144. *Syntheses of Long-chain Acids. Part III.*[1] *A Synthesis of Acetylenic Acids.*

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Condensation of an ω-bromo-acid with excess of a lithio-alkyne in liquid ammonia–tetrahydrofuran gives the long-chain acetylenic acid in high yield. Attempts to condense ω-acetylenic acids with alkyl halides under similar conditions were unsuccessful.

The preparation of *NN*-dimethyl-amides of long-chain acetylenic acids by condensation of an ω-acetylenic dimethyl-amide with an alkyl halide (or of a ω-bromodimethyl-amide with a 1-alkyne) in the presence of sodamide in liquid ammonia has been described previously.[1,2] Hydrolysis of the acetylenic amide gives the acid, but the value of the method is limited by the drastic conditions necessary for hydrolysis.

In the hope of obtaining an amide which might hydrolyse more readily, 1-dec-9′-ynoylpyrrolidine was condensed with hexyl bromide to give 1-hexadec-9′-ynoylpyrrolidine.

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[1] Part II, Ames and Islip, *J.*, 1961, 4409.
[2] Part I, Ames and Islip, *J.*, 1961, 351.

The corresponding *NN*-dimethyl-amide was prepared similarly. Hydrolysis of the pyrrolidine derivative with potassium hydroxide in 2-methoxyethanol was even slower than that of the dimethyl-amide under similar conditions.

Treatment of ω-acetylenic acids with ethylmagnesium bromide and condensation of the resulting complex with prop-2-ynylic or allylic halides in the presence of cuprous cyanide has been described by Osbond and his collaborators,[3] but the process is apparently not effective with alkyl halides. We treated undec-10-ynoic acid with excess of sodamide in liquid ammonia but the precipitated sodio-compound failed to condense with heptyl bromide. Attempts to effect this condensation in dimethylformamide or tetrahydrofuran were also unsuccessful.

As far as we are aware, the direct condensation of alkylacetylenes with ω-halogeno-acids has not been described although condensation with ω-halogeno-esters has been reported (with rather low yields).[4] Acetylenic acids have usually been prepared indirectly from a 1-alkyne and an ω-chloroiodide followed by conversion *via* nitrile into acid (Strong's method).[5]

Condensation of ω-bromo-acids (II) with the sodio-derivatives of 1-alkynes (I) in liquid ammonia–tetrahydrofuran was therefore examined. Excess of the sodio-alkyne was used to allow for formation of the sodium salt of the bromo-acid. Yields of about 20% of acetylenic acids were obtained when three molar proportions of sodio-alkyne were used. Higher yields were obtained by using larger proportions of sodio-alkyne and by longer refluxing of the mixture (see Table). In these experiments most of the unchanged bromo-acid and some of the excess of alkyne could be recovered.

$$\underset{\text{(I)}}{CH_3\cdot[CH_2]_m\cdot C\equiv CH} + \underset{\text{(II)}}{Br\cdot[CH_2]_n\cdot CO_2H} \xrightarrow[\text{or } LiNH_3]{NaNH_2} \underset{\text{(III)}}{CH_3\cdot[CH_2]_m\cdot C\equiv C\cdot[CH_2]_n\cdot CO_2H}$$

The use of the more soluble and more reactive lithioalkynes[6] gave high yields of acetylenic acids (see Table). In view of the accessibility of many ω-bromo-acids, the process appears to offer a convenient route to long-chain acetylenic acids and thence to olefinic and saturated acids.

Synthesis of acetylenic acids.

Acid	(III) *m*	*n*	Condensing agent	Ratio (I : II)	Reflux time	Yield (%) [a]	Recovered (%) [b] (I)	(II)
Tetradec-9-ynoic ...	3	7	$NaNH_2$	3	8	28	—	53
Pentadec-9-ynoic ...	4	7	,,	3	8	19	—	55
Heptadec-12-ynoic...	3	10	,,	3	8	18	—	50
Octadec-9-ynoic......	7	7	,,	10	8	24	—	—
Octadec-12-ynoic ...	4	10	,,	3	8	18	—	37
,, ...	,,	,,	,,	5	40	41	—	26
,, ...	,,	,,	,,	10	20	70	—	—
Nonadec-12-ynoic ...	5	10	,,	10	20	53	—	—
Pentadec-9-ynoic ...	4	7	$LiNH_2$	5	8	86	—	—
Hexadec-7-ynoic ...	7	5	,,	10	8	92	54	—
Octadec-9-ynoic......	7	7	,,	3	8	25	—	—
,, ...	,,	,,	,,	10	8	68	54	20
Octadec-12-ynoic ...	4	10	,,	3	8	42	—	43
,, ...	,,	,,	,,	5	8	71	—	20
,, ...	,,	,,	,,	10	8	83	42	—

[a] Based on bromo-acid taken; no allowance was made for recovered bromo-acid. [b] Based on total amount taken.

