74. *Fatty Acids. Part X.* The Synthesis of the* cis-*Isomers of Tetradec-*8-*enoic, Hexadec-*10-*enoic, Octadec-*12-*enoic, and Eicos-*14-*enoic Acid.*

By C. D. BAKER and F. D. GUNSTONE.

The above-named acids have been synthesised by way of their acetylenic analogues.

THAT animals require certain unsaturated fatty acids for normal health is accepted though not fully understood. It is further known that linoleic acid is one such dietary requirement and that this can be metabolised to arachidonic (eicosa-5,8,11,14-tetraenoic) acid. The metabolic interconversions of unsaturated fatty acids have been reviewed by Mead [1] who concludes: " In short, the animal body appears to possess the capability of further desaturating any unsaturated fatty acid presented to it, and, moreover, to synthesise many of the monounsaturated acids which can be used as starting materials. It is possible that linoleic and linolenic acids are not synthesised largely because the starting monoenoic acids are not available. In this connection, the transformation of 12-octadecenoic acid should be investigated despite its reported failure [2] as an essential fatty acid."

A number of monoethenoid acids having unsaturation between the sixth and the seventh carbon atom from the methyl group, some of which may be capable of bioconversion into linoleic acid, have accordingly been synthesised. These are to be examined elsewhere for activity as essential fatty acids. After this work was complete a paper was communicated to the Sixth Congress of the International Society for Fat Research [3] in which it was stated that unsaturated fatty acids show biological activity when they have double bonds at the 6 *and* 9 position (counted from the terminal CH_3 group) and that acids with a double bond at only one of these positions are inactive. Recently, however, it has been reported that laying hens are able to produce linoleic acid from oct-2-enoic acid.[4]

Hept-1-yne was converted by standard chain-extension procedures into tetradec-8-ynoic acid (Ia), semihydrogenation of which gave the *cis*-olefinic acid (IIa). Anodic synthesis of the C_{14} acetylenic acid with the acid ester of the appropriate dibasic acid gave the C_{16} (Ib), C_{18} (Ic), and C_{20} (Id) acetylenic acids and each of these was reduced to its olefinic analogue. Some difficulty was encountered in separating the methyl C_{16} acetylenic ester from the C_{14} ester and, though this was partly overcome with the benzyl esters, the C_{16} acetylenic acid was prepared more conveniently from the hept-1-yne and 1,8-dibromo-octane.

$$CH_3\cdot[CH_2]_4\cdot C\vdots CH \longrightarrow CH_3\cdot[CH_2]_4\cdot C\vdots C\cdot[CH_2]_n\cdot CO_2H \text{ (I) a, b, c, d: } n = 6, 8, 10, 12, \text{ respectively}$$

$$\longrightarrow CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot[CH_2]_n\cdot CO_2H \text{ (II) a, b, c, d: } n = 6, 8, 10, 12, \text{ respectively}$$

EXPERIMENTAL

Light petroleum is the fraction of boiling range 40—60°. Gas–liquid chromatography was carried out with a Pye argon chromatograph incorporating Apiezon L columns (5, 10, or 20%), and relative retention times are reported as " carbon numbers." [5]

Tetradec-8-ynoic Acid (Ia).—Hept-1-yne [6] (9·6 g.) was added during 30 min. to a stirred suspension of sodamide and liquid ammonia (250 ml.) prepared from sodium (2·53 g.) by the ferric nitrate process.[7] After a further 3 hours' stirring, 1-chloro-6-iodohexane [8] (25·9 g.) was

---

* Part IX, *J.*, 1962, 3063.

[1] Mead, " Lipide Metabolism," ed. Bloch, J. Wiley and Sons, Inc., New York, 1960, p. 66.

[2] Turpeinen, *J. Nutrit.*, 1938, **15**, 351.

[3] van Dorp, Pabon, and van der Steen, Paper communicated to the Sixth Congress of the International Society of Fat Research, London, 1962.

[4] Reiser, Murty, and Rakoff, *J. Lipid Res.*, 1962, **3**, 56.

[5] Woodford and van Gent, *J. Lipid Res.*, 1960, **1**, 188.

[6] Campbell and Campbell, *Org. Synth.*, 1950, **30**, 15.

