798. *Synthetic Long-chain Aliphatic Compounds. Part X.** *21-Methoxyheneicosanoic Acid*† *and Some Related Compounds.*

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The compounds mentioned in the title have been prepared by standard methods.

Since the earlier report (Part V; *J.*, 1951, 2748 ‡) of our experiments on methods of ascending the homologous series of saturated fatty acids, we have concentrated our efforts on the preparation of suitable starting materials. Since there appears little likelihood of our completing the work for a considerable time, we report progress to date.

Our preliminary objective was the preparation of 21-methoxyheneicosanoic acid which could be converted into the corresponding bromo-acid. Interaction of very pure methyl 11-bromoundecanoate (I) and sodium methoxide in methanolic solution followed by fractionation furnished methyl 11-methoxyundecanoate (II) in good yield and thence the acid by hydrolysis. The ester (II) was reduced by the Blaise–Bouveault method to 11-methoxyundecanol, converted by phosphorus tribromide into (III). Cason's modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2078) of the Gilman–Nelson ketone synthesis (*Rec. Trav. chim.*, 1946, **55**, 518), as indicated in the scheme, furnished the keto-acid (IV) but in poor yield; a small quantity of 1 : 22-dimethoxydocosane was also isolated, having arisen, presumably, during the preparation of the Grignard reagent. The keto-acid (IV) was readily obtained pure by crystallisation of its potassium salt and was reduced by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to the saturated acid (V).

$$\underset{\text{(I)}}{\mathrm{Br{\cdot}[CH_2]_{10}{\cdot}CO_2Me}} \longrightarrow \underset{\text{(II)}}{\mathrm{MeO{\cdot}[CH_2]_{10}{\cdot}CO_2Me}} \xrightarrow[\text{(2) PBr}_3]{\text{(1) Redn.;}} \underset{\text{(III)}}{\mathrm{MeO{\cdot}[CH_2]_{11}{\cdot}Br}}$$

$$\xrightarrow[\text{(2) Cl·CO·[CH}_2]_8\text{·CO}_2\text{Et}]{\text{(1) Mg; CdCl}_2} \underset{\text{(IV)}}{\mathrm{MeO{\cdot}[CH_2]_{11}{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2H}} \longrightarrow \underset{\text{(V)}}{\mathrm{MeO{\cdot}[CH_2]_{20}{\cdot}CO_2H}}$$

By standard methods, the acid (V) has been converted in high yields into 21-bromo- and 21-hydroxy-heneicosanoic acid and 21-methoxyeicosanol. However, overall yields of (V) are low, and other approaches to similar bifunctional compounds will be examined.

Experimental

Unless otherwise specified, light petroleum refers to the grade of b. p. 60—80°.

Methyl 11-*Methoxyundecanoate* (II).—11-Bromoundecanoic acid was prepared by Ashton and Smith's method (*J.*, 1934, 438) and carefully purified by repeated recrystallisation from light petroleum, to give material of m. p. 50·5—51°. A mixture of the acid (365 g.), methanol (600 ml.), and concentrated sulphuric acid (60 ml.) was refluxed for 4 hours and the cooled mixture poured into water. Methyl 11-bromoundecanoate (366 g.), isolated in the usual manner, distilled as a colourless oil, b. p. 131—132°/5 mm., n_D^{20} 1·4652. The ester (277 g.) was then added during 0·5 hour to a solution of sodium methoxide (1·1 mols.) in dry methanol (350 ml.). After 4 hours' heating under reflux, most of the methanol was removed by distillation and the cooled mixture poured into acidulated water. The product was isolated as usual, and submitted to careful fractionation through a Fenske column (25 cm.) fitted with a reflux head, the course of the fractionation being followed by refractive-index observations. In this manner a total of 203 g. of required ester was obtained, having b. p. 104—105°/0·5 mm., n_D^{20} 1·4375. On hydrolysis the free acid was obtained as a solid, which crystallised from light petroleum at 0° in needles, m. p. 34·5—35·0°, and formed a p-*phenylphenacyl* ester, nacreous leaflets (from aqueous ethanol), m. p. 70° (Found : C, 76·3; H, 8·4. $C_{26}H_{34}O_4$ requires C, 76·1; H, 8·3%). Hunsdiecker (*Ber.*, 1942, **75**, 1190) reported the acid, prepared in the same manner, as having m. p. 32·7° but, since no mention is made of careful fractionation of the product, his material was very likely contaminated with unsaturated acid formed by the elimination reaction.

11-*Methoxyundecanol.*—The foregoing methyl ester was reduced with sodium and ethanol, as in *Org. Synth.*, Coll. Vol. II, p. 372. By re-esterifying recovered acid and submitting this to

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* Part IX, *J.*, 1952, 1057.

† Geneva notation (CO_2H = 1) is used throughout.

‡ Dr. J. H. Gorvin has kindly drawn our attention to a gross error of nomenclature in Part V where the expression -cosanoic acid was used throughout in place of -contanoic acid. Ed.

the same process, an 85% overall yield of the *alcohol*, b. p. 122—124/1 mm., n_D^{20} 1·4473, was obtained (Found: C, 71·2; H, 13·0. $C_{12}H_{26}O_2$ requires C, 71·2; H, 13·0%). In pyridine it gave the 3 : 5-*dinitrobenzoate*, prisms, m. p. 58° (Found: C, 57·4; H, 6·8. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1%).

