16. *Wool Wax. Part III.* Synthesis of Some* iso-*Acids.*

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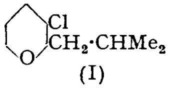
8 - Methylnonanoic,† 10 - methylundecanoic, 12 - methyltridecanoic, 16-methylheptadecanoic, and 18-methylnonadecanoic acids have been synthesised. The melting points and long *X*-ray crystal spacings of the solid acids and amides have been recorded for comparison with those of *iso*-acids from wool wax.

A series of *iso*-acids was required in connection with the branched-chain compounds which exist in both the acid (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447) and alcoholic (Murray and Hatt, personal communication) fractions of saponified wool wax. We investigated four modern methods of chain lengthening for convenience of preparation of reasonable quantities of the necessary pure saturated *iso*-compounds. Some of the difficulties encountered since this work was initiated three years ago have been noted by others.

14-Methylpentadecanoic acid was not prepared since it has been satisfactorily identified in wool wax (Weitkamp, *loc. cit.*).

The dihydropyran method (Crombie and Harper, *J.*, 1950, 1707; Brandon, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1950, **72**, 2120) was used with *iso*butylmagnesium bromide, giving *cis*- and *trans*-2-*iso*butyl-3-chlorotetrahydropyran (I), which on ring scission and hydrogenation gave 7-methyloctanol, converted through the bromide and nitrile into 8-methylnonanoic acid (II).



(I)

$Pr^i{\cdot}[CH_2]_n{\cdot}CO_2H$

(II; $n = 6$) (V; $n = 14$)
(III; $n = 8$) (VI; $n = 16$)
(IV; $n = 10$)

10-Methylundecanoic acid (III) was prepared from two sets of intermediates by a modification of Bowman's ketone method (*J.*, 1950, 174) in that the acid chlorides (4-methylpentanoylchloride, 2-methylpropanoyl chloride) reacted in the presence of one equivalent of sodium with polymethylene αω-dimalonic esters [benzyl pentane-1 : 1 : 5 : 5-tetracarboxylate (VII), benzyl heptane-1 : 1 : 7 : 7-tetracarboxylate (VIII)] instead of with monomalonic esters. Yields of the keto-acids after debenzylation were poor so that the advantage of using the more readily available dimalonic esters is outweighed by losses probably arising, in part,

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* Part II, Rossouw and von Rudloff (*J. Appl. Chem.*, 1952, **2**, 335).

† Geneva nomenclature ($CO_2H = 1$) is used throughout this paper for naming the *iso*-acids.

from the occurrence of addition of acid chloride to both functional ends of the dimalonic ester molecule; in agreement with Nunn's report (*J.*, 1951, 1740) undesired ketonic hydrolysis of the intermediate β-keto-esters also occurred. A third source of loss in the case of (VII) arose from Dieckmann cyclisation, in the presence of the sodium, detected

$$\mathrm{Pr^i{\cdot}[CH_2]_{\mathit{n}}{\cdot}COCl + (CH_2Ph{\cdot}O_2C)_2CH{\cdot}[CH_2]_{\mathit{m}}{\cdot}CH(CO_2{\cdot}CH_2Ph)_2} \xrightarrow{\mathrm{Na}}$$

$$\text{(VII; } m = 3\text{) (VIII; } m = 5\text{)}$$

$$\mathrm{Pr^i{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO{\cdot}C(CO_2{\cdot}CH_2Ph)_2{\cdot}[CH_2]_{\mathit{m}}{\cdot}CH(CO_2{\cdot}CH_2Ph)_2} \xrightarrow[\text{(2) }-3\mathrm{CO_2}]{\text{(1) }\mathrm{H_2}\text{–catalyst}} \mathrm{Pr^i{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO{\cdot}[CH_2]_{\mathit{m}+2}{\cdot}CO_2H}$$

by the identification of *cyclo*hexanone at the end of the series of operations; the use of malonic esters is therefore best restricted to those in which the chain is either too long or too short to favour intramolecular cyclisation. The keto-acids obtained after the hydrogenolysis step were smoothly reduced by Huang-Minlon's procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487).

