[Contribution from School of Medicine, University of California at Los Angeles]

A Total Synthesis of Linoleic Acid[1]

By Harry M. Walborsky,[2] Robert H. Davis and David R. Howton

As a prerequisite to the anticipated preparation of material tagged with isotopic carbon in specific positions, a total synthesis of linoleic acid was designed and carried to successful conclusion. A six-step process starting with 1,9-decadiyne yields 9,12-octadecadiynoic acid, catalytic semi-hydrogenation of which gives a product containing linoleic acid, identified by bromination to the characteristic tetrabromostearic acid, m.p. 114°. Preparation of linoleic acid in this manner provides chemical evidence substantiating its *cis,cis* configuration.

In connection with studies in these laboratories on the metabolism and function of the so-called "essential fatty acids"[3] the availability of samples of linoleic acid tagged with isotopic carbon is highly desirable. With the possible exception of random tagged (presumably preparable by growing linoleic-acid-producing plants in an atmosphere containing isotopic carbon dioxide) or of carboxyl-tagged linoleic acid,[4] realization of the desired goal requires a total synthesis of linoleic acid, preferably employing an intermediate readily available with isotopic carbon content and giving good yields in all steps subsequent to the incorporation of such an intermediate.

At the time the present work was conceived, linoleic acid had not been synthesized.[5] Employing methods which would not have been expected to yield products of stereospecific character, Noller and Girvin[8] and Baudart[9] synthesized materials containing identifiable amounts of linelaidic acid, the isomer (presumably *trans,trans*-9,12-octadecadienoic acid) produced by elaidinization[10] of the natural product. No linoleic acid was detectable in these synthetic products.

Indeed, although it was shown many years ago on the basis of reduction to stearic acid[11] and of identification of oxidation fragments[12] that linoleic acid is one of the four geometric isomers of 9,12-octadecadienoic acid, no convincing evidence of a chemical nature had been offered in support of any one of the four possible structures. Evidence that the 9-double bond of linoleic acid has the *cis*-configuration appears in the painstaking studies of McKay and Bader[13]; by a process involving, in essence, hydrogenation of the 12-double bond and stereospecific hydroxylations of the 9-double bond, products identical with those formed by hydroxylating oleic (*cis*-9-octadecenoic) acid[14] in the same ways were obtained. After examining the Raman and infrared spectra of the ethyl ester of linoleic acid, McCutcheon and his co-workers[21] concluded that both double bonds of the parent acid have the *cis*-configuration.

These few pertinent facts regarding the intimate details of the structure of linoleic acid indicated that any attempt to establish its structure by unequivocal total synthesis would have as its primary objective the preparation of *cis,cis*-9,12-octadecadienoic acid; the method of synthesis should, however, be readily adaptable to the preparation of any one of the other three geometric isomers.

The successes of Strong and his co-workers[7,22] in synthesizing straight-chain, mono-*cis*-olefinic fatty acids by catalytic semihydrogenation of the corresponding acetylenic acids suggested strongly

---

(1) This paper is based on work performed under Contract AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles; it was presented before the Organic Division of the American Chemical Society in Chicago, Ill., September, 1950.

(2) Chemistry Department, Florida State University, Tallahassee, Florida.

(3) G. O. Burr and M. M. Burr, *J. Biol. Chem.*, **86**, 587 (1930); G. O. Burr, *Federation Proc.*, **1**, 224 (1942).

(4) A procedure by which such material may be produced by the decarboxylation and reconstitution of linoleic acid isolated from plant sources is being developed in these laboratories and will be reported shortly.

(5) While the work described here was in progress, Raphael and Sondheimer[6] published a preliminary note on the first total synthesis of linoleic acid by a method resembling in some respects that employed in these laboratories. Dr. W. J. Gensler has recently informed us (private communication, September 5, 1950) that his group at Boston University has also succeeded in preparing linoleic acid by a method similar to that employed by the British workers. Report of less successful ventures in the same direction by Taylor and Strong[7] appeared during the present writing.

(6) R. A. Raphael and F. Sondheimer, *Nature*, **165**, 235 (1950).

(7) R. W. Taylor and F. M. Strong, This Journal, **72**, 4263 (1950).

(8) C. R. Noller and M. D. Girvin, *ibid.*, **59**, 606 (1937).

(9) G. Baudart, *Bull. soc. chim.*, [5] **11**, 336 (1944).

(10) J. P. Kass and G. O. Burr, This Journal, **61**, 1062 (1939).

(11) W. Dieff and A. Reformatsky, *Ber.*, **20**, 1211 (1877); A. Reformatsky, *J. prakt. Chem.*, [2] **41**, 529 (1890).

