[Contribution No. 924 from the Department of Chemistry, University of Pittsburgh]

THE ISOMERIC NORMAL NONYNOIC ACIDS

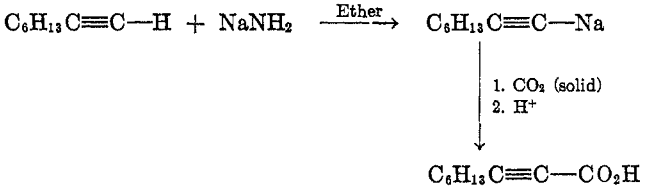
JOHN H. WOTIZ and EDWARD S. HUDAK[1]

Received March 8, 1954

The recent preparation of all the isomeric normal octynoic acids (1) suggested generally applicable methods for the synthesis of acetylenic acids containing the triple bond any number of carbon atoms removed from the carboxy group. It was thought to be desirable to synthesize other heretofore unknown isomeric acetylenic compounds in order to compare their physical, chemical, and physiological properties. The latter was desirable because the octynoic acids showed fungistatic activity (2). The normal nonynoic acids were selected as important comparisons between related even and odd (eight and nine carbon) acetylenic acids and derivatives would thus be made possible. The physiological properties of these new compounds will be published separately.

SYNTHESIS

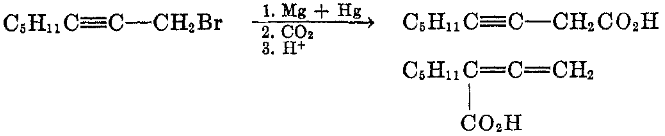
2-Nonynoic acid



$$C_6H_{13}C{\equiv}C{-}H + NaNH_2 \xrightarrow{\text{Ether}} C_6H_{13}C{\equiv}C{-}Na \xrightarrow[\text{2. } H^+]{\text{1. } CO_2 \text{ (solid)}} C_6H_{13}C{\equiv}C{-}CO_2H$$

The over-all yield was 55%. Carbonation by pouring 1-octynylsodium on Dry Ice resulted in higher yields than the carbonation in which Dry Ice was added in lumps to 1-alkynylsodium (3). However, only a 3% yield of acidic material was obtained when 1-octynylmagnesium bromide was poured on Dry Ice. The low reactivity of acetylenic Grignard reagents was already noted (4) in their reaction with benzonitrile.

3-Nonynoic acid

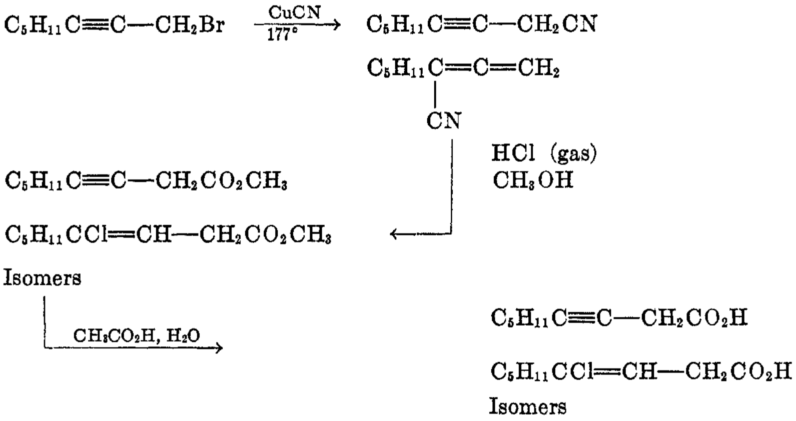


$$C_5H_{11}C{\equiv}C{-}CH_2Br \xrightarrow[\text{2. } CO_2 \;\; \text{3. } H^+]{\text{1. } Mg + Hg} C_5H_{11}C{\equiv}C{-}CH_2CO_2H \quad C_5H_{11}\underset{CO_2H}{C}{=}C{=}CH_2$$

The formation of 3-nonynoic acid in a 13% over-all yield along with a 23% yield of 2-amylbutadienoic acid was previously (5) described. The preparation of 3-nonynoic acid using the following reactions was not satisfactory.

