[CONTRIBUTION FROM DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Synthesis of Unsaturated Fatty Acids[1]

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The method for synthesis of unsaturated fatty acids recently developed in this Laboratory[3] has been used for the preparation of six additional monoethenoid acids of chain lengths varying from seven to fourteen carbon atoms, (Table III).[4] The position of the unsaturated bond was verified by oxidative degradation which in each case yielded the expected monocarboxylic acid fragment. Chromatography of these products established their homogeneity and thus provided strong evidence for the purity of the original unsaturated acids. Evidence of contamination with minor amounts of position isomers was obtained in three cases.

The general synthetic procedure followed was to condense an alkylacetylene with an iodochloride and convert the product into the olefinic acid *via* the nitrile and partial hydrogenation

$$CH_3(CH_2)_mC{\equiv}CH + I(CH_2)_nCl \longrightarrow CH_3(CH_2)_mC{\equiv}C\ (CH_2)_nCl \longrightarrow \underset{\text{I}}{CH_3(CH_2)_mCH{=}CH(CH_2)_nCOOH}$$

In the present work m has been varied from three to five and n from four to five. In two cases acetylene itself was condensed to produce ω-olefinic acids.

An attempt to prepare petroselinic acid (I, $m = 10$, $n = 4$) by the present method was unsuccessful because of the failure of tridecyne to condense with iodochlorobutane. It would appear that this step in the synthesis occurs readily only if m is less than ten. The condensation proceeded satisfactorily when n was nine,[3b] but failed when n was one or two.[5] It may be concluded that the present method of synthesis offers a convenient and practical route to monoethenoid acids of formula I, where m is less than ten and n may be varied from three to at least nine.

An attempt was also made to extend the synthesis to a diolefinic acid of the linoleic type. It was proposed to build the carbon chain by the reaction sequence

$$CH_3(CH_2)_4C{\equiv}CH \longrightarrow \text{Grignard reagent} \xrightarrow[\text{2. } H_2O]{\text{1. HCHO}}$$

$$CH_3(CH_2)_4C{\equiv}C{-}CH_2OH \xrightarrow{PBr_3}$$

$$\underset{\text{II}}{CH_3(CH_2)_4{-}C{\equiv}C{-}CH_2Br} \xrightarrow[Cu_2Cl_2]{BrMgC{\equiv}C{-}(CH_2)_5Cl} \underset{\text{III}}{CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_5Cl}$$

Condensation of 1-bromo-2-octyne[6] (II) with the sodium salt of 1-chloro-6-heptyne in liquid ammonia failed to yield the expected product. Condensation through the Grignard reagent was successful provided cuprous chloride was used as a catalyst,[7] but the diacetylenic chloride (III) was obtained in poor yields, and all efforts to convert it to the acid failed.

However, preliminary results have been obtained which indicate that the synthesis can be applied successfully to the preparation of diethenoid acids in which the unsaturated bonds are separated by several carbon atoms.[8]

Experimental

Chlorinated Acetylenic Hydrocarbons.—The 1-chloroacetylenic hydrocarbons listed in Table I were prepared by condensing 1-iodo-4-chlorobutane[3a] or 1-iodo-5-chloropentane with the sodium salts of acetylene, 1-hexyne, 1-

TABLE I

CHLORINATED ACETYLENIC HYDROCARBONS

Compound	B. p., °C.	mm.	$n^{25}D$	% yield	Chlorine, % Calcd.	Found
1-Chloro-5-hexyne	47–48	17	1.4480	80	30.41	30.33
1-Chloro-6-heptyne[a]	78–80	33	1.4490	85	27.15	25.80
1-Chloro-5-decyne[b]	78–80	2	1.4594	82	20.53	20.28
1-Chloro-5-hendecyne	90–92	1.5	[c]	61	18.99	17.61[c]
1-Chloro-6-hendecyne	77–79	1	1.4502	72	18.99	18.88
1-Chloro-5-dodecyne	98–100	1	1.4597[d]	48[e]	17.66	17.11
1-Chloro-6-dodecyne	105–106	2	[c]	94	17.66	15.87[c]
1-Chloro-6-tridecyne	112–113	2	1.4593	86	16.51	16.46

[a] Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949), found b. p. 166° (1 atm.); $n^{25}D$ 1.4507. [b] Ahmad and Strong[3] found b. p. 110–112° (15 mm.); $n^{25}D$ 1.4592. [c] Used without further purification. [d] 29.5°. [e] Low yield due to accidental loss.