(12) G. L. Goldsobel, *Chem. Ztg.*, **30**, 825 (1906), and *J. Russ. Phys.-Chem. Soc.*, **38**, 182 (1906); C. Thieme, Inaugural Dissertation, Kiel, 1906 [*cf.* M. Stoll and A. Rouve, *Helv. Chim. Acta*, **27**, 950 (1944)]; see also R. D. Haworth, *J. Chem. Soc.*, 1456 (1929); T. Maruyama, *J. Chem. Soc. Japan*, **54**, 1082 (1933); and L. C. A. Nunn and I. Smedley-Maclean, *Biochem. J.*, **29**, 2742 (1935).

(13) A. F. McKay and A. R. Bader, *J. Org. Chem.*, **13**, 75 (1948).

(14) The burden of proof provided by this evidence rests, of course, on knowledge of the configuration of the double-bond in oleic acid; although this subject has remained controversial even until rather recently,[15] oleic was established unequivocally as the *cis* member of the oleic–elaidic isomeric pair by the work of Gonzáles[16] on stereospecific semi-reductions of stearolic acid, the acetylenic analog of oleic. This work was published in an obscure journal in 1926, before more recent studies[17] had established confidence in the stereospecificity of such reductions. The statement of Adkins and Billica[18] that semi-hydrogenation of stearolic acid yields elaidic acid (in direct contrast to the finding of Gonzáles) is in error; Gonzáles' results have been confirmed in these laboratories[19] and in those of Dr. J. B. Brown of The Ohio State University.[20]

(15) S. H. Bertram and E. C. S. Kipperman, *Chem. Weekblad*, **32**, 624 (1935), presented physical measurements which they interpreted in favor of the *trans*-configuration for oleic acid; an interesting series of polemics between Bertram and J. Stuurman (*ibid.*, **33**, 3, 201, 216, 255, 700 (1936)) ensued. We are indebted to Dr. E. C. Kooyman, N. V. De Bataafsche Petroleum Maatshattij, Amsterdam, for accurate translations of and comments on these papers.

(16) A. Gonzáles, *Anales soc. españ. fís. y quím.*, **24**, 156 (1926) [*C. A.*, **20**, 2310 (1926)].

(17) *Cf.* K. N. Campbell and L. T. Eby, This Journal, **63**, 216 (1941), and K. N. Campbell and B. K. Campbell, *Chem. Revs.*, **31**, 77 (1942).

(18) H. Adkins and H. R. Billica, This Journal, **70**, 695 (1948).

(19) Unpublished experiments.

(20) Private communication.

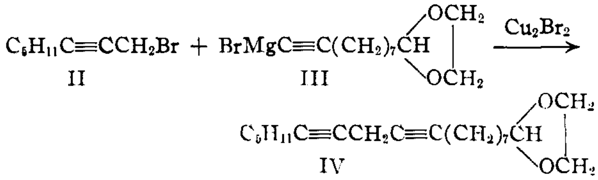
(21) J. W. McCutcheon, M. F. Crawford and H. L. Welsh, *Oil and Soap*, **18**, 9 (1941).

(22) K. Ahmad and F. M. Strong, This Journal, **70**, 1699 (1948); K. Ahmad, F. M. Bumpus and F. M. Strong, *ibid.*, **70**, 3391 (1948).

that the logical precursor of the *cis,cis*-acid would be 9,12-octadecadiynoic acid (I).

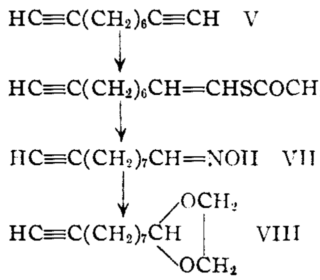
$$C_6H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH \quad \text{I}$$

Methods employed in the relatively few successful syntheses of 1,4-diynes[23] and the closely analogous 1,4-enynes[24] led to use of the following reaction to prepare IV, the initial intermediate containing potentially all features desired in the final product.



$$\underset{\text{II}}{C_6H_{11}C{\equiv}CCH_2Br} + \underset{\text{III}}{BrMgC{\equiv}C(CH_2)_7CH\begin{matrix}OCH_2\\|\\OCH_2\end{matrix}} \xrightarrow{Cu_2Br_2} \underset{\text{IV}}{C_6H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_7CH\begin{matrix}OCH_2\\|\\OCH_2\end{matrix}}$$

Preparation of the acetylenic acetal (VIII) (of which III is the Grignard derivative) was accomplished as follows



$$\begin{array}{ll} HC{\equiv}C(CH_2)_6C{\equiv}CH & \text{V} \\ \downarrow & \\ HC{\equiv}C(CH_2)_6CH{=}CHSCOCH_3 & \text{VI} \\ \downarrow & \\ HC{\equiv}C(CH_2)_7CH{=}NOH & \text{VII} \\ \downarrow & \\ HC{\equiv}C(CH_2)_7CH\begin{matrix}OCH_2\\|\\OCH_2\end{matrix} & \text{VIII} \end{array}$$

1,9-Decadiyne (V), prepared[25] by the action of sodium acetylide on hexamethylene iodide or bromide, reacted with thioacetic acid[26] to give the acetylenic enol thioacetate (VI) in 65% yield. Treatment of VI with hydroxylamine acetate gave a 91% yield of the crystalline oxime (VII), m.p. 80°. Using a procedure similar to that employed by Baudart[9] to convert glutaraldoxime into the ethyl acetal of glutaraldehyde, the ethylene-glycol acetal (VIII) was prepared from VII in 80% yield.

