## **868.** Syntheses of Long-chain Acids. Part II.<sup>1</sup> A Synthesis of Linoleic Acid.

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Condensation of NN-dimethyldec-9-ynamide with *trans*-oct-2-enyl bromide in the presence of sodamide and liquid ammonia gave *trans*-NN-dimethyloctadec-12-en-9-ynamide. Treatment of this olefin with perbenzoic acid, followed by hydrolysis, yielded *erythro*-12,13-dihydroxyoctadec-9-ynoic acid which was semihydrogenated and brominated. The resulting oil, containing two isomers of *threo*-9,10-dibromo-*erythro*-12,13-dihydroxyoctadecanoic acid, was converted into the known *threo-threo*-9,10,12,13-tetrabromoctadecanoic acid and thence into linoleic acid.

IN Part I<sup>1</sup> we described the preparation of acetylenic acids by condensation of an alkyl halide with a sodioalkylacetylene, the NN-dimethylamide being used as protected carboxyl group in either reactant during the condensation. This procedure has now been extended to the synthesis of long-chain enynoic dimethylamides by the use of an unsaturated alkyl halide.

The readily accessible NN-dimethylundec-10-ynamide (I; n = 8) was first condensed with *trans*-oct-2-enyl bromide in the presence of sodamide and liquid ammonia, *trans*-NNdimethylnonadec-13-en-10-ynamide (II; n = 8) being obtained in 20% yield. Hydroxylation, by treatment with perbenzoic acid and then formic acid, followed by alkaline hydrolysis gave *erythro*-13,14-dihydroxynonadec-10-ynoic acid (III; n = 8).



To apply this procedure to the synthesis of linoleic acid, NN-dimethyldec-9-ynamide (I; n = 7) was prepared from 8-bromo-NN-dimethyloctanamide and sodioacetylene.

<sup>1</sup> Ames and Islip, J., 1961, 351, is regarded as Part I.

The sodio-derivative of the acetylenic amide with trans-oct-2-enyl bromide gave trans-NN-dimethyloctadec-12-en-9-ynamide (II; n = 7) in 50% yield. Attempts to hydrolyse this to the corresponding acid were unsuccessful owing to the formation of mixtures containing mainly conjugated acids. However, when the olefinic bond in amide (II; n = 7) was "protected" by hydroxylation, with perbenzoic acid followed by formic acid, the amide group could be hydrolysed with alkali to afford erythro-12,13-dihydroxyoctadec-9-ynoic acid (III; n = 7). Complete hydrogenation of the latter gave erythro-12,13-dihydroxyoctadecanoic acid.<sup>2</sup>

The acetylenic acid (III; n = 7) was semihydrogenated by the method of Cram and Allinger<sup>3</sup> to erythro-cis-12,13-dihydroxyoctadec-9-enoic acid (IV). Addition of bromine gave an oil, presumably containing the two possible isomers of three-9,10-dibromo-erythro-12,13-dihydroxyoctadecanoic acid (V). This oil was converted into 9,10,12,13-tetrabromoctadecanoic acids (VI) by reaction with hydrogen bromide in acetic-sulphuric acids. Only the isomer, m. p. 114°, which is obtained by addition of bromine to linoleic acid, could be isolated. The expected isomeric acid was presumably present in the oily fraction but could not be obtained crystalline.

Debromination of the ethyl ester of the crystalline tetrabromo-acid gave ethyl linoleate and thence, by alkaline hydrolysis, linoleic acid. The product contained less than 1%of conjugated dienes (as shown by the low intensity of ultraviolet absorption at ca. 238

$$\begin{split} \mathsf{CH}_3\cdot[\mathsf{CH}_2]_4\cdot\mathsf{CH}(\mathsf{OH})\cdot\mathsf{CH}(\mathsf{OH})\cdot\mathsf{CH}_2\cdot\mathsf{CH}=\mathsf{CH}\cdot([\mathsf{CH}_2]_7\cdot\mathsf{CO}_2\mathsf{H}\quad(\mathsf{IV})\\ erythro-&cis-\\ \mathsf{CH}_3\cdot[\mathsf{CH}_2]_4\cdot\mathsf{CH}(\mathsf{OH})\cdot\mathsf{CH}(\mathsf{OH})\cdot\mathsf{CH}_2\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{[CH}_2]_7\cdot\mathsf{CO}_2\mathsf{H}\quad(\mathsf{V})\\ erythro-&threo-\\ \mathsf{CH}_3\cdot[\mathsf{CH}_2]_4\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{CH}_2\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{CH}\mathsf{Br}\cdot\mathsf{[CH}_2]_7\cdot\mathsf{CO}_2\mathsf{H}\quad(\mathsf{VI})\\ threo-&threo-\\ \end{split}$$

mµ). The intermediate ethyl linoleate contained approximately 2–3% of trans-isomers (estimates based on the intensity of band at 969 cm.<sup>-1</sup>). Small amounts of trans-isomers were presumably also present in the linoleic acid but could not be detected as a broad band at 934 cm.<sup>-1</sup> masked the band at 969 cm.<sup>-1</sup>.