---

[1] Abstracted from the thesis of E. S. H. presented in partial fulfillment of the requirements for the degree of Master of Science, 1954.



When 1-bromoöctyne-2 was heated with cuprous cyanide in boiling xylene (b.p. 138°) no reaction took place. This was unexpected because such conditions were used when 1-bromoheptyne-2 was converted into 1-cyanoheptyne-2 in 90% yield (1). It was found necessary to replace the boiling xylene with *p*-cymene (b.p. 177°). The yield of cyanide was then 74%. However, the 1-cyanoöctyne-2 was contaminated with an allenic cyanide, most likely 3-cyanoöctadiene-1,2, $C_6H_{11}—\overset{\overset{CN}{|}}{C}=C=CH_2$, as evidenced by the double peak at 1910 and 1930 cm^{-1} (5) in its infrared spectrum. The mixture of nitriles, which boiled within one degree, was hydrolyzed with hydrogen chloride in the presence of methanol. The product was a mixture of acetylenic, allenic, and chlorolefinic esters as evident from elementary and infrared analyses. The fractional distillation and crystallization of the esters and the acids obtained on hydrolysis did not result in the isolation of pure 3-nonynoic acid.

The *4-* and *8-nonynoic* acids were prepared in good yields from acetylenic halides by the malonic ester synthesis (MES).

$$C_4H_9C{\equiv}C—CH_2Br \xrightarrow{(MES)} C_4H_9C{\equiv}C—CH_2CH_2CO_2H$$

$$HC{\equiv}C—(CH_2)_5I \xrightarrow{(MES)} HC{\equiv}C—(CH_2)_6CO_2H$$

The *5,6,* and *7-nonynoic* acids were prepared as outlined.

$$R—C{\equiv}C—Na + Br(CH_2)_nCl \xrightarrow{NH_3\ (l.)} R—C{\equiv}C—(CH_2)_nCl$$

$$R—C{\equiv}C(CH_2)_nCO_2H \xleftarrow[2.\ H^+]{1.\ NaOH} R—C{\equiv}C(CH_2)_nCN \xleftarrow{} \begin{matrix}1.\ NaI\ in\ acetone\\ 2.\ KCN\end{matrix}$$

$$R = C_3H_7,\ C_2H_5,\ CH_3$$

$$n = 3 \quad 4 \quad 5$$

The yields of reactions were generally in agreement with the yields observed for the preparation of the octynoic acids (1). The acids were characterized by their melting and boiling points, elementary analyses, neutral equivalents, and