The acetylenic acids prepared during this work were reduced to the saturated acids

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[3] Osbond, Philpott, and Wickens, *J.*, 1961, 2779; cf. Sarycheva, Myagkova, and Preobrazhenskii, *Zhur. obshchei Khim.*, 1959, **29**, 2318.

[4] Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678; Bhattacharyya, Chakravarty, and Kumar, *Chem. and Ind.*, 1959, 1352; Isabelle and Leitch, *Canad. J. Chem.*, 1958, **36**, 440.

[5] Taylor and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4263.

[6] Elsner and Paul, *J.*, 1951, 893; Lumb and Smith, *J.*, 1952, 5032.

and were also characterised by semihydrogenation by the procedure of Cram and Allinger [7] to the *cis*-olefinic acids, and subsequent hydroxylation with performic acid to give the *threo*-dihydroxy-acids.

The hexadec-7-ynoic acid prepared had m. p. 38—39°; Bodenstein [8] reported m. p. 47°. He described the preparation of this acid from hexadec-7-enoic acid obtained by fusion of octadec-9-ynoic acid (stearolic acid) with potassium hydroxide (the Varrentrapp reaction). In a systematic study of this reaction Ackman, Dytham, Wakefield, and Weedon [9] concluded that myristic acid was the major product formed and that the only C_{16}-acid (a small amount of by-product) was palmitic acid. Bodenstein's "hexadecenoic acid," m. p. 33—34°, was presumably a mixture of stearolic, myristic, and palmitic acid and the acetylenic acid derived from it appears to have been stearolic acid, m. p. 47·5—48·5°.[9]

EXPERIMENTAL

1-8′-*Bromo-octanoylpyrrolidine*.—8-Bromo-octanoic acid [1] (45 g.) was warmed with thionyl chloride (60 c.c.) at 30° for 1 hr. and at 100° for 2 hr. After thionyl chloride had been removed under reduced pressure, the acid chloride was dissolved in ether (500 c.c.). The solution was stirred and cooled while pyrrolidine (36 g.) was added dropwise. Water was added and the mixture extracted with ether. The extracts were washed with sodium carbonate solution and water, dried (Na_2SO_4), and distilled. The *amide* (48 g.) had b. p. 140—142°/0·25 mm., n_D^{20} 1·5111 (Found: C, 52·4; H, 7·8; N, 4·8. $C_{12}H_{22}BrNO$ requires C, 52·3; H, 8·0; N, 5·1%).

1-*Dec*-9′-*ynoylpyrrolidine*.—Acetylene was passed for 2 hr. through a suspension of sodamide [from sodium (4·1 g.)] in liquid ammonia (250 c.c.) and tetrahydrofuran (250 c.c.). The bromo-amide (47 g.) in tetrahydrofuran (100 c.c.) was added slowly; the mixture was refluxed for 5 hr. then left to evaporate. Addition of water and isolation with ether gave the acetylenic *amide* (23 g.), b. p. 134—140°/0·3 mm. (Found: C, 75·9; H, 10·4; N, 6·3. $C_{14}H_{23}NO$ requires C, 76·0; H, 10·5; N, 6·3%).

1-*Hexadec*-9′-*ynoylpyrrolidine*.—The acetylenic amide (23 g.) in tetrahydrofuran (120 c.c.) was added to a stirred suspension of sodamide (3·9 g.) in liquid ammonia (200 c.c.). After 1 hr., hexyl bromide (16·5 g.) in tetrahydrofuran (50 c.c.) was added; the mixture was refluxed for 5 hr. and left to evaporate. Isolated in the same manner, 1-*hexadec*-9-*ynoylpyrrolidine* (10 g.) had b. p. 181—185°/0·2 mm., n_D^{22} 1·4841 (Found: C, 78·7; H, 11·3; N, 4·8. $C_{20}H_{35}NO$ requires C, 78·6; H, 11·1; N, 4·6%).