Several syntheses of *cis-cis-*linoleic acid have been described  $^4$  but none gives the *cis-trans*-isomers. The conversion of the envnamide (II; n = 7) into these isomers is therefore being examined.

## EXPERIMENTAL

Ultraviolet spectra were measured on a Unicam S.P. 700 recording spectrophotometer.

trans-NN-Dimethylnonadec-13-en-10-ynamide.-Sodamide (3.9 g.) was stirred with liquid ammonia (ca. 300 c.c.) and NN-dimethylundec-10-ynamide 1 (21 g.) in ether (50 c.c.) was added during 5 min. Oct-2-enyl bromide 5 (19 g.) was added and the mixture was refluxed for 5 hr. and then allowed to evaporate. After addition of dilute hydrochloric acid, the product was isolated with ethyl acetate; repeated fractional distillation gave the enynamide (6.5 g.), b. p. 187—190°/0·4 mm.,  $n_{\rm p}^{20}$  1·4819 (Found: C, 78·3; H, 12·0; N, 4·4. C<sub>21</sub>H<sub>37</sub>NO requires C, 78·9; H, 11·7; N, 4·4%),  $\nu_{\rm max}$ . 1646 ((CO·NMe<sub>2</sub>) and 971 cm<sup>-1</sup> (trans-CH=CH=). There was no band at about 995 cm<sup>-1</sup> (-CH=CH<sub>2</sub>), showing the absence of the alternative product from coupling at the 3-position of the allylic halide.

erythro-13,14-Dihydroxynonadec-10-ynoic Acid.-The enynamide (5.8 g.) was treated with 98% formic acid (20 c.c.) and 30% hydrogen peroxide (5 c.c.) at 40°. The mixture was cooled

<sup>2</sup> Huber, J. Amer. Chem. Soc., 1951, 73, 2730.
 <sup>3</sup> Cram and Allinger, J. Amer. Chem. Soc., 1956, 78, 2522.

<sup>4</sup> Inter al., Raphael and Sondheimer, J., 1950, 2100; Walborsky, Davis, and Howton, J. Amer. Chem. Soc., 1951, 73, 2590; Gensler and Thomas, *ibid.*, p. 4601; Osbond, Philpott, and Wickens, J., 1961, 2779.
 <sup>5</sup> Naves, Helv. Chim. Acta, 1943, 26, 1998.

to moderate the exothermic reaction and then warmed at 40° for 20 hr., more formic acid (10 c.c.) and hydrogen peroxide (2.5 c.c.) being added after 2 hr. The gum obtained by evaporation *in vacuo* was refluxed for 4 hr. with ethanol (100 c.c.) and 5N-sodium hydroxide (100 c.c.). Acidification, followed by isolation with ethyl acetate, gave the *dihydroxy-acid*, plates, m. p. 99—100° (from ethyl acetate) (Found: C, 69.6; H, 10.0.  $C_{19}H_{34}O_4$  requires C, 69.9; H, 10.5%).

8-Bromo-octanoic Acid.—6-Bromohexan-1-ol <sup>6</sup> (181 g., 1 mol.) was added to sodiomalonic ester (1·2 mol.) in ethanol (500 c.c.) and the mixture was refluxed for 6 hr. After removal of most of the solvent by distillation, dilute sulphuric acid was added and the product isolated in benzene. The solvent-free oil was slowly distilled with acetic acid (200 c.c.) and 48% hydrobromic acid (200 c.c.) for 4 hr.; 20N-sulphuric acid (20 c.c.) was added and the mixture was refluxed until decarboxylation was complete. 48% Hydrobromic acid (250 c.c.) and concentrated sulphuric acid (75 c.c.) were added and the mixture was heated at 110° (internal) for a further 7 hr. After addition of water (1250 c.c.) and repeated extraction with carbon tetrachloride, the combined organic layers were washed with 2N-sodium acetate and water, dried (Na<sub>2</sub>SO<sub>4</sub>), and distilled. The bromo-acid (151 g., 68%), b. p. 149—153°/1·5 mm., had m. p. 34—36°. Chuit and Hausser <sup>7</sup> gave m. p. 38·5—39°.