As indicated above, VIII, after conversion to the Grignard by exchange with ethylmagnesium bromide, was condensed with 2-octynyl bromide[7,23a,27] (II) under conditions designed (see Experimental) to minimize undesirable side-reactions resulting from the high reactivity of the central methylene group[28] of the product. Obtained in 53% yield, the product (IV), m.p. −1°, analyzed correctly and showed molecular refractivity in good agreement with that calculated on the basis of its anticipated structure. It has been suggested[29] that the reaction of II with III might be expected to yield some non-linear isomeric material which would presumably contain the conjugated allene-yne system: $CH_2{=}C{=}\overset{|}{C}{-}C{\equiv}C{-}$. Solutions of IV were, however, transparent in the wave length range in which such conjugated materials would be expected to absorb ultraviolet radiation. The infrared absorption spectrum of IV (see Fig. 1, Curve E) shows no significant absorption at the 1950 cm.$^{-1}$ frequency attributed[30] to the allenic structure in conjugation with a carboxyl group; in the absence of data on model compounds containing such systems, it would be conjectural to predict the effect on this infrared absorption band of substituting an acetylenic for a carboxyl moiety.

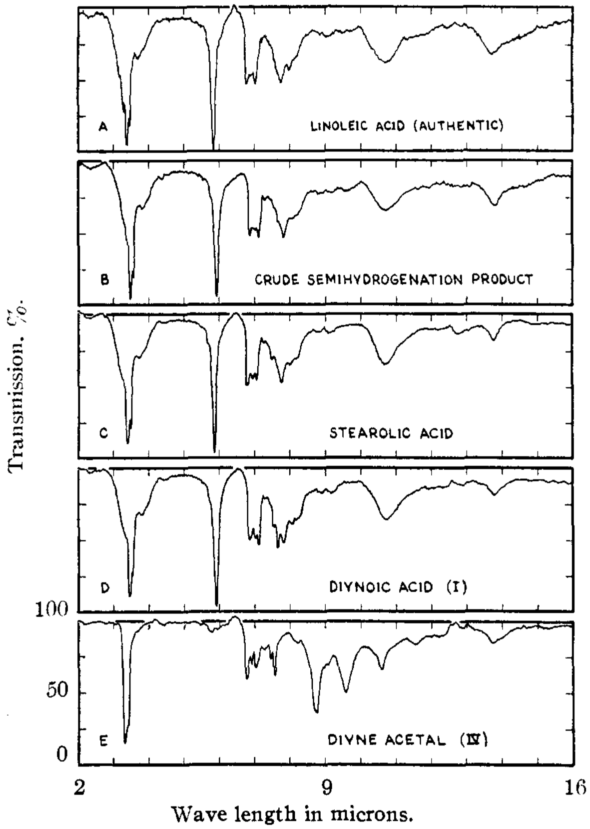


Fig. 1.—Infrared absorption curves obtained using a Baird infrared spectrophotometer, cell thickness 0.1 mm., solutions 5% by weight in carbon tetrachloride (2–10μ) or in carbon disulfide (10–16μ). The authentic linoleic acid, m.p. −8.5 to −7.5°, was prepared from poppy-seed oil as described by McCutcheon[32]; the stearolic acid was supplied by the Farchan Research Laboratories and recrystallized to constant m.p. (46.4–46.8°) from 96% ethanol.

Hydrolysis of IV was accomplished in aqueous dioxane solution, an equivalent amount of periodic acid being used to destroy the ethylene glycol on liberation. The crude intermediate aldehyde (V), dissolved in absolute ethanol containing sodium hydroxide and treated with a solution of silver nitrate in the same solvent,[31] gave the crystalline diynoic acid (I), m.p. 43–45°, isolated in 38% yield (based on IV) by crystallization from solution of the crude product in 96% ethanol at −15°.

---

(23) (a) T. Y. Lai, *Bull. soc. chim.*, [4] **53**, 1533 (1933); (b) G. F. Hennion and E. P. Bell, This Journal, **65**, 1847 (1943).

(24) J. P. Danehy, D. B. Killian and J. A. Nieuwland, *ibid.*, **58**, 611 (1936).

(25) W. M. Lauer and W. J. Gensler, *ibid.*, **67**, 1174 (1945).