12-Methyltridecanoic acid (IV) was prepared by the chloro-iodide–alkylacetylene method of Strong *et al.* (*ibid.*, 1948, **70**, 1699, 3391) starting from 6-methylhept-1-yne and 1-chloro-5-iodopentane :

$$\mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\vdots}CNa + I{\cdot}[CH_2]_5{\cdot}Cl} \longrightarrow \mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\vdots}C{\cdot}[CH_2]_5{\cdot}Cl} \xrightarrow[\text{(2) NaOH}]{\text{(1) NaCN}}$$

$$\mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\vdots}C{\cdot}[CH_2]_5{\cdot}CO_2H} \xrightarrow{2\mathrm{H_2}} \underset{\text{(IV)}}{\mathrm{Pr^i{\cdot}[CH_2]_{10}{\cdot}CO_2H}}$$

No difficulties were encountered, but attempts to condense 6-methylhept-1-yne with 1-chloro-10-iododecane were abortive. This is analogous to the failure of Taylor and Strong (*ibid.*, 1950, **72**, 4263) to condense alkylacetylenes containing more than nine methylene groups with chloro-iodides. Huber (*ibid.*, 1951, **73**, 2730) has since caused hept-1-yne to react with 1-chloro-10-iododecane, and Lumb and Smith (*Chem. and Ind.*, 1952, 358) have condensed the lithium derivative of *n*-tridec-1-yne with 1-chloro-3-iodopropane so that the limitations noted by Taylor and Strong and by us can be overcome at least in some cases. In practice the use of chloro-iodides is restricted by the difficulty of separating, by fractional distillation, dichloride–chloro-iodide–di-iodide mixtures when the chain is long.

The anodic method of Linstead *et al.* (*J.*, 1950, 3326) was used to synthesise 8-methylnonanoic acid (II) (from 4-methylpentanoic acid and ethyl hydrogen adipate), 10-methylundecanoic acid (III) (from 3-methylbutanoic acid and ethyl hydrogen azelate), 12-methyltridecanoic acid (IV) (from 4-methylpentanoic acid and ethyl hydrogen sebacate), 16-methylheptadecanoic acid (V) (from 12-methyltridecanoic acid and ethyl hydrogen adipate), and 18-methylnonadecanoic acid (VI) (from 10-methylundecanoic acid and ethyl hydrogen sebacate). This method proved the best, for our purpose, because of the ready availability of the starting materials, the reasonable yields obtained, and the smallness of the working losses arising from the fact that it is a one-step synthesis.

In both the Bowman and the Linstead method, it has been advisable to choose the starting materials so that the unwanted dicarboxylic acids arising from ketonic hydrolysis and symmetrical coupling are readily separable by fractional distillation from the desired products. To a lesser extent, dicarboxylic acid by-products also arise in the acetylenic method in cases where the chloro-iodide cannot be fractionated entirely free from di-iodide. It is suggested that, in such cases, the use of Craig's counter-current distribution method (*Ann. N.Y. Acad. Sci.*, 1951, **53**, 1015) is appropriate for purification of the end product since there are large differences in solubility in polar and non-polar solvents between aliphatic monocarboxylic and dicarboxylic acids of similar boiling points. Two examples are in the Experimental.

The properties of the synthetic acids and their amides are compared in the Table with those which Weitkamp (*loc. cit.*) and Velick (*J. Amer. Chem. Soc.*, 1947, **69**, 2317) recorded for wool wax *iso*-acids and with those taken from the compilation in the paper of Ställberg, Stenhagen, *et al.* (*Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 19). Direct comparison of our synthetic C_{12} and C_{20} *iso*-acids with specimens isolated by Dr. Weitkamp from wool wax showed that there was no depression of melting points; this and the close comparisons of properties in the Table confirm the validity of Weitkamp's structural assignments.

	M. p.		Long crystal spacing (Å)	
Acid *	Acid	Amide	Acid	Amide
8-Methylnonanoic	23·7—24·0°	103·8°	19·93	19·80 [c]
	Liquid [4]	103·1 [1]	—	19·9 [2]
10-Methylundecanoic	41·4—41·5	108·1—108·4 [b]	23·38	24·13 [b]
	41·2 [1]	108 [1]	—	24·1 [2]
12-Methyltridecanoic	53·3—53·6	—	26·82	—
	53·4—53·6 [a]	108·1—108·3 [a]	26·80 [a]	27·14 [a]
	53·3 [1]	107·3 [1]	26·8,[2] 27·0 [3]	27·0,[2] 26·7 [3]
	53·3—53·6 [3]	—	—	—
16-Methylheptadecanoic	69·5—69·7	107·8—107·9	33·75	34·7
	69·5 [1]	107·3 [1]	33·8 [2, 3]	35·0,[2] 34·5 [3]
18-Methylnonadecanoic	75·3—75·6	105·9—106·1	37·52	36·70
	75·3 [1]	105·1 [1]	37·8 [2]	36·8 [2]

* Specimens were prepared by the anodic method, unless indicated as [a] (Strong), [b] (Bowman), or [c] (Crombie and Harper).