8-Bromo-NN-dimethyloctanamide.—The bromo-acid (151 g.) was warmed with thionyl chloride (180 c.c.) at 30° for 1 hr. and then at 100° for 2 hr. After removal of excess of thionyl chloride, dimethylamine was passed into an ice-cooled, stirred solution of the acid chloride in ether (200 c.c.) until the exothermic reaction ceased. The mixture was washed with water, 2N-sulphuric acid, 2N-sodium carbonate, and water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The amide was a yellow oil (142 g.), b. p. 133—136°/0.8 mm.,  $n_{\rm D}^{20}$  1.4920 (Found: C, 48.0; H, 8.1; N, 5.2.  $C_{10}H_{20}$ BrNO requires C, 48.0; H, 8.0; N, 5.6%).

NN-Dimethyldec-9-ynamide.—Acetylene was passed into a stirred suspension of sodamide (25 g.) in liquid ammonia (700 c.c.) and tetrahydrofuran (700 c.c.) for 1.5 hr. The bromo-amide (122 g.) in tetrahydrofuran (250 c.c.) was added and the mixture was refluxed for 5 hr. and then allowed to evaporate. Addition of water and isolation with ether yielded the acetylenic *amide* which was distilled through a short Fenske column. This product (79 g.) had b. p. 103—105°/0·15 mm. and solidified as large prisms, f. p. 25° (thermometer in liquid) (Found: C, 74·1; H, 11·2; N, 7·0.  $C_{12}H_{21}NO$  requires C, 73·8; H, 10·8; N, 7·2%).

trans-NN-Dimethyloctadec-12-en-9-ynamide.—NN-Dimethyldec-9-ynamide (25·4 g.) in dry tetrahydrofuran (150 c.c.) was added to a stirred suspension of sodamide (5·1 g.) in liquid anmonia (250 c.c.). After 1 hr., oct-2-enyl bromide (32·9 g.) in tetrahydrofuran (50 c.c.) was added and the mixture was stirred under reflux for 5 hr. When the ammonia had evaporated, the product was isolated in the usual manner. The *enynamide* (20 g.) distilled as a pale yellow oil, b. p. 175—177°/0·15 mm.,  $n_{\rm D}^{20}$  1·4812 (Found: C, 78·2; H, 11·6; N, 4·3. C<sub>20</sub>H<sub>35</sub>NO requires C, 78·6; H, 11·5; N, 4·6%).

erythro-12,13-Dihydroxyoctadec-9-ynoic Acid.—The enynamide (50.5 g.) in chloroform (190 c.c.) was treated with 380 c.c. of 0.52M-perbenzoic acid in chloroform at 0°. After 18 hr., 1 mol. of per-acid had been consumed; the solution was washed with 2N-sodium carbonate and water and evaporated. After the addition of 98% formic acid (100 c.c.) the solution was refluxed for 1 hr. and then evaporated *in vacuo*. The residual oil was refluxed with potassium hydroxide (60 g.) in water (60 c.c.) and 2-methoxyethanol (600 c.c.) under nitrogen for 14 hr. Water (100 c.c.) was added and solvent (350 c.c.) was removed by distillation. The hot solution was acidified with acetic acid and then poured into ice-dilute sulphuric acid. erythro-12,13-Dihydroxyoctadec-9-ynoic acid (20 g.), prisms, m. p. 93·5—94·5°, was obtained by filtration and recrystallisation from methanol (Found: C, 69·0; H, 10·7. C<sub>18</sub>H<sub>32</sub>O<sub>4</sub> requires C, 69·2; H, 10·3%).

erythro-12,13-Dihydroxyoctadecanoic Acid.—The acetylenic acid (250 mg.) in ethanol (50 c.c.) was hydrogenated over 5% palladised charcoal (100 mg.). Filtration and evaporation gave the dihydroxy-acid, prisms (from methanol), m. p. 117—118° (Found: C, 68.5; H, 11.3. Calc. for  $C_{18}H_{36}O_4$ : C, 68.3; H, 11.5%). Huber <sup>2</sup> gives m. p. 119—120°

erythro-cis-12,13-Dihydroxyoctadec-9-enoic Acid.—erythro-12,13-Dihydroxyoctadec-9-ynoic acid (4.0 g.) in methanol (80 c.c.) was hydrogenated over 5% palladised barium sulphate (0.2 g.) in the presence of quinoline (0.2 g.).<sup>3</sup> The rate of absorption fell sharply when about 0.98 mol. of hydrogen had been taken up; hydrogenation was then interrupted and the filtered

<sup>&</sup>lt;sup>6</sup> Degering and Boatright, J. Amer. Chem. Soc., 1950, 72, 5137.