NN-*Dimethylhexadec*-9-*ynamide*.—*NN*-Dimethyldec-9-ynamide [1] (19·5 g.) was converted into the sodio-derivative and condensed with hexyl bromide as in the previous experiment. The *amide* (12 g.) had b. p. 160—164°/0·2 mm. (Found: C, 76·8; H, 11·4; N, 5·1. $C_{18}H_{33}NO$ requires C, 77·4; H, 11·9; N, 5·0%).

Hydrolysis of Hexadec-9-*ynamides*.—The amide (5 g.) was treated with a solution of potassium hydroxide (3 g.) in water (3 c.c.) and 2-methoxyethanol (20 c.c.). The solution was refluxed under nitrogen for 10 hr. (evolution of dimethylamine had then ceased) and poured into dilute sulphuric acid, the products being isolated with ethyl acetate and fractionally distilled.

The *NN*-dimethyl-amide gave *hexadec*-9-*ynoic acid* (2·5 g.), b. p. 138—142°/0·25 mm., m. p. 39—39·5° (Found: C, 76·1; H, 11·7. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%). The acetylenic acid was reduced catalytically to palmitic acid, m. p. and mixed m. p. 61—62°. The pyrrolidine derivative gave the acetylenic acid (1·0 g.) and starting material (1·5 g.).

Acetylenic Acids.—*General preparation*. The 1-alkyne (1 mol.) was added to a stirred suspension of lithamide (1 mol.) in liquid ammonia (*ca.* 1·5 l.), and the mixture was stirred under reflux for 1 hr. After addition of ω-bromo-acid (0·2 mole) in tetrahydrofuran (750 c.c.), the mixture was refluxed for 8 hr. and then allowed to evaporate. Dilute hydrochloric acid was added and the mixture was extracted with ether. The washed and dried (Na_2SO_4) solution was evaporated under reduced pressure and the residue fractionally distilled (results shown in Table). In experiments in which alkyne was recovered, the ether was removed through a 10 in. Vigreux column.

The following acetylenic acids were thus prepared: *Tetradec*-9-*ynoic acid*, m. p. 31·5—32°,

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[7] Cram and Allinger, *J. Amer. Chem. Soc.*, 1956, **78**, 2522.

[8] Bodenstein, *Ber.*, 1894, **27**, 3400.

[9] Ackman, Dytham, Wakefield, and Weedon, *Tetrahedron*, 1960, **8**, 239; cf. Ackman, Linstead, Wakefield, and Weedon, *ibid.*, p. 221.

b. p. 135—138°/0·15 mm. (Found: C, 75·2; H, 10·5%; equiv., 223. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%; equiv., 224). *Pentadec*-9-*ynoic acid*, m. p. 32—33°, b. p. 145—149°/0·25 mm. (Found: C, 75·7; H, 11·0. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). Hexadec-7-ynoic acid, m. p. 38—39°, b. p. 160—163°/0·6 mm. (Found: C, 76·1; H, 11·4. Calc. for $C_{16}H_{28}O_2$: C, 76·1; H, 11·2%). Bodenstein[8] gave m. p. 47° for the product obtained in the manner already described. *Heptadec*-12-*ynoic acid*, m. p. 35—36°, b. p. 158—163°/0·15 mm. (Found: C, 76·2; H, 11·0. $C_{17}H_{30}O_2$ requires C, 76·6; H, 11·4%). Octadec-9-ynoic acid, m. p. 46—47°, b. p. 168—172°/0·2 mm. (Found: C, 76·8; H, 11·4. Calc. for $C_{18}H_{32}O_2$: C, 77·1; H, 11·5%). Huber[10] gives m. p. 46·4—47·6°. Octadec-12-ynoic acid, m. p. 46—47°, b. p. 166—171°/0·18 mm. (Found: C, 76·9; H, 11·4%). Huber[10] gives m. p. 46·2—47·2°. *Nonadec*-12-*ynoic acid*, m. p. 45—45·5°, b. p. 180—186°/0·7 mm. (Found: C, 77·6; H, 11·5. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·6%).

