, 74.6, and 91.3% complete. Assuming second-order kinetics as the reaction approaches completion, we estimated from these data that heating at 125°C for 32 min is required for 99% conversion. *Pentadecanenitrile*, prepared in this way and purified by silicic acid column chromatography (see Fig. 1), melts at 22.5–23.0°C.

Typically, an 18.82 g sample of crude *VA* containing some of the corresponding iodide (*IXA*) was stirred and heated with a 14% excess of granular NaCN (based on total halogen content of the crude *V*) in 29 ml of dimethyl sulfoxide to 125°C in 27 min and maintained at this temperature for 32 min. The cooled reaction mixture was partitioned between 92 ml of water and 25 ml of pentane (a third, brown, oily phase, presumably consisting for the most part of dinitrile, which collects at the interface, is carried along with the epiphase in subsequent operations). After the less dense phases had been washed with 25 ml of 6 N HCl and water, dried over $MgSO_4$, and freed of material (including solvent) readily volatile at 100°C, 10.49 g of straw-colored oil remained. Analysis by GLC at 119°C showed halides to be absent and, with pentadecanenitrile as internal standard, 63.3 wt % *VIA* to be present. Chromatography of a 200 mg sample of the crude product on SiO_2 resolved the mixture cleanly (see Fig. 1)¹ into hydrocarbon (5% of charge), *VI* (62.9%, colorless oil), and dinitrile (17%). On this basis, total yield of *VIA* was 6.61 g (6.55 g would be expected on the basis of conversion of both *V* and *IX* in the starting material to *VI*). The quantity (1.78 g) of dinitrile in the crude product is considerably less than expected (4.90 g), presumably because of its poor extractability by pentane. Larger quantities of *VI* were isolated by batch chromatography of 630-mg samples on SiO_2 by means of a simplified elution scheme: 150 ml of 1% ether in pentane to remove hydrocarbons; 400 ml of 4% ether in pentane to elute *VI*; and 200 ml of ether to sweep dinitrile from the column before reactivating with a 100 ml wash of pentane and introduction of the next batch.

¹ Presence of the acetylenic center in these substances (*VI*) increases the SiO_2 adsorptivity to a surprising degree; as indicated in Fig. 1, the acetylenic nitriles (the 8-, 9-, and 10-isomers behave identically) can be separated cleanly from the saturated analogue, pentadecanenitrile, by SiO_2 -column chromatography. Interestingly, the effect is not nearly so pronounced in the corresponding methyl esters; methyl stearate (only slightly less strongly adsorbed than stearonitrile) is, in fact, eluted from the SiO_2 column somewhat earlier than methyl stearolate (9-octadecynoate), but mixtures of the two substances are incompletely resolved.

The infrared spectrum of *VIA* in CCl_4 is very similar to that of the saturated analogue, stearonitrile (Bios Laboratories, Inc., New York), including a weak $C\equiv N$ absorption at 4.37 μ (intensity about 7.4% of that of the C–H stretching group); as expected, no absorption attributable to the symmetrically loaded $C\equiv C$ group; and as noted in spectra of lower homologues by Wotiz and Miller (20), a weak “anomalous” spike (intensity 5.6% vs. C–H stretch) at 5.77 μ which might ordinarily be taken for $C=O$ absorption.

Acetylenic Acids (VII). 1.95 g (8.92 mmoles) of chromatographically purified *VIA* was refluxed with 1.2 g of NaOH in 1.5 ml of water and 7 ml of 95% ethanol for 8 hr, and the mixture then freed of ethanol at 45°C under reduced pressure on a rotary evaporator. The solid residue was taken up in 12.5 ml of water, the solution was acidified with 3 ml of 12 N HCl, and the oil thus thrown out was taken up in ether. The ether extract was washed with water, dried over $MgSO_4$, and freed of solvent, leaving 2.08 g (97.8%) of *VIIA*, pale-yellow oil; crystallization from solution in 18 ml of acetone at –40°C yielded 1.17 g of the pure substance, mp 21.0–22.0°C.

Similarly obtained, pure *VII B* was found to melt at 33.8–34.3°C (lit. 34.9–35.7°C [5] and 32.3°C [6]) and *VII C* at 24.8–25.3°C.

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00

Found (*VII A*): C, 75.20; H, 10.87

(*VII B*): C, 75.48; H, 10.86

(*VII C*): C, 75.39; H, 10.98.

Dioxopentadecanoic Acids. 8,9-Dioxopentadecanoic acid needed in other studies was obtained by ozonization of 1.10 g of *VIIA* in 50 ml of methylene chloride cooled in solid CO_2 -acetone, addition of 1.20 g of triphenylphosphine to the resulting solution, and recrystallization of the crude product from acetone–water 10:3. (Application of this procedure to stearic acid yields the well-known 9,10-dioxostearic acid.) Three such recrystallizations gave 0.71 g (57%) of the desired diketo acid, mp 81–81.5°C, raised to 81.5–82°C by passage through a column of silicic acid (the substance is readily eluted by 20% ether in pentane but not by 10%). Similarly, *VII B* yielded 9,10-dioxopentadecanoic acid, mp 76–76.3°C; and *VII C* gave 10,11-dioxopentadecanoic acid, mp 80–80.5°C.

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69

Found (8,9-): C, 66.80; H, 9.64

(9,10-): C, 66.85; H, 10.00

(10,11-): C, 66.70; H, 9.70.

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