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(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station.

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(3) (a) Ahmad and Strong, THIS JOURNAL **70**, 1699 (1948); (b) Ahmad, Bumpus and Strong, *ibid.*, **70**, 3391 (1948).

(4) In addition the preparation of 6-hendecenoic acid[3a] was repeated. Previous results were confirmed in every respect except that the over-all yield from 1-hexyne was raised from 8.5 to 26%.

(5) Henne and Greenlee, THIS JOURNAL, **67**, 484 (1945).

(6) Tchao, *Bull. soc. chim.*, [4] **53**, 1533 (1933).

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

(8) Clayton, Taylor and Strong, unpublished work.

TABLE II

PHYSICAL CONSTANTS AND ANALYSES OF ACETYLENIC ACIDS AND DERIVATIVES

					Analyses								Derivative			
					Carbon, %		Hydrogen, %		Neut. equiv.		H_2 absorbed				Nitrogen, %	
Acid	B. p., °C. 1 mm.	M. p.,[a] °C.	$n^{25}D$	% yield	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Type	M. p., °C.	Calcd.	Found
6-Heptynoic	93–94	.....	1.4495	63	66.64	66.71	7.99	7.61	126.2	126.0	2.00	2.02	*p*-Toluidide	84–85	6.50	6.53
7-Octynoic[b]	97–97.5	.....	1.4506	52	68.53	68.64	8.62	8.45	140.2	139.0	2.00	1.98	Anilide	59–60	6.50	6.41
6-Hendecynoic[c]	128–130	−1–+1	1.4566	60	72.48	72.22	9.95	9.70	182.3	183.3	2.00	1.98	*p*-Nitroanilide	78–79	9.26	9.35
6-Dodecynoic	112–114	< −20	1.4462	57	73.42	73.55	10.27	10.00	196.3	197.5	2.00	1.97	[d]	.....	..	..
7-Dodecynoic	142–143	18.5–19	1.4568	65	73.42	73.02	10.27	10.05	196.3	195.9	2.00	1.95	Anilide	40–41	5.16	5.18
6-Tridecynoic	149–151	7.5–8.5	1.4574	63	74.24	73.98	10.55	10.45	210.3	211.1	2.00	2.02	Anilide	41–41.5	4.91	4.90
7-Tridecynoic	152–153	22–24	1.4563	76	74.24	74.50	10.55	10.35	210.3	209.6	2.00	1.97	Anilide	51.5–52	4.91	4.88
7-Tetradecynoic	......	29.5–30	1.4571[e]	84	74.95	75.31	10.78	10.52	224.3	225.7	2.00	1.99	Anilide	47.5–48	4.67	4.39

[a] Bulb immersed. [b] Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949), b. p. 123° (2 mm.), m. p. 20°, $n^{25}D$ 1.4502. [c] Ahmad and Strong,[3a] b. p. 124–125° (0.17 mm.), $n^{25}D$ 1.4566. [d] No solid derivative obtained. [e] Measured at 32°.

TABLE III

PHYSICAL CONSTANTS AND ANALYSES OF ETHYLENIC ACIDS AND DERIVATIVES

				Analyses								Derivative			
				Carbon, %		Hydrogen, %		Neut. equiv.		H_2 absorbed				Nitrogen, %	
Acid[a]	B. p., °C. 1 mm.	n_D (°C.)	% yield	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Type	M. p., °C.	Calcd.	Found
6-Heptenoic	81–82	1.4355 (27)	81	65.57	65.30	9.43	9.34	128.2	129.3	1.00	1.02	*p*-Toluidide	57–58	6.45	6.44
7-Octenoic	90–92	1.4340 (27)	78	67.56	66.61	9.92	9.87	142.2	144.0	1.00	0.98	*p*-Toluidide	56–57	6.05	6.15
6-Hendecenoic	[b]	1.4492 (26)	53	71.67	71.52	11.01	10.84	184.3	183.1	1.00	0.99	Amide	64–66	7.64	7.44
7-Dodecenoic	[b]	1.4486 (27.5)	70	72.66	71.93	11.18	10.83	198.3	199.8	1.00	0.99	Amide	69–70	7.10	6.96
6-Tridecenoic	[b]	1.4509 (28)	62	73.52	73.54	11.39	11.28	212.3	214.0	1.00	1.04	Amide	65–67	6.63	6.40
7-Tridecenoic	[b]	1.4526 (27)	84	73.52	73.21	11.39	11.08	212.3	211.3	1.00	1.02	Amide	60–62	6.63	6.61
7-Tetradecenoic	[b]	1.4527 (27)	85	74.26	74.03	11.57	11.33	226.4	224.8	1.00	1.04	Amide	58–60	6.21	6.07