(26) *Cf.* H. Bader, L. C. Cross, I. Heilbron and E. R. H. Jones, *J. Chem. Soc.*, 619 (1949); and H. Behringer, *Ann.*, **564**, 219 (1949).

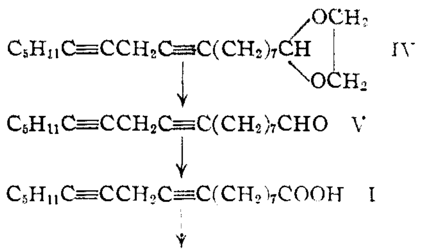
(27) J. von Braun and L. Tauber, *Ann.*, **458**, 104 (1927); J. H. Wotiz, This Journal, **72**, 1640 (1950).

(28) *Cf.* J. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene," Reinhold Publishing Corp., New York, N. Y., 1945, pp. 71–78. Although time limitations did not permit running control experiments which would provide evaluation of the special conditions employed in coupling II with III, much higher yields were obtained than those reported for analogous coupling reactions[7,23a] in which no such special precautions were taken.

(29) J. H. Wotiz, private communication.

(30) J. H. Wotiz, This Journal, **72**, 1639 (1950).

(31) *Cf.* M. Delépine and P. Bonnet, *Compt. rend.*, **149**, 39 (1909).



$$C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_7CH\begin{matrix}\diagup OCH_2\\ \diagdown OCH_2\end{matrix} \quad \text{IV}$$

$$C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_7CHO \quad \text{V}$$

$$C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH \quad \text{I}$$

cis,cis-9,12-octadecadienoic acid

Exhaustive catalytic hydrogenation of I gave stearic acid, identified by the fact that its melting point was not depressed by admixture with an authentic sample.

Interruption after two mole-equivalents of hydrogen had been taken up in the hydrogenation of I in 96% ethanol at room temperature and atmospheric pressure, using Raney nickel catalyst, yielded an oil which, on treatment with bromine in petroleum ether solution at 0°, gave a crystalline product, m.p. 113–114°, undepressed by mixing with a sample of the characteristic tetrabromostearic acid produced by similar bromination of an authentic sample of linoleic acid isolated from poppy-seed oil.[32] On the assumption that the impurities present in this crude semi-hydrogenation product would have about the same effect on the solubility of the 114° tetrabromide in petroleum ether as does oleic acid,[33] it is possible to estimate its linoleic acid content to be about 28%.

Reference to Fig. 1 shows that the infrared absorption spectrum of the crude semi-hydrogenation product (Curve B) is almost identical with that (Curve A) of authentic linoleic acid regenerated by the action of zinc on the 114°-tetrabromostearic acid isolated from saponified and brominated poppy-seed oil.[32] However, the significance of the agreement between these two curves is more apparent than real since the spectra of other conceivable components of the crude semi-hydrogenation mixture (compare spectra of I (Curve D), stearolic acid (Curve C), and oleic acid[34]) differ very little from that of linoleic acid. The absence of absorption at 10.3μ (aside from that of the short wave length shoulder of the 10.7-μ peak) in Curve B does show, however, that the crude semihydrogenation mixture is essentially free of *trans*-olefin content. The absence of appreciable carbon-carbon triple bond absorption in Curves C, D and E is noteworthy but not unexpected in view of the results of a study of the infrared absorption spectra of a number of acetylenic compounds by Wotiz and Miller.[35]

The primary objective, that of synthesizing linoleic acid by a stereospecific method substantiating its geometric configuration, has been realized. The ultimate goal of preparing isotopic carbon labeled linoleic acid requires much additional study to establish optimum-yield conditions; it should be pointed out that the yields reported in this communication are based in many cases on but a few experiments for which no claims of perfection of conditions can be made. Further studies on the application of methods used here to the synthesis of the other three geometric stereoisomers of linoleic acid are also contemplated.

Experimental

All melting points above room temperature were taken using Anschütz total-immersion thermometers with a 1°/min. rate of heating at the melting point. Those below room temperature were taken by introducing the material in the liquid state into a conventional melting point capillary, centrifuging the slug of liquid to the closed end of the tube, solidifying the sample, usually by cooling in crushed Dry Ice, and quickly placing the tube in a melting point apparatus whose liquid had been previously cooled to a point somewhat below that of the expected melting point; inasmuch as the point at which such solids begin to melt is very difficult to define reproducibly, in contrast to that at which the last crystal is no longer discernible in the melt, the latter is reported as the melting point.

Microanalyses were done by Dr. A. Elek, Los Angeles, infrared spectrophotometry by Dr. Ralph Nusbaum and Mr. George Alexander of the spectroscopy section of this project.