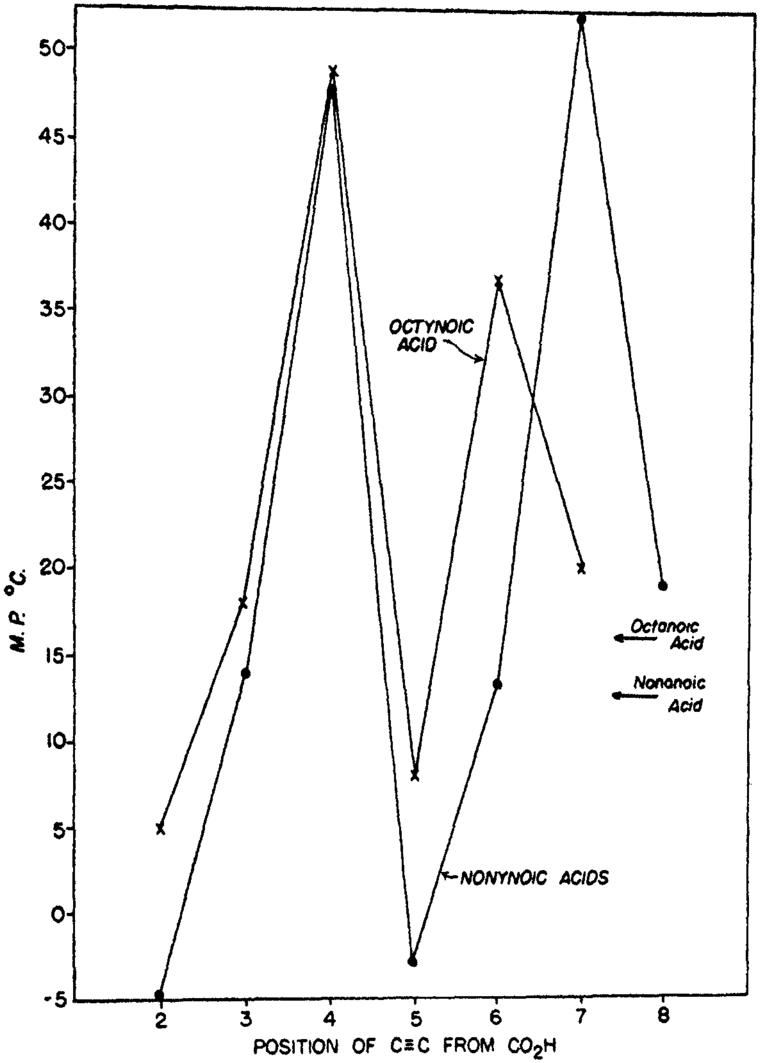


Fig. 1. Melting Points of Nonynoic and Octynoic Acids

conversion to methyl esters and solid amides. The 7 and 8-nonynoic acids were mixed with samples of 7 and 8-nonynoic acid prepared independently[2] and there was no depression of melting points. Similar observations were made with melting points of mixtures of 7 and 8-nonynoamides.

The melting points of the isomeric octynoic and nonynoic acids are shown in Figure 1. In both series the 2-isomer has the lowest melting point, and the 5-isomer also melts low. The 4-isomers melt significantly higher that the 3- and 5-isomers. Moving the unsaturation from the end of the chain by one

---

[2] Arndt-Eistert synthesis, Wotiz and Buco, unpublished.