Long-chain Saturated Acids.—The following acids were obtained in almost quantitative yields by hydrogenation of the acetylenic acids in ethanol with palladised charcoal catalyst; they were recrystallised from methanol or light petroleum (b. p. 40—60°): Myristic acid, m. p. and mixed m. p. 51—52°. Pentadecanoic acid, m. p. and mixed m. p. 51—51·5°. Palmitic acid, m. p. and mixed m. p. 61—62°. Heptadecanoic acid had m. p. 60·5—61·5°, undepressed by admixture with a sample prepared by a different method.[11] Stearic acid, m. p. and mixed m. p. 69—70°. Nonadecanoic acid had m. p. 68—68·5° (Found: C, 76·1; H, 12·7. Calc. for $C_{19}H_{38}O_2$: C, 76·5; H, 12·8%). Smith and Fuzek[12] report m. p. 69·0—69·4°.

cis-*Olefinic Acids.*—The acetylenic acid (2 g.) in methanol (50 c.c.) was hydrogenated in the presence of 5% palladised barium sulphate (0·2 g.) and quinoline (0·2 g.) until the rate of absorption fell sharply after 1 mol. of hydrogen had been absorbed (cf. Cram and Allinger[7]). Distillation of the filtered solution gave the olefinic acid.

The following acids were isolated (others were converted directly into the saturated dihydroxy-acids): *cis*-Tetradec-9-enoic acid, b. p. 126—130°/0·25 mm., n_D^{20} 1·4562 (Found: C, 73·9; H, 11·3. Calc. for $C_{14}H_{26}O_2$: C, 74·3; H, 11·6%). Boughton, Bowman, and Ames[13] give b. p. 144°/0·6 mm., n_D^{20} 1·4563. cis-*Pentadec*-9-*enoic acid*, b. p. 142—144°/0·25 mm., n_D^{20} 1·4557 (Found: C, 75·2; H, 11·9. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%). cis-*Hexadec*-7-*enoic acid*, b. p. 165—167°/0·9 mm., n_D^{20} 1·4608 (Found: C, 75·7; H, 12·2. $C_{16}H_{30}O_2$ requires C, 75·5; H, 11·9%). This acid has been shown to be present in herring oil[14] but was not isolated.

threo-*Dihydroxy-acids.*—The olefinic acid (2 g.) was warmed at 40° for 2 hr. with formic acid (6·0 c.c.) and 30% hydrogen peroxide (1·0 c.c.). After addition of excess of 3N-sodium hydroxide, the solution was refluxed for 1 hr. and poured into dilute hydrochloric acid containing ice. The products were filtered off and recrystallised.

threo-9,10-Dihydroxytetradecanoic acid had m. p. 78·5—80° (from methanol) (Found: C, 64·8; H, 10·8. Calc. for $C_{14}H_{28}O_4$: C, 64·6; H, 10·8%). Boughton, Bowman, and Ames[13] give m. p. 80°. threo-9,10-*Dihydroxypentadecanoic acid* had m. p. 82—82·5° (from aqueous ethanol) (Found: C, 65·4; H, 10·8. $C_{15}H_{30}O_4$ requires C, 65·7; H, 11·0%). threo-7,8-*Dihydroxyhexadecanoic acid* had m. p. 86—87° (from aqueous ethanol) (Found: C, 66·2; H, 10·9. $C_{16}H_{32}O_4$ requires C, 66·6; H, 11·2%). threo-12,13-*Dihydroxyheptadecanoic acid* had m. p. 89—90° (from aqueous ethanol) (Found: C, 67·2; H, 11·1. $C_{17}H_{34}O_4$ requires C, 67·5; H, 11·3%). *threo*-9,10-Dihydroxyoctadecanoic acid had m. p. 92·5—93·5° undepressed by admixture with a sample obtained from oleic acid. *threo*-12,13-Dihydroxyoctadecanoic acid had m. p. 95·5—96° (from ethanol) (Found: C, 68·3; H, 11·4. Calc. for $C_{18}H_{36}O_4$: C, 68·3; H, 11·5%). Huber[10] gives m. p. 97°. threo-12,13-*Dihydroxynonadecanoic acid* formed plates, m. p. 95·5—96° (from methanol) (Found: C, 69·4; H, 11·7. $C_{19}H_{38}O_4$ requires C, 69·0; H, 11·6%).

We are indebted to Dr. J. F. McGhie for helpful discussions.

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[*Received, June 8th*, 1962.]

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[10] Huber, *J. Amer. Chem. Soc.*, 1953, **71**, 2730.

[11] Ames and Bowman, *J.*, 1951, 1079.

[12] Smith and Fuzek, *J. Amer. Chem. Soc.*, 1946, **68**, 229.

[13] Boughton, Bowman, and Ames, *J.*, 1952, 671.

[14] Klenk and Steinbach, *Z. physiol. Chem.*, 1959, **316**, 31.