1,9-Decadiyne (V) was prepared as described by Lauer and Gensler,[25] except that acetylene was continuously passed into the reaction mixture during the addition of the hexamethylene halide. The use of either hexamethylene iodide (prepared in 60–76% yield by the action[36] of sodium iodide and phosphoric acid on hexamethylene glycol[37]) or hexamethylene bromide (Sapon Laboratories, Inc.) yielded 67% of the desired product (V), b.p. 71–72° at 13 mm. The higher yields obtained here (Lauer and Gensler[25] report 44%) are probably attributable to the more prolonged introduction of acetylene.

1-Decen-9-ynyl Thiolactate[26] **(VI)**.—A mixture of 15.7 g. (0.12 mole) of V and 4.5 g. (0.06 mole) of thioacetic acid was cautiously heated until the highly exothermic reaction was initiated. After the reaction had subsided, the mixture was heated on a steam-bath for one hour. Distillation yielded 10 g. of recovered V and 6.1 g. (65% based on unrecovered V) of VI, b.p. 102–106° at 0.2 mm.

Anal. Calcd. for $C_{12}H_{18}OS$: C, 68.52; H, 8.63; S, 15.24. Found: C, 68.32; H, 8.52; S, 14.91.

9-Decynaldoxime (VII).—Seven and four-tenths grams (0.035 mole) of VI, 4.9 g. (0.07 mole) of hydroxylamine hydrochloride, 5.8 g. (0.07 mole) of sodium acetate, 20 ml. of water and 100 ml. of ethanol were refluxed together overnight (hydrogen sulfide was evolved). Solvent was then distilled off until the vapor temperature reached 82°. At this point the residue was cooled and the oxime taken up in 60–70° petroleum ether. On cooling this solution to 0°, the product (VII) crystallized, yield 5.3 g. (0.032 mole, 91%), m.p. 77–79°; recrystallization from petroleum ether raised the melting point to 79.2–80.6°.

Anal. Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.84; H, 10.28; N, 8.35.

The corresponding 2,4-dinitrophenylhydrazone, obtained by the action of acidified aqueous alcoholic 2,4-dinitrophenylhydrazine on the acetal (VIII, see below) formed golden micaceous flakes from methanol, m.p. 73–74° with prior sintering.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.89; H, 6.00; N, 16.79.

2-(8′-Nonynyl)-1,3-dioxolane (VIII).—In a 100-ml. beaker equipped with a stirrer and surrounded by an ice-salt cooling mixture were placed 10 ml. of ethylene glycol, 1 ml. of water and two drops of concentrated sulfuric acid. To the mixture were alternately added, in small portions and with stirring, 5 g. (0.03 mole) of VII and 3.2 g. (0.032 mole) of butyl nitrite. The mixture was stirred rapidly until nitrogen oxide evolution ceased and homogeneity was attained. Ethylene glycol (20 ml.) and benzene (100 ml.) were then added and the water formed in the acetal formation removed by azeotropic distillation. The reaction mix-

---

(32) J. W. McCutcheon in *Org. Syntheses*, **22**, 75 (1942).

(33) *Cf.* M. F. White and J. B. Brown, *J. Am. Oil Chem. Soc.*, **26**, 385 (1949).

(34) P. C. Rao and B. F. Daubert, THIS JOURNAL, **70**, 1103 (1948).

(35) J. H. Wotiz and F. A. Miller, *ibid.*, **71**, 3441 (1949).

(36) *Cf.* H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

(37) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

ture was diluted with 5% aqueous sodium hydroxide and the benzene layer removed, washed with water and distilled free of benzene. Distillation of the residual oil gave 4.6 g. (0.024 mole, 80%) of VIII, b.p. 128–131° at 10 mm., $n^{26.5}{}_{D}$ 1.4551, $d^{23.2}{}_{20}$ 0.9388, M_D 56.74 (calcd. 56.72).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.22.

2-(8′,11′-Heptadecadiynyl)-1,3-dioxolane (IV).—The condensation of VIII with II was carried out in a dry nitrogen filled, all-glass apparatus of the type conventionally employed in the continuous extraction of aqueous solutions with ether; flask B was connected in such a way that vapors rising from a liquid refluxing in it would, after condensation, pass down through an inner funnel to the bottom of flask A, the overflow from which would then pass, *via* the tube provided for the passage of its vapors to the condenser, into flask B. By appropriate regulation of the heating of flask B, it was possible with this apparatus to transfer a reagent in A into B at any desired slow rate. A separatory funnel set to drip directly into the funnel leading to the bottom of flask A was also provided, in addition to a three-way stopcock at the top of the reflux condenser permitting the system to be communicated either to a source of dry nitrogen or, through a calcium chloride drying tube, to a water filled gas volume measuring buret. Both flasks (A and B) were provided with magnetic stirrers and were of 500-ml. capacity.