[7] Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120.

[8] Raphael and Sondheimer, *J.*, 1950, 2100.

added during 30 min. and stirring was continued overnight. After addition of ammonium chloride (10 g.) the ammonia was allowed to evaporate at room temperature; ether was then added and the ether extract was washed successively with water, dilute sulphuric acid, aqueous sodium hydrogen carbonate solution, and water. The crude 1-chlorotridec-7-yne (21·7 g.), still containing about 15% of unchanged iodochloride, was suitable for the next stage.

The C_{13} chloride (21·7 g.), sodium iodide (17·3 g.), sodium cyanide (17·3 g.), and 80% aqueous ethanol (170 ml.) were refluxed for 48 hr. and for a similar period after further addition of potassium hydroxide (58 g.) in water (144 ml.). Neutral material was removed by extraction with light petroleum, and the remaining alkaline solution was acidified with dilute sulphuric acid and extracted, first, with light petroleum to remove the monobasic acid and afterwards with ether to recover suberic acid. The *tetradecynoic acid* (80—85% based on heptyne), after vacuum-distillation, was chromatographically pure apart from a trace of the iso-acid. This arose from a little isopentyl bromide in the n-pentyl bromide used to prepare heptyne. The acetylenic acid had m. p. 22—22·5°, n_D^{25} 1·4604, "carbon number" 14·0 (Found: C, 75·2; H, 10·7%; equiv., 224. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%; equiv., 224). Oxidative degradation by the von Rudloff procedure [9] gave only hexanoic and suberic acid; catalytic hydrogenation gave myristic acid (m. p. 53—55°) after absorption of 2·0 mol. of hydrogen.

Hexadec-10-*ynoic Acid* (Ib).—This was prepared in a similar manner by treating hept-1-yne with 1,8-dibromo-octane, to give 1-bromopentadec-9-yne (30%, about 95% pure, b. p. 140°/0·5 mm., n_D^{22} 1·4759) which was then converted into *hexadecynoic acid*. The crude acid (93%) was purified by distillation at 10^{-4} mm. and by crystallisation from methanol and aqueous methanol; the pure acid (72%) had m. p. 35—36°, "carbon-number" 16·0 (Found: C, 75·8; H, 10·9. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%).

Hexadec-10-*ynoic Acid* (Ib), *Octadec*-12-*ynoic Acid* (Ic), *and Eicos*-14-*ynoic Acid* (Id), *by Anodic Synthesis*.—The apparatus consisted of a cylindrical glass cell (5 × 24 cm. or 3·5 × 15 cm.) containing two parallel platinum-foil electrodes (2·5 × 3 cm.) kept 2 mm. apart by glass spacers. The cell was cooled externally in ice–water, and the temperature of the electrolysing solution, measured near the plates, was not allowed to exceed 50°. Stirring was not necessary because of the vigorous evolution of carbon dioxide. Electrical power was supplied by a 120 v D.C. source. The solvent was methanol containing sufficient sodium to neutralise about 2% of the acids. Electrolysis was continued until the electrolyte became slightly alkaline (pH 7—8). During electrolysis the direction of the current was reversed periodically; this helped to remove the insoluble product which was usually formed on the electrodes, but it was still necessary to reduce the current in the later stages of electrolysis to keep the temperature down to 50°. After electrolysis any insoluble product was removed, water was added, and the product extracted with ether. Neutral material, freed from acidic contaminants, was distilled under reduced pressure. The distillate was examined by gas–liquid chromatography, and fractions containing the desired ester were combined and hydrolysed with 2N-potassium hydroxide in 1 : 4 v/v aqueous methanol. The monobasic acid was extracted with light petroleum and purified by distillation and/or crystallisation.

Hexadec-10-ynoic acid was prepared by coupling the C_{14} acetylenic acid with methyl hydrogen succinate [10] and, more satisfactorily, with benzyl hydrogen succinate [11] (3 mol.). With the methyl ester several distilled fractions containing both C_{16} and C_{14} esters were obtained, but none contained more than 85% of the C_{16} ester. The benzyl ester furnished fractions from which the C_{16} acetylenic acid could be isolated (21%), but this still contained about 2% of C_{14} acid.