[a] 6-Dodecenoic acid was also prepared but was not obtained in pure form. [b] Purified by low-temperature recrystallization from acetone. All melt below −15°.

heptyne or 1-octyne, respectively, in liquid ammonia solution by the general procedure previously described.[3b,9] The 1-iodo-5-chloropentane was prepared in 62% yield by reaction of 1,5-dichloropentane[10] with sodium iodide in acetone solution as described for other homologs.[3a,3b] The redistilled product showed the constants: b. p. 104–105° (14 mm.), $n^{25}D$ 1.5282.

Anal. Calcd. for $C_5H_{10}ClI$; I, 54.58. Found: I, 54.15.

Acetylenic Acids.—The chloroacetylenic hydrocarbons were converted over the nitriles to the corresponding acetylenic acids as previously described,[3] and the products purified by distillation *in vacuo*, except for 7-tetradecynoic acid which was recrystallized from acetone at −60°. Physical properties and analyses of the acids and derivatives are given in Table II.

Ethylenic Acids.—The acetylenic acids were reduced over Raney nickel at low pressure as previously described.[3] Using the catalyst prepared by the method of Adkins and Billica[11] the reduction was accomplished smoothly in from four to fifteen minutes. The products were purified by low temperature recrystallization from acetone, except for 6-heptenoic and 7-octenoic acids which could not be induced to crystallize and were therefore distilled. All of the acids were colorless oily liquids when freshly prepared. 7-Dodecenoic acid turned light yellow on standing thirty days but the others remained colorless. Physical properties and analytical data are collected in Table III.

2-Octyne-1-ol.—A modification of the methods of Guest[12] and Tchao[13] was used. To an ether solution of ethylmagnesium iodide prepared from 12.2 g. (0.5 g. atom) of magnesium was added 48 g. (0.5 mole) of 1-heptyne with constant stirring during a period of two hours. After one hour additional refluxing gaseous formaldehyde generated from 45 g. of paraformaldehyde was swept by means of dry nitrogen into the reaction flask through a 14 mm. inlet tube reaching to within 1 cm. of the surface of the reaction mixture. This process required two hours. The Grignard complex was then decomposed with 100 g. of crushed ice and 100 ml. of cold 10% sulfuric acid, and the ether layer separated. The aqueous layer was extracted with ether and the combined ether solutions were washed with water and dried overnight at −5° with calcium chloride after the addition of 50 mg. of hydro-

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[9] Additional experimental details found to be helpful in securing consistently good yields are given in the Ph.D. dissertation of W. R. Taylor, University of Wisconsin, 1949.

[10] Kindly supplied by the Electrochemicals Department, E. I. du Pont de Nemours Co., Wilmington, Delaware.

[11] Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

[12] H. H. Guest, *ibid.*, **47**, 860 (1925).

[13] V. L. Tchao, *Bull. soc. chim.*, (4) **53**, 682 (1933).

quinone. The ether and unreacted 1-heptyne were removed as quickly as possible at reduced pressure, and the residue distilled through a 15 cm. Vigreux column. A yield of 35.6 g. (56.5%), b. p. 75–80° (2 mm.) was obtained. The higher boiling material in the distilling flask (30–40 g.) was found to be explosive if allowed to come in contact with air before cooling. The products from five runs were combined and redistilled to give 155 g. of colorless liquid, b. p. 76–78° (2 mm.), n^{20}_D 1.4550.

1-Bromo-2-octyne.—In a 500-ml., r. b. flask equipped with stirrer, condenser and dropping funnel, and protected by magnesium perchlorate drying tubes, was placed 63.1 g. (0.5 mole) of 2-octyne-1-ol, 10 ml. of dry pyridine, and 75 ml. of ether. The flask was cooled in an ice–salt-bath and 54.1 g. (0.2 mole) of redistilled phosphorus tribromide added with constant stirring over the course of thirty minutes. Stirring and refluxing were continued for three hours. After cooling, 100 ml. of water was slowly added, and the organic material was collected in ether. The dried (calcium chloride) solution on distillation gave 71 g. (72.8%) of the bromide, b. p. 74–78° (2 mm.). Redistillation of the crude products from three runs through a 30 cm. Vigreux column gave a purified product, b. p. 69.5–70.5° (1 mm.), n^{20}_D 1.4839, d^{20}_4 1.1666.