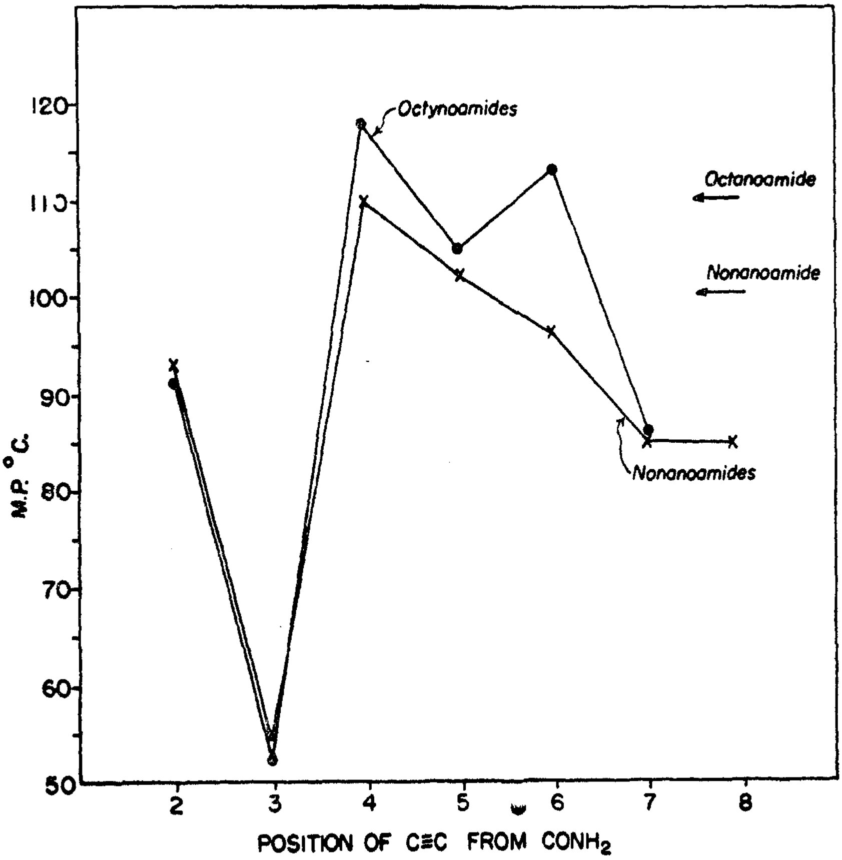


FIG. 2. MELTING POINTS OF NONYOAMIDES AND OCTYNOAMIDES

carbon atom results in a significant increase in the melting point. An over-all comparison of the two series reveals that the octynoic acids melt higher than the nonynoic acids provided that the triple bond is the same number of carbon atoms from the carboxy group. However, the acids with the unsaturation in the seven position are an exception. The reason for this is the fact that 7-octynoic acid has a terminal triple bond which is not the case in the 7-nonynoic acid. It should also be noted that the introduction of a triple bond into octanoic acid (m.p. 16°) and nonanoic acid (m.p. 12.5°) increases as well as decreases the melting point depending upon the position of the triple bond.

The melting points of the isomeric normal octynoamides and nonynoamides (Figure 2) show an increase of about 50° over the corresponding acetylenic acids. An exception is the case of the 2-isomers where there is a difference of about 100°. This may be due to the unusually low melting point of the acids. In the acetylenic amides the minimum melting point is found in the 3-isomer and the maximum in the 4-isomer. Generally, there are small differences in the melting

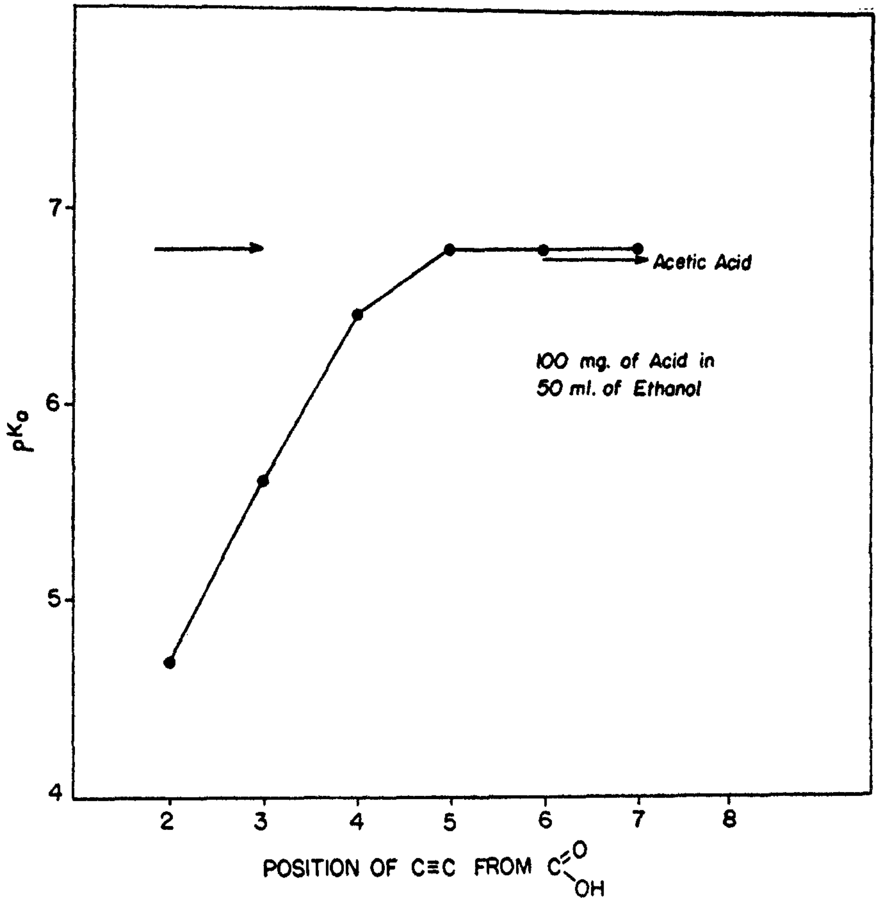


FIG. 3. *p*K VALUE OF ISOMERIC NORMAL NONYNOIC ACIDS

points of amides having the triple bond in comparable positions. Placing the unsaturation into octanamide (m.p. 105°) and nonanamide (m.p. 100°) increases or decreases the melting point depending upon the position of the triple bond.