The C_{14} acetylenic acid was electrolysed with methyl hydrogen adipate [12] in methanol. The neutral product boiling above 130°/0·25 mm. was hydrolysed and octadec-12-ynoic acid isolated by extraction with light petroleum in 28% yield, with m. p. 46—47° (lit.,[13] 46·2—47·2°) after crystallisation from ethanol ("carbon number" 18·0) (Found: C, 77·1; H, 11·6. Calc. for $C_{18}H_{32}O_2$: C, 77·1; H, 11·5%).

With methyl hydrogen suberate [12] the C_{14} acid gave a neutral product from which, after hydrolysis, *eicos*-14-*ynoic acid* was isolated. The crude acid (36%) when crystallised from

---

[9] Lemieux and von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701.

[10] Bone, Sudborough, and Sprankling, *J.*, 1904, **85**, 539.

[11] Linstead, Weedon, and Wladislaw, *J.*, 1955, 1097.

[12] Swann, Oehler, and Buswell, *Org. Synth.*, Coll. Vol. II, p. 276.

[13] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.

ethanol melted at 54·5—55·5° and had " carbon number " 20·0 (Found: C, 78·8; H, 11·9. $C_{20}H_{36}O_2$ requires C, 77·9; H, 11·8%).

Semihydrogenation of Acetylenic Acids.—Semihydrogenation of the acetylenic acids was effected at room temperature and atmospheric pressure with Lindlar's catalyst and ethyl acetate containing a little quinoline as solvent.[14] After purification the content of *trans*-isomer was determined by infrared spectrophotometry [15] and the position of the unsaturated centre was confirmed by oxidative fission.[9]

Semihydrogenation (1·04 mol. of hydrogen) of the tetradecynoic acid gave, after distillation at 2·5 × 10^{-4} mm., *tetradec-8-enoic acid* as a colourless liquid, n_D^{17} 1·4569, containing 1·5% of *trans*-isomer (Found: C, 74·4; H, 11·5. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·6%). The product was chromatographically pure (" carbon number " 13·8) and gave only hexanoic and suberic acid when oxidised.

After absorption of 1·04 mol. of hydrogen and purification with charcoal and by distillation the C_{16} acetylenic acid furnished *hexadec-10-enoic acid*, m. p. 15—16°, n_D^{20} 1·4593, containing $\not>$0·5% of *trans*-isomer, " carbon number " 15·8 (Found: C, 75·9; H, 11·9. $C_{16}H_{30}O_2$ requires C, 75·5; H, 11·9%). Gas–liquid chromatography showed the product to be free from acetylenic and saturated acids and oxidation gave only hexanoic and sebacic acid.

Octadec-12-enoic acid was obtained and purified as described for the C_{16} acid (hydrogen absorbed, 1·05 mol.); m. p. 26·5—27·5° (lit.,[13] 26·8—27·6°); $\not>$1·7% of *trans*-isomer; " carbon number " 17·8 (Found: C, 76·4; H, 12·1. Calc. for $C_{18}H_{34}O_2$: C, 76·5; H, 12·1%). Gas–liquid chromatography showed the product to be free from acetylenic and saturated acids and oxidation gave only hexanoic and dodecanedioic acid.

Semihydrogenation of the C_{20} acetylenic acid and purification of the product as described gave a C_{20} acid containing 7·5% of *trans*-isomer. This was readily separated by crystallisation from ethanol to give *eicos-14-enoic acid*, m. p. 42·5°; *trans*-content nil; " carbon number " 19·8 (Found: C, 77·5; H, 12·3. $C_{20}H_{38}O_2$ requires C, 77·4; H, 12·3%). Gas–liquid chromatography showed the absence of both saturated and acetylenic acids and oxidation gave only hexanoic and tetradecanedioic acid.

We thank the D.S.I.R. for a maintenance allowance (to C. D. B.) and Mr. Z. M. Zochowski for assistance with the infrared measurements.

THE UNIVERSITY, ST. ANDREWS. [*Received, August* 10*th*, 1962.]

---

[14] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.

[15] O'Connor, *J. Amer. Oil Chemists' Soc.*, 1959, **36**, 627.