To 107 ml. (0.129 mole) of a 1.2 molar ethereal solution of ethylmagnesium bromide in flask A was added 300 ml. of dry tetrahydrofuran and the ether distilled out. An equivalent amount of VIII (25.1 g., 0.128 mole) was then added through the separatory funnel and the mixture stirred until the ethane evolved in the exchange had passed into the buret; the gas was evolved slowly (3 hours) but approximated the theoretical in amount. Flask B, charged with 28.4 g. (0.15 mole) of II,[7,23a,27] 350 ml. of tetrahydrofuran and about 0.2 g. of cuprous bromide,[24] was brought to gentle reflux through the agency of an infrared lamp and the reagent in flask A thus slowly carried into B overnight. Water was then added to the reaction mixture (cautiously at first, since some heat is evolved), inorganic solids filtered out with the aid of Celite, the layers separated, the aqueous phase extracted with a little 60–70° petroleum ether and the combined organic phases dried over potassium carbonate and freed of solvent. Rapid distillation of the residual oil gave, in addition to recovered starting and other lower-boiling materials, 24.2 g. (53%) of yellow, viscous oil, b.p. 163–182° at 0.35 mm. Redistillation gave an essentially colorless material in good recovery boiling in the range 179–182° at 0.7 mm. Ultraviolet spectroscopic examination of this material (IV) showed no detectable absorption which might be ascribed to conjugation of the centers of unsaturation. IV had $n^{21.3}{}_{D}$ 1.4781 and $d^{21.3}{}_{20}$ 0.939; these figures give M_D 91.80 (calcd. 91.68). On standing at −15°, IV solidified, radiating colorless needle clusters, m.p. −1°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.70; H, 10.51.

IV gave a 2,4-dinitrophenylhydrazone, m.p. 68–69°.

9,12-Octadecadiynoic Acid (I).—A mixture of 1.60 g. (0.0070 mole) of potassium periodate, 2.0 ml. of 6 *N* sulfuric acid and 100 ml. of water was warmed briefly to bring the inorganic solids into solution and then cooled; 2.00 g. (0.0066 mole) of IV and 240 ml. of dioxane were added, the resulting cloudy mixture heated rapidly to boiling (solution became clear) and the flask containing the mixture stoppered tightly and allowed to stand for about 3 hours. Three hundred milliliters of water and enough sodium bicarbonate to yield a weakly basic mixture were added and the product (presumably 9,12-octadecadiynal) taken up in 60–70° petroleum ether. Drying over magnesium sulfate and removal of solvent left 2.44 g. of viscous, light-yellow oil which solidified on leaving overnight at −15°. A small sample of this material distilled in an Emich tube at 0.14 mm. gave an essentially colorless, viscous oil showing (after freezing) the following melting behavior: visible meniscus at 8°, translucent liquid at 13°, clear at 18.6°. A single analysis of this material unavoidably run several days later gave results interpretable on the basis of very substantial oxygen uptake (almost one full molecular equivalent):

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84; C:H, 7.66. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.76; H, 9.83; C:H, 7.61.

The undistilled remainder (2.34 g.) of this crude aldehyde was transferred almost immediately, with the aid of 40 ml. of absolute ethanol, to a solution of 2.32 g. (0.0137 mole) of silver nitrate in 100 ml. of absolute ethanol. While passing a slow stream of nitrogen over the surface of the mixture and stirring (magnetically), 8 ml. (0.04 mole) of 5 *N* NaOH diluted to 40 ml. with absolute ethanol was added dropwise over a period of 10 minutes. The resulting jet-black suspension (dark brown initially) was stirred overnight at room temperature with exclusion of air. After centrifugation, the clear brown supernatant solution was freed of solvent *in vacuo* at *ca.* 35–40° and the residual light-brown solid taken up in 50 ml. of water, washed several times with 60–70° petroleum ether, acidified with 6 *N* hydrochloric acid, and the crude acids (containing I)[38] thus thrown out taken up in a total of 80 ml. of petroleum ether. Dried over magnesium sulfate and freed of solvent, the yellow solution yielded 1.27 g. (73%) of crude I, reddish-brown viscous oil, solidifying readily and essentially completely at 0°.

A second experiment, identical with the first with the exception that 4.5 (instead of 8) ml. of 5 *N* NaOH was employed, gave 1.42 g. (78%) of crude I.

A solution of a sample of this material in isoöctane showed an absorption maximum at 220 mμ; although this is rather clear evidence of the presence of conjugated (probably allene-acetylene, $-CH{=}C{=}CH{-}C{\equiv}C-$) material in this crude I, the amount is presumably small in view of the low molecular extinction (ϵ_{max} 867). The somewhat similarly constituted crystalline methyl 9,11-octadecadienoate[40] absorbs maximally at 230.5 mμ with a molecular extinction of 2.9 × 10^4; to the best of our knowledge, ultraviolet absorption data on an authentic substance containing the conjugated allene–acetylene system are not known.