A comparison of *p*K values (Figure 3) shows that the 2-isomer is the strongest acid and that the location of the triple bond past the five position no longer affects the acidity. The values reach a constant at *p*K 6.8 which is the acidity of saturated acids in the medium employed. These findings demonstrate the electron-attracting influence of the triple bond which was already pointed out for other α-acetylenic acids (7, 8).

EXPERIMENTAL

2-Nonynoic acid. To a suspension of 50 g. (1.27 moles) of sodium amide in one liter of dry ether was added 142 g. (1.27 moles) of octyne-1 at a rate so as to have a rapid evolution of ammonia. The mixture was stirred and refluxed for four hours, after which time the evolution of ammonia was very slow. The mixture was poured on one kg. of crushed Dry Ice and allowed to stand overnight. The product was hydrolyzed with a saturated solution of am-

TABLE I

PHYSICAL CONSTANTS FOR NONYNOIC ACIDS, AMIDES, AND METHYL ESTERS

Compound	—COOH								—CONH₂				—COOCH₃				
	M.P.,[e] °C.	B.P., °C.	mm	n_D^{25}	Analyses Found[a]				M.P.,[e] °C.	Analyses Found[b]			B.P., °C.	mm	n_D^{25}	Analyses Found[c]	
					C	H	Neut. Equiv.	pK[f]		C	H	N				C	H
$C_6H_{13}C{\equiv}C$-	−5	122	2.2	1.4605	70.1	8.9	156	4.67	94	70.3	9.7	9.4	85	2.3	1.4470	71.5	9.4
$C_5H_{11}C{\equiv}C{-}CH_2$-	14	118	2.0	1.4603	70.4	9.3	154	5.60	54	70.3	9.9	9.3	[d]	[d]	[d]	[d]	[d]
$C_4H_9C{\equiv}C(CH_2)_2$-	48	135	5.0	—	69.9	8.8	154	6.47	110	70.5	9.6	9.2	85	3.0	1.4440	71.3	9.7
$C_3H_7C{\equiv}C(CH_2)_3$-	−3	115	1.0	1.4558	69.8	9.1	156	6.80	102	70.5	9.7	9.4	79	1.5	1.4420	71.8	9.7
$C_2H_5C{\equiv}C(CH_2)_4$-	14	130	3.0	1.4578	70.3	9.2	152	6.79	96	70.4	9.8	9.4	85	4.0	1.4453	71.1	9.4
$CH_3C{\equiv}C(CH_2)_5$-	52	118	1.0	—	70.4	8.9	155	6.83	85	70.7	9.9	9.1	85	1.5	1.4436	71.6	9.7
$HC{\equiv}C(CH_2)_6$-	19	128	4.0	1.4524	69.9	9.1	155	6.84	85	70.5	9.5	9.5	87	3.9	1.4411	71.1	9.4

[a] *Anal.* Calc'd for $C_9H_{14}O_2$: C, 70.1; H, 9.1; Neut. Equiv., 154. [b] *Anal.* Calc'd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.2. [c] *Anal.* Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. [d] Not synthesized. [e] Melting points with one degree range, upper limit listed. [f] Using the same conditions *n*-octanoic acid, 6.50; and acetic acid, 6.75. In aqueous solution acetic acid, 4.74.

monium chloride and worked up in the usual manner. On distillation 107 g. (55% yield) of 2-nonynoic acid was obtained. The properties are listed in Table I.

1-Cyanoöctyne-2. To 20 g. of *p*-cymene was added 47 g. (0.25 mole) of 1-bromoöctyne-2 (6) and 30 g. (0.33 mole) of anhydrous cuprous cyanide. The mixture was stirred and heated. When the inside temperature reached 182° an exothermic reaction set in. Outside cooling was provided so that the inside temperature did not exceed 190°. The product was viscous and dark. It was diluted with ether and filtered. On distillation 25 g. (74% yield) of 1-cyanooctyne-2, b.p. 64–65° at 0.5 mm., n_D^{25} 1.4481 was obtained.