11-*Methoxyundecyl Bromide* (III).—A mixture of the foregoing alcohol (152 g., 0·75 mol.), redistilled quinoline (33 g., 0·25 mol.), and dry carbon tetrachloride (300 ml.) was cooled to −10° and phosphorus tribromide (70 g., ; 0·26 mol.) added with stirring at such a rate that the temperature did not rise above −5°. The resulting mixture was then boiled under reflux for 1 hour and, after cooling, poured into water. The organic extract was washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, and solvent removed *in vacuo*. The crude residue (150 g.) was then dissolved in light petroleum (b. p. 40—60°; 300 ml.) and extracted with concentrated sulphuric acid (3 × 25 ml.). The acid extracts were quickly diluted with water, whereupon the *methoxy-bromide* separated as an oil. Isolated in the usual manner, it distilled as a colourless oil, b. p. 114—115°/0·25 mm., n_D^{20} 1·4624 (119 g.) (Found: C, 54·8; H, 9·5. $C_{12}H_{25}OBr$ requires C, 54·4; H, 9·4%).

10-*Keto*-21-*methoxyheneicosanoic Acid* (IV).—The preparation of di-(11-methoxyundecyl)-cadmium from the bromide (0·42 mol.) and its reaction with ω-carbethoxynonanoyl chloride were carried out as described by Cason (*Org. Synth.*, 1948, **28**, 75). The total crude reaction product was hydrolysed on the steam-bath for 1 hour with potassium hydroxide (38 g.) in ethanol (750 ml.). The cooled solution deposited impure potassium salts which were filtered off. After being washed with ethanol (150 ml.), they were extracted with boiling acetone (750 ml.) and then ether (750 ml.) and dried. Evaporation of the organic extracts and crystallisation from ethanol furnished 1 : 22-*dimethoxydocosane* (9 g.) as needles, m. p. 53° (Found: C, 77·6; H, 13·4. $C_{24}H_{50}O_2$ requires C, 77·8; H, 13·6%). The residual potassium salts (108 g.) were then dissolved in acetic acid (300 ml.) and treated at the b. p. with concentrated hydrochloric acid (50 ml.) for 5 minutes. The mixture was poured into water (700 ml.), the product separating (82 g.; m. p. 81—83°). On crystallisation from ethyl acetate (500 ml.; norite) the *keto-acid* (61 g.) separated as plates, m. p. 82·5—83°, unchanged by further crystallisation from acetone or light petroleum (Found: C, 71·4; H, 11·2. $C_{22}H_{42}O_4$ requires C, 71·3; H, 11·4%).

21-*Methoxyheneicosanoic Acid* (V).—The keto-acid was reduced with hydrazine and sodium hydroxide as described for the preparation of *n*-tricosanoic acid (Ames, Bowman, and Mason, *J.*, 1950, 174), to give the *acid*, plates (from acetone), m. p. 74·5—75·0° (Found: C, 74·2; H, 12·4. $C_{22}H_{44}O_3$ requires C, 74·1; H, 12·4%). It formed a *phenacyl* ester, which crystallised from light petroleum (norite) in plates, m. p. 68·5—69·0° (Found: C, 75·8; H, 10·5. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%).

21-*Bromoheneicosanoic Acid.*—A mixture of the foregoing acid (2 g.), hydrogen bromide in acetic acid (12 ml. of 50%), and concentrated sulphuric acid (4 ml.) was heated at 100° over 4 hours. The cooled mixture was poured into water, and the resulting solid (m. p. 77—79°) re-treated in a similar manner for 6 hours at 100°. The crude product then had m. p. 78—81° and furnished on crystallisation from light petroleum (norite) the *bromo-acid* (1·8 g.) as leaflets, m. p. 82·5—83° (Found: C, 62·3; H, 10·1. $C_{21}H_{41}O_2Br$ requires C, 62·2; H, 10·1%).

21-*Hydroxyheneicosanoic Acid.*—The corresponding bromo-acid (1 g.) was heated under reflux with a solution of potassium acetate (3 g.) in acetic acid (15 ml.) for 4 hours and the solution poured into water. The solid was collected by filtration and treated with N-sodium hydroxide (50 ml.) and pure dioxan (40 ml.) for 2 hours at the b. p. 20N-Sulphuric acid (6 ml.) was added and, after 3 minutes' refluxing, the mixture was poured into water, and the solid product filtered off. Crystallisation from acetone furnished the *hydroxy-acid* as laths, m. p. 99·5—100° (Found: C, 73·8; H, 12·2. $C_{21}H_{42}O_3$ requires C, 73·6; H, 12·4%).

21-*Methoxyheneicosanol.*—21-Methoxyheneicosanoic acid (2 g.) was added to lithium aluminium hydride (1·5 g.) in ether (30 ml.) containing toluene (15 ml.), and the mass heated under reflux for 12 hours. The cooled mixture was treated with ethanol and then dilute hydrochloric acid. The organic extract was washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, and dried ($CaSO_4$). Evaporation furnished the crude *alcohol* which crystallised from light petroleum, and then acetone, in rhombohedra (1·7 g.), m. p. 69—69·5° (Found: C, 77·1; H, 13·2. $C_{22}H_{46}O_2$ requires C, 77·1; H, 13·5%).

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