<sup>&</sup>lt;sup>†</sup> Chuit and Hausser, Helv. Chim. Acta, 1929, 12, 466.

solution was evaporated. Recrystallisation from methanol gave erythro-cis-12,13-dihydroxyoctadec-9-enoic acid (3·1 g.), prisms, m. p. 76-77.5° (Found: C, 69·1; H, 11·0. C<sub>18</sub>H<sub>34</sub>O<sub>4</sub> requires C, 68.8; H, 10.9%). This compound was mentioned by Reinger <sup>8</sup> who did not report the m. p. Barucha and Gunstone 9 described an optically active form, m. p. 87-88°.

threo-threo-9,10,12,13-Tetrabromoctadecanoic Acid.-Bromine in chloroform (358 c.c. of 0.406 n-solution) was added dropwise to the olefinic acid (22.8 g.) in chloroform (700 c.c.) at  $20^{\circ}$ . The solution was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated but the dibromodihydroxy-acid did not crystallise. It was dissolved in hydrogen bromide in acetic acid (344 c.c.; d 1.3) and concentrated sulphuric acid (86 c.c.). Next day the solution was warmed to 100° during 1 hr. and kept at 100° for 7 hr., more hydrogen bromide-acetic acid (86 c.c.) being added after 3 hr. The cooled solution was poured into water  $(2 \ l.)$  and extracted with 1:1ether-light petroleum (b. p.  $40-60^{\circ}$ ). Evaporation of the washed and dried extracts gave oil containing some solid, which was recrystallised from ethylene dichloride. The tetrabromoacid (8.5 g.) had m. p.  $114-115^{\circ}$ , undepressed on admixture with a sample prepared from natural linoleic acid.10

Ethyl Linoleate.-The tetrabromo-acid (10 g.) was esterified azeotropically with benzene (400 c.c.), ethanol (200 c.c.), and concentrated sulphuric acid (1 c.c.). The ester (9 g.), isolated in the usual manner, had m. p. 58-59°. Palmer and Wright <sup>11</sup> give m. p. 58-58.5°.

Zinc dust (15 g.) was heated with ethanol (150 c.c.) to the b. p. and 48% hydrobromic acid (0.1 c.c.) was added. After the mixture had been refluxed under nitrogen for 5 min., the bromo-ester (9.0 g.) in ethanol (50 c.c.) was added slowly and the mixture was refluxed for  $\mathbf{1}$ hr. The zinc was collected and washed with light petroleum; after the combined filtrates had been poured into dilute sulphuric acid, the separated organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and distilled under nitrogen. Ethyl linoleate (3.6 g.) thus obtained had b. p. 156°/0·5 mm., n<sub>D</sub><sup>22</sup> 1·4581 [Found: C, 78·2; H, 11·7%; I val. (Wijs 30 min.), 162·2. Calc. for  $C_{20}H_{36}O_2$ : C, 77.9; H, 11.8%]. It showed  $\lambda_{max}$ , 235 ( $\epsilon$  48) and 278 m $\mu$  ( $\epsilon$  11) and a weak band at 969 cm.<sup>-1</sup> corresponding to 2-3% of *trans*-isomers.

Linoleic Acid.—The ester (3.6 g.) was dissolved in 5% ethanolic sodium hydroxide (50 c.c.) under argon and left overnight at room temperature. After addition of warm water (100 c.c.), the solution was washed with ether, and the aqueous layer was acidified with dilute sulphuric acid. Isolated with ether, the linoleic acid was distilled under argon; it  $(2\cdot3 \text{ g})$  had b. p.  $177^{\circ}/0.5 \text{ mm.}, n_{p}^{23} 1.4672, \text{ m. p.} -6^{\circ} \text{ to } -6.5^{\circ} \text{ (capillary) [Found: C, 77.4; H, 11.5%; I val.$ (Wijs, 30 min.), 179.4. Calc. for C<sub>18</sub>H<sub>32</sub>O<sub>2</sub>: C, 77.1; H, 11.5%]. It showed λ<sub>max</sub>, 238 (ε 15.0) and 270 m $\mu$  ( $\epsilon$  18.2). The infrared spectra of both acid and ester were superimposable on those of specimens obtained from natural sources.

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