Anal. Calc'd for $C_9H_{14}N$: C, 80.8; H, 9.6; N, 10.4.
Found:[3] C, 78.5; H, 9.7; N, 10.5.

Its infared[4] analysis showed it to be contaminated with an allenic impurity.

Attempted preparation of 3-nonynoic acid. Anhydrous hydrogen chloride was passed through a solution of 97 g. (0.71 mole) of 1-cyanoöctyne-2 (see above), 250 ml. of methanol, and 15 ml. of water. The reaction was exothermic. When the refluxing ceased, the gas addition was stopped. The precipitated ammonium chloride was removed and the filtrate was distilled yielding 70 g. of liquid, b.p. 70–72° at 0.5 mm., n_D^{25} 1.4515. Elementary analysis showed the ester to contain chlorine.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.4.
Calc'd for $C_{10}H_{17}ClO_2$: C, 58.5; H, 8.3.
Found: C, 63.9; H, 8.5.

The ester was mixed with dilute acetic acid (1:1) and *p*-toluenesulfonic acid (1 g.) and refluxed. On distillation 22 ml. of methyl acetate was collected. The residue was distilled fractionally from 52 to 128° at 0.2 mm. On redistillation 22.5 g. (35% yield) of liquid, b.p. 132–134° at 0.2 mm., n_D^{25} 1.4683, was collected. It was most likely *4-chloro-3-nonenoic acid.*

Anal. Calc'd for $C_9H_{15}ClO_2$: C, 56.7; H, 7.8; Cl, 17.5; Neut. equiv., 195.
Found: C, 56.3; H, 7.5; Cl, 18.1; Neut. equiv., 193.

A portion of this acid was converted in 80% yield into its amide, presumably *4-chloro-3-nonennoamide*; m.p. 107–108° from petroleum ether.

Anal. Calc'd for $C_9H_{16}ClNO$: C, 56.9; H, 8.4; N, 7.4.
Found: C, 54.3; H, 8.0; N, 7.8.

A solution of 30 g. (0.15 mole) of the chlorononenoic acid and 25 g. (0.44 mole) of potassium hydroxide in methanol was refluxed for two days. The product was acidified with hydrochloric acid and the organic portion was dissolved in ether and dried. On distillation, which was accomplished with much decomposition, 10 g. of product boiling at 105–115° at 2 mm. was collected. This portion solidified on cooling and was crystallized from petroleum ether to a constant melting point of 65–66°. Its infrared spectrum showed it to be free from acetylenic, allenic, and olefinic material. It was identified as 4-ketononenoic acid.[5]

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.8; H, 9.3.
Found: C, 62.7; H, 8.9.

The preparation of *3-nonynoic acid* by the carbonation of the Grignard reagent prepared from 1-bromoöctyne-2 was previously described (6). The properties are listed in Table I.

4-Nonynoic acid. To a solution of 12.6 g. (0.55 mole) of sodium and 160 g. (1.0 mole) of diethyl malonate in 500 ml. of absolute alcohol was added 87.5 g. (0.5 mole) of 1-bromoheptyne-2 (6), and the mixture was refluxed for eight hours. The precipitated sodium bromide was removed and the filtrate was distilled yielding 79 g. (60% yield) of product, b.p. 89–159° at 3 mm. On redistillation 67 g. of *diethyl (2-heptynyl)malonate*, b.p. 134–137° at 3 mm., n_D^{25} 1.4451 was collected.

Anal. Calc'd for $C_{14}H_{22}O_4$: C, 66.1; H, 8.6.
Found: C, 66.3; H, 8.6.

---

[3] Analyses by the Microanalytical Laboratory of the University of Pittsburgh.

[4] Infrared analyses by Dr. Foil A. Miller and co-workers at the Mellon Institute, Pittsburgh, Pa.

[5] Lukeš, *Collection Czechoslov. Chem. Commun.*, **1**, 119 (1929) [*Chem. Abstr.*, **23**, 4469 (1929)] reports it to melt at 69°.

A portion of this product was refluxed with dilute sodium hydroxide for two days. The solution was acidified and the separated solid, *(2-heptynyl)malonic acid*, was recrystallized from ether to a constant melting point (with decomposition) of 93–94.°

Anal. Calc'd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1.