Anal. Calcd. for $C_8H_{13}Br$: Br, 42.26. Found: Br, 41.28.

1-Chloro-6,9-Pentadecadiyne.—Preliminary experiments indicated that the Grignard reagent from 1-chloro-6-heptyne could be condensed with 1-bromo-2-octyne provided cuprous chloride was used as the catalyst. If no catalyst was present, the reactants were recovered unchanged.

To an ether solution of ethylmagnesium bromide prepared from 2.97 g. (0.12 g. atom) of magnesium was added 15.5 g. (0.12 mole) of 1-chloro-6-heptyne with stirring over the course of one hour. Stirring and refluxing were continued for two hours longer after which time the evolution of ethane had apparently ceased. The mixture was allowed to cool and 50 mg. of cuprous chloride previously well dried at 125° was added. A solution of 23 g. (0.12 mole) of 1-bromo-2-octyne in 75 ml. of ether was then run in with stirring during one hour. Since after fourteen hours of stirring and refluxing the Michler ketone test for the presence of Grignard reagent was still positive, an additional 2.4 g. of 1-bromo-2-octyne was introduced and the reaction continued six hours longer until the test became negative.

The mixture was decomposed with ice and solid ammonium chloride, and the ether layer washed with water and dried over calcium chloride. The ether was removed, and the residue quickly distilled through a 15 cm. column. After a 40–60° forerun, the desired product distilled at 136–140° (1 mm.). There was obtained 7.1 g. (24.7%) of a clear, colorless liquid, which, however, began to turn yellow after standing ten minutes at room temperature. Since experience had shown that very extensive decomposition occurred on redistillation, no further purification was attempted.

Anal. Calcd. for $C_{15}H_{23}Cl$: Cl, 14.84; H_2 uptake, 4.00 moles. Found: Cl, 13.22; H_2 uptake, 3.82 moles.

All attempts to convert this chloride to the corresponding acid *via* the nitrile or Grignard reagent were unsuccessful. The Grignard reagent could be formed after conversion to the iodide, but reaction with carbon dioxide yielded only resinous material. Attempted formation and alkaline hydrolysis of the nitrile gave a low yield of impure acidic material from which nothing definite could be isolated.

Degradation of Ethylenic Acids.—Each of the ethylenic acids prepared (Table III) was subjected to an oxidative degradation process designed to reveal the presence of position isomers present as impurities. Details of the procedure have been presented elsewhere.[14] Briefly each unsaturated acid was cleaved at the double bond, and the lower saturated monocarboxylic acid or mixture of acids analyzed by partition chromatography. The expected degradation acid was obtained in each case, and was identified by comparing the position which it assumed in the chromatogram with that of known acids. In questionable cases mixed chromatograms were carried out. The formic acid from 6-heptenoic and 7-octenoic acids was accompanied by 7–8% of higher acids, probably propionic or above, thus indicating that these two products were not entirely homogeneous, but were contaminated by small amounts of isomeric acids in which the double bond had shifted toward the carboxyl group.

Of the remaining acids listed in Table III all gave rise to homogeneous lower acids except 7-dodecenoic acid. The acids recovered from the chromatographic column in this case consisted of 92.9% valeric and 7.1% caproic acid.

Attempted Preparation of 1-Chloro-5-heptadecyne.[15]—A number of attempts were made to condense 1-tridecyne with 1-iodo-4-chlorobutane with the object of synthesizing petroselinic acid. Reaction of the sodium and lithium salts in liquid ammonia and of the potassium salt in *t*-butyl alcohol led only to recovery of unreacted starting materials. More drastic conditions were not tried.

Summary

Seven monoethylenic straight chain fatty acids varying in chain length from seven to fourteen carbon atoms were prepared from the corresponding 1-chloroacetylenic hydrocarbons. Efforts to extend the synthesis to a doubly unsaturated acid of the linoleic type and to petroselinic acid were unsuccessful.

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[14] (a) Bumpus, Taylor and Strong, THIS JOURNAL, in press; (b) Taylor, W. R. Doctoral Dissertation, University of Wisconsin, 1949.

[15] Work carried out by K. Ahmad.