[1] Weitkamp (*loc. cit.*). [2] Velick (*loc. cit.*). [3] Ställberg and Stenhagen (*loc. cit.*). [4] Nelson and Dawson (*J. Amer. Chem. Soc.*, 1923, **45**, 2179).

The long *X*-ray spacings were measured on a Philips high-angle Geiger counter spectrometer previously calibrated with a silicon standard. Filtered Cu-K_α radiation was used (λ = 1·541 Å). The specimens were prepared by melting them between two microscope slides and allowing them to cool under slight pressure. For every specimen it was possible to observe at least ten orders of "reflection."

EXPERIMENTAL

M. p.s are corrected.

Anodic Syntheses.—These were carried out under the conditions described under "Method B1" (Linstead *et al.*, *loc. cit.*, p. 3328) with dry methanol as solvent.

Craig Counter-current Distribution Separation of a Mono- and Di-carboxylic Acid Mixture.—Pimelic acid (0·15 g.) and 10-methylundecanoic acid (0·15 g.) were introduced into tube No. 0 of a 25-tube steel counter-current apparatus containing a two-phase solvent system made up from hexane (100), acetone (25), ethanol (13), and water (62) (figures in parentheses denote parts by volume). After 24 transfers had been applied the contents of the tubes were evaporated, giving pimelic acid, m. p. 105—106°, in tubes 0—4 inclusive (peak in tube 1) and 10-methylundecanoic acid, m. p. 40—41°, in tubes 20—24 inclusive (peak in tube 23).

8-*Methylnonanoic acid* (II).—(a) *From* cis- *and* trans-2-iso*butyl*-3-*chlorotetrahydropyran.* A mixture of *cis*- and *trans*-*iso*butyl-3-chlorotetrahydropyrans (11·8 g., 0·067 mole), prepared by the reaction of *iso*butylmagnesium bromide with 2 : 3-dichlorotetrahydropyran, was treated with powdered sodium (5 g., 0·218 g.-atom) in dry ether following the procedure of Crombie and Harper (*loc. cit.*); the product was poured into water and extracted with ether, to yield after distillation 7-methyloct-4-en-1-ol (5·5 g., 58% based on the 2-alkyl-3-chlorotetrahydropyran), b. p. 107°/21 mm. (Found: C, 75·8; H, 12·8. Calc. for $C_9H_{18}O$: C, 76·0; H, 12·8%). Hydrogenation afforded 7-methyloctanol (Found: C, 74·6; H, 14·0. Calc. for $C_9H_{20}O$: C, 74·9; H, 14·0%), characterised as its phenylurethane, m. p. 65° (Cason, *J. Amer. Chem. Soc.*, 1942, **64**, 1102, records m. p. 65°). The 7-methyloctanol was converted into the bromide (3·5 g.; b. p. 107°/27 mm.) (Found: Br, 38·6. Calc. for $C_9H_{19}Br$: Br, 38·6%) with hydrogen bromide and thence through the nitrile into 8-methylnonanoic acid [cf. the preparation of (IV), method (*a*)] (1·03 g., 9% overall yield) (Found: C, 69·7; H, 11·7%; equiv., 173. Calc. for $C_{10}H_{20}O_2$: C, 69·5; H, 11·8%; equiv., 172·3). The amide had m. p. 103·8° (from acetone) (Found: C, 69·6; H, 12·7; N, 7·9. Calc. for $C_{10}H_{21}ON$: C, 70·1; H, 12·4; N, 8·2%).

(b) *From* 4-*methylpentanoic acid and ethyl hydrogen adipate.* The anodic method was used: 4-methylpentanoic acid (11·6 g., 0·1 mole), ethyl hydrogen adipate (33·6 g., 0·2 mole), and sodium (0·14 g., 0·006 g.-atom) were electrolysed to yield 8-methylnonanoic acid (6·58 g., 38% based on the 4-methylpentanoic acid), b. p. 106°/1 mm., f. p. 22·6° (from f. p. curve); after three recrystallisations from hexane at −50° it had m. p. 23·7—24·0°.