Found: C, 60.4; H, 7.0.

An alcoholic solution of 40 g. (1.0 mole) of sodium hydroxide and 111 g. (0.44 mole) of diethyl (2-heptynyl)malonate was refluxed for 10 hours. The solution was acidified with hydrochloric acid and refluxed for three hours. The organic layer was separated, dried and distilled. Decarboxylation proceeded during distillation, and the product boiling from 77 115° at 3 to 17 mm. was collected. The higher-boiling distillate (26 g.) solidified on cooling. It was therefore heated at 180° in the presence of *p*-toluenesulfonic acid for one week. The product and the lower-boiling distillate were combined and saponification with dilute sodium hydroxide was repeated. The solution was acidified and the organic layer was taken into ether, dried, and distilled, b.p. 134–35° at 5 mm., yielding 40 g. (59%) of crude *4-nonynoic acid* melting at 44–45°. On recrystallization from a mixture of petroleum ether and benzene it melted at 47–48°. The properties are listed in Table I.

5-Nonynoic acid. To 56.5 g. (1.45 moles) of sodium amide in 3 liters of liquid ammonia and 101 g. (1.48 moles) of pentyne-1 was added 230 g. (1.45 moles) of trimethylenechlorobromide over a period of six hours. After working up in the previously described manner (1), the product was distilled to yield 83 g. (39%) of crude *1-chloroöctyne-4*. The main fraction (25 g.) which boiled at 87° at 23 mm., n_D^{25} 1.4583 was analyzed.

Anal. Calc'd for $C_8H_{13}Cl$: C, 65.3; H, 9.0.

Found: C, 67.8; H, 9.4.

A solution of 389 g. (2.69 moles) of the crude chloride and 550 g. (3.4 moles) of sodium iodide in 2 liters of dry acetone was stirred and refluxed for 28 hours. The precipitated sodium chloride was removed, 1.5 liters of acetone were removed by distillation, and the residue was washed with water. The organic portion was dissolved in ether, dried, and distilled and 473 g. of crude 1-iodoöctyne-4 boiling from 50–70° at 0.5 mm. was collected. A mixture of 120 g. (0.5 mole) of the crude iodide and 85 g. (1.3 mole) of potassium cyanide in 500 ml. of acetone was refluxed for 4 days. Most of the acetone was removed by distillation and one mole of dilute sodium hydroxide was added. The mixture was refluxed for 48 hours after which time the evolution of ammonia ceased. The solution was acidified with hydrochloric acid and the organic portion was dissolved in ether, and dried. On distillation 35 g. (47%) of *5-nonynoic acid* was collected. The properties are listed in Table I.

6-Nonynoic acid. The procedure was similar to the one described for the preparation of the 5-nonynoic acid. To sodium acetylide (prepared from four moles of sodium) in 3 liters of liquid ammonia was added 438 g. (4.0 moles) of ethyl bromide (1). After stirring for one hour, 156 g. (4.0 moles) of solid sodium amide was added followed by 688 g. (4.0 moles) of tetramethylenechlorobromide (1). On distillation 389 g. (66% yield) of crude *1-chloroöctyne-5* boiling from 48–59° at 1.9 mm. was collected. On redistillation the portion boiling at 188° at 740 mm., n_D^{25} 1.4590 was analyzed.

Anal. Calc'd for $C_8H_{13}Cl$: C, 65.3; H, 9.0.

Found: C, 65.6; H, 9.9.

The chloride (389 g. or 2.64 moles) was coverted to the iodide, 473 g. or 69% yield, b.p. 53–69° at 0.4 mm. The main impurity was the dihalide. The crude 1-iodoöctyne-5 (300 g.) was converted to the nitrile which on hydrolysis yielded 86 g. (63%) of *6-nonynoic acid.* The properties are listed in Table I.