Crude I (1.42 g.) from the second experiment mentioned above was taken up in 4 ml. of 96% ethanol and allowed to stand overnight at −15°, giving 0.60 g. of crystalline I, dense radiating clusters of fine white needles. Concentration of mother liquors to 2 ml., followed by similar cooling, gave an additional 0.10 g., but inappreciable additional amounts of crystalline material were produced by further concentration and cooling. The yield of crystalline I, m.p. 42.6–44.7° (Raphael and Sondheimer[6] give m.p. 42–43°), not raised by further recrystallization, was 38% based on IV. I turns to a brown oil overnight when left exposed to air at room temperature, but is apparently stable when kept at −15° in an atmosphere of carbon dioxide or nitrogen.

Shaking an 80-mg. sample of crude I with 10 ml. of 96% ethanol, 9.4 mg. of platinum oxide (American Platinum Works) and moist hydrogen at room temperature and atmospheric pressure resulted in the uptake of approximately four molecular equivalents of the gas. Removal of catalyst and solvent left a residue which solidified readily at room temperature and was, after recrystallization from methanol, identified as stearic acid by virtue of the fact that its melting point (68–69°) was not affected by admixture with an authentic sample.

***cis,cis*-9,12-Octadecadienoic (Linoleic) Acid.**—A solution of 0.83 g. (0.003 mole) of crystalline I in 10 ml. of 96% ethanol was shaken with W-5 Raney nickel[18] and moist hydrogen at atmospheric pressure and room temperature until two molecular equivalents of the gas had been taken up. About 3 hours were required and hydrogen was still being consumed at an appreciable rate when the hydrogenation was interrupted. The catalyst (*ca.* 0.7 ml. centrifugally packed) was centrifuged off and the yellow solution freed of solvent. A sample of the residual oil (which crystallized rapidly at −15°) was used to obtain the infrared absorption Curve B (Fig. 1). Another sample (0.60 g.) was dissolved in 10 ml. of 60–70° petroleum ether and cooled in an ice-mush while 0.69 g. (two molecular equivalents) of bromine was passed into the solution by means of a stream of nitrogen. The resulting precipitate was washed twice with 10-ml.

---

(38) As Cason[39] has pointed out, such conventional procedures for the separation of acidic from neutral materials may be far from quantitative when applied to substances of this type. That only about half of this crude I can be obtained in crystalline form (see below) may well reflect incompleteness of the hydrolysis and/or oxidation steps employed in converting IV to I.

(39) J. Cason, G. Sumrell and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950), footnote 1.

(40) Data on the ultraviolet absorption spectrum of this substance was kindly furnished by Dr. James F. Mead of these laboratories.

portions of ice-cold petroleum ether and dried, yield 0.065 g. The data of White and Brown[31] on the effect of oleic acid on the yield of cold petroleum ether insoluble tetrabromostearic acid obtained from linoleic acid under these conditions permit the calculation of a 28% content of linoleic acid in this crude semi-hydrogenation product. The crude bromination product, after recrystallization from ethylene chloride, melted at 113.2–113.8°; after mixing with an approximately equal amount of authentic linoleic acid tetrabromide[32] (m.p. 114.4–115.2°), the mixture melted at 113.8–115.3°.

ORIGINAL PAPER RECEIVED MAY 18, 1950
LOS ANGELES, CALIF. RECEIVED OCTOBER 16, 1950

Tris-(hydroxymethyl)-aminomethane Derivatives. II. Alkylation Products[1,2]

BY J. STANTON PIERCE AND JOHN WOTIZ[3]

Tris - (hydroxymethyl) - aminomethane, $(HOCH_2)_3CNH_2$, (I) by reason of the plurality of functional groups, presents interesting possibilities as an intermediate for synthetic work. In a previous publication from this Laboratory,[4] highly water-soluble aliphatic polyhydroxyamines derived from I were described.

We now wish to report the preparation of the N-alkyl and N-arylalkyl derivatives listed in Table I.

TABLE I

ALKYL- AND ARYLALKYLTRIS-(HYDROXYMETHYL)-METHYLAMINE HYDROBROMIDES AND HYDROCHLORIDES[a] $RNHC(CH_2OH)_3 \cdot HX$

R	Empirical formula	M.p., °C. (uncor.)	Halogen,[b] % Calcd.	Found
C_2H_5	$C_6H_{16}O_3BrN$	90–92	34.73	35.28
n-C_4H_9	$C_8H_{20}O_3BrN$	93–94	30.96	31.07
n-C_6H_{13}	$C_{10}H_{24}O_3BrN$	99–100.5	27.92	28.55
$CH_2{=}CHCH_2$	$C_7H_{16}O_3BrN$	Sirup	33.01	32.54
$CH_2BrCHBrCH_2$[5,c]	$C_7H_{16}O_3Br_3N$	118–120	19.88[d]	19.92
n-$C_5H_{11}OCOCH_2$	$C_{11}H_{24}O_6ClN$	Sirup	12.41	12.77
$HOOCCH_2$	$C_6H_{14}O_5ClN$	Sirup	16.44	16.56
p-$O_2NC_6H_4CH_2$	$C_{11}H_{17}O_5ClN_2$	160–162	12.11	12.06
p-$H_2NC_6H_4CH_2$[5,e]	$C_{11}H_{20}O_3Cl_2N_2$[f]	171–172	23.70	23.31[g]