7-Nonynoic acid. The procedure was similar to the one described for the 5-nonynoic acid. To 62.4 g. (1.6 moles) of sodium amide in 3 liters of ammonia were added 75 g. (1.9 moles) of propyne[6] followed by 300 g. (1.6 moles) of pentamethylenechlorobromide (1). The yield was 160 g. (57%) of 1-chloroöctyne-6 which was not distilled.[7] It was converted

---

[6] Courtesy of the Air Reduction Co., Murray Hill, N. J. This gift is gratefully acknowledged.

[7] It was found, Ref. 1, that replacing Br in RBr by the propynyl group, $CH_3C{\equiv}C{-}$, the boiling point is not appreciably changed.

into 273 g. (slightly over 100% yield due to the presence of pentamethylene diiodide) of *1-iodoöctyne-6*, b.p. 65–82° at 1 mm. The fraction boiling at 76–78° at 1 mm., n_D^{25} 1.5248 was analyzed.

Anal. Calc'd for $C_8H_{13}I$: C, 40.7; H, 5.5; I, 53.8.
Found: C, 40.3; H, 5.8; I, 53.4.

All of the crude iodide was converted into the nitrile which was hydrolyzed. Distillation yielded 105 g. (57%) of *7-nonynoic acid*, b.p. 117–118°, m.p. 51–52° (from a petroleum ether-ether mixture). Analyses are listed in Table I.

8-Nonynoic acid. The procedure was similar to the one used for the preparation of the 4-nonynoic acid. From 207 g. (0.94 mole) of 1-iodoheptyne-6 (see above) were prepared 87 g. of crude *diethyl (6-heptynyl)malonate*, b.p. 139–160° at 5 mm. On redistillation 73.0 g. (30% yield), b.p. 142–143°, n_D^{25} 1.4451 was obtained which was analyzed.

Anal. Calc'd for $C_{14}H_{22}O_4$: C, 66.1; H, 8.6.
Found: C, 65.6; H, 8.6.

On hydrolysis and decarboxylation *8-nonynoic acid* was prepared in 18% yield. The properties are listed in Table I.

Preparation of amides. To about 5 g. of the nonynoic acids was added in parts phosphorus pentachloride until further addition no longer resulted in the evolution of gas. The resulting solution was poured into a mixture of ammonium hydroxide and ice. The amide thus formed was dissolved in ether, washed and crystallized from a petroleum ether-ether mixture to a constant melting point. The yields were about 85% of theory. The yields and properties are listed in Table I.

Preparation of methyl esters. A solution of about 20 g. of the acid and one gram from *p*-toluenesulfonic acid in 150 ml. of methanol was refluxed for 24 hours. The product was distilled. The yields were about 80% of theory. The physical properties are listed in Table I.

Determination of pK values and neutral equivalents. Accurately weighed samples (about 100 mg.) of the nonynoic acids were dissolved in 50 ml. of ethanol and were potentiometrically titrated with 0.01907 *N* sodium hydroxide using a Beckman Model H *p*H meter. The *p*H value of one-half neutralization was taken as the *p*K value. Individual values are listed in Table I.

SUMMARY

All of the isomeric normal nonynoic acids, amides, and methyl esters were synthesized by a series of reactions starting with acetylene. Some of their physical properties were compared.

PITTSBURGH, PENNA.

REFERENCES

(1) NEWMAN AND WOTIZ, *J. Am. Chem. Soc.*, **71**, 1292 (1949).
(2) COX, FORBES, AND WOTIZ, *J. Am. Pharm. Assoc.*, **39**, 55 (1950).
(3) ZOSS AND HENNION, *J. Am. Chem. Soc.*, **63**, 1151 (1941).
(4) GILMAN, ST. JOHN, ST. JOHN, AND LICHTENWALTER, *Rec. trav. chim.*, **55**, 577 (1936).
(5) WOTIZ *J. Am. Chem. Soc.*, **72**, 1639 (1950).
(6) WOTIZ AND CELMER, *J. Am. Chem. Soc.*, **74**, 1860 (1952).
(7) HIXON AND JONES, *J. Am. Chem. Soc.*, **49**, 1786 (1927).
(8) JOHNSON, *The Chemistry of Acetylenic Compounds, Vol. II, The Acetylenic Acids*, p. 35, Longmans, Green and Co., New York, 1950.