[a] Acknowledgment is made to Dr. R. S. Murphey for assistance in the preparation of some of these compounds. [b] Acknowledgment is made to E. E. Bowden for most of the analyses and to R. L. Kersey and W. E. Reid, Jr., for a few of the analyses. [c] Prepared in 92% yield by bromination of allyltris-(hydroxymethyl)-methylamine hydrobromide, in chloroform solution. Purified by solution in methanol, precipitation with ether and recrystallization from acetone and benzene. [d] Ionizable halogen. [e] Prepared by reduction of p-nitrobenzyltris-(hydroxymethyl)-methylamine with hydrogen gas with Raney nickel as catalyst and conversion of the free base to the dihydrochloride. [f] In this case type formula is $RNHC(CH_2OH)_3 \cdot 2HX$. [g] The chloride analysis was made after decomposition of this compound in a Parr bomb. Volhard titration could not be carried out because of the unexpected solubilizing action of this substance on silver chloride.

Experimental

General Alkylation Procedure.—N-Alkylation of I was carried out in alcohol solution, usually in glass tubes at approximately 110° for 12 to 15 hours, with the alkyl halide and I in equimolar quantities. By this method I was alkylated with ethyl, n-propyl, n-butyl, n-amyl and n-hexyl bromides, with p-nitrobenzyl chloride and amyl chloroacetate.

In the isolation and purification of n-hexyltris-(hydroxymethyl)-methylamine hydrobromide, excess hydrobromic acid was added to the reaction mixture, the mixture was evaporated to a sirup and extracted with acetone. The product was precipitated from the acetone solution with ether and recrystallized three times from nitromethane and three times from acetone and dry ether. By the same general method, except for the use of nitromethane, ethyl- and n-butyltris-(hydroxymethyl)-methylamine hydrobromides were obtained in crystalline form but the n-propyl and n-amyl derivatives were obtained as sirups with bromine analyses distinctly high. On similar treatment, except vacuum evaporation of the solvent, n-amyl tris-(hydroxymethyl)-methylaminoacetate hydrochloride was obtained as a sirup. On hydrolysis of this compound, evaporation of the solvent and drying in a desiccator, tris-(hydroxymethyl)-methylaminoacetic acid hydrochloride was obtained as a sirup.

Allyltris-(hydroxymethyl)-methylamine Hydrobromide, $CH_2{=}CHCH_2NHC(CH_2OH)_3 \cdot HBr$.—A mixture of 48.4 g. of (I) (0.4 mole), 24.2 g. of allyl bromide (0.2 mole) and 200 ml. of absolute ethanol was refluxed for 72 hours. Excess (I)·HBr was removed by filtering, concentrating the filtrate and filtering, treatment of the filtrate with anhydrous hydrogen bromide until it was acidic and filtering. The total recovery of (I)·HBr was 46.5 g. (0.23 mole). This indicated a reaction of 0.17 mole or 85% of theory. On evaporation of the filtrate and drying the residue in a vacuum oven there was obtained 41.9 g. (86.4%) of crude allyltris-(hydroxymethyl)-methylamine hydrobromide, a viscous red oil.

p-Nitrobenzyltris-(hydroxymethyl)-methylamine, p-$O_2NC_6H_4CH_2NHC(CH_2OH)_3$.[5]—The reaction mixture of p-nitrobenzyl chloride and (I), in alcohol, was acidified with hydrochloric acid and diluted with water to form a 25% aqueous alcohol solution. The solution was extracted with toluene, made basic with sodium hydroxide and extracted immediately with ether. A precipitate started to form in the lower, light yellow layer within a few minutes. This precipitate of p-nitrobenzyltris-(hydroxymethyl)-methylamine and others obtained by concentration of the mother liquor, were purified by recrystallization from alcohol and water; m.p. 137–138°. *Anal.* Calcd. for $C_{11}H_{16}O_5N_2$: N, 10.94. Found: N, 10.78.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF RICHMOND
RICHMOND, VIRGINIA

RECEIVED AUGUST 9, 1950

---

[1] Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

[2] This research was assisted by a grant from Charles C. Haskell and Co., Inc., Richmond, Va.

[3] Taken in part from a thesis submitted by John Wotiz in partial fulfillment of the requirements for the degree of Master of Science.

[4] J. S. Pierce and John Wotiz, THIS JOURNAL, **66**, 879–881 (1944).

[5] Reported by H. E. Thompson, C. P. Swanson and A. G. Norman, *Bot. Gazette*, **107**, 476 (1946), but no m.p. or analysis is given.