10-*Methylundecanoic Acid* (III).—(a) *From* 4-*methylpentanoyl chloride and benzyl pentane*-1 : 1 : 5 : 5-*tetracarboxylate.* Ethyl pentane-1 : 1 : 5 : 5-tetracarboxylate (36 g., 0·1 mole) was heated under reflux in dry benzene (150 c.c.) with powdered sodium (2·3 g., 0·1 g.-atom) until all the latter had dissolved (6 hr.). Benzyl alcohol (43·2 g., 0·4 mole) was added and distillation effected through a Fenske-helices-packed column until the theoretical quantity of ethanol (0·4 mol.) had been removed as the benzene–ethanol azeotrope (5 hr.) (cf. Bowman, *loc. cit.*, and Nunn, *loc. cit.*). 4-Methylpentanoyl chloride (13·45 g., 0·1 mole) was added slowly with stirring while cooling with ice–water, and the mixture was then refluxed (1 hr.) and cooled. Distilled water (250 c.c.) was added and the organic layer was taken up in ether, separated, washed (water), and dried (Na_2SO_4). The solvents were removed in a vacuum at <40°, leaving a light yellow oil (70 g., 0·1 mole) which was shaken in dry ethanol–ethyl acetate (1 : 1; 200 c.c.) with hydrogen at 50 lb./sq. in. in the presence of palladium–calcium carbonate (10 g.; Pd, 1%); no hydrogen was absorbed; the catalyst was filtered off and replaced by the same amount of fresh catalyst which was filtered off after no hydrogen had been taken up; palladium–carbon (5 g.; Pd, 10%) was added and hydrogen was taken up (*ca.* 85% theor.) during 3 hours. The catalyst was filtered off and the solvents were removed in a vacuum; the residue was heated at 95° and then at 180° for a short period to complete the decarboxylation. The product was distilled through a short Vigreux column to give: (*a*) 6·65 g., b. p. 110°/25 mm., (*b*) 1·35 g., b. p. 110°/25 mm. to 85°/2 mm., (*c*) 1·8 g., b. p. 85—110°/2 mm., (*d*) 0·5 g., b. p. 127—135°/1 mm., (*e*) 5·3 g., b. p. 140—157°/1 mm., (*f*) 0·8 g., b. p. 157°/1 mm., (*g*) 1·3 g., b. p. 165—195°/1 mm. and (*h*) 1·3 g., b. p. 195—200°/1 mm. Fraction (*a*) contained *cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. 157°; semicarbazone, m. p. 165°; and oxime m. p. 89°; mixed m. p.s gave no depression) and 4-methylpentanoic acid (*p*-bromophenacyl ester, m. p. 79°; amide m. p. 117°; mixed m. p.s gave no depression). Fractions (*e*) and (*f*) contained the required 7-keto-10-methylundecanoic acid; they were combined and reduced without purification by Huang-Minlon's procedure (*loc. cit.*) to give a product from which 10-methylundecanoic acid (1·0 g., 5%), m. p. 40—41°, was separated by fractional distillation (b. p. 130°/1 mm.) followed by crystallisation from aqueous methanol (Found: C, 71·6; H, 12·1%; equiv., 201. Calc. for $C_{12}H_{24}O_2$: C, 72·0; H, 12·1%; equiv., 200·3); the amide was recrystallised from *iso*hexane to m. p. 108·1—108·4° (Found: C, 72·7; H, 12·7. Calc. for $C_{12}H_{25}ON$: C, 72·4; H, 12·55%). Fraction (*h*) contained pimelic acid which was purified by crystallisation from aqueous hydrochloric acid (m. p. and mixed m. p. 105°).

(b) *From 2-methylpropanoyl chloride and benzyl heptane-*1 : 1 : 7 : 7*-tetracarboxylate.* By the above procedure but starting with 0·15 mole of ester with the appropriate amounts of sodium, benzyl alcohol, and the acid chloride, 10-methylundecanoic acid was obtained in 2 g. (6·7%) yield together with some azelaic acid.

(c) *From 3-methylbutanoic acid and ethyl hydrogen azelate.* The anodic method was used: 3-Methylbutanoic acid (88 g., 0·86 mole), ethyl hydrogen azelate (88 g., 0·41 mole), and sodium (0·6 g., 0·03 g.-atom) were electrolysed. 10-Methylundecanoic acid (37 g., 45% based on the ethyl hydrogen azelate) was recovered by distillation (b. p. 130°/1 mm.). After recrystallisation from 96% ethanol it had m. p. 41·4—41·5° and gave no depression of m. p. in admixture with the specimen supplied by Dr. Weitkamp.

12-*Methyltridecanoic Acid* (IV).—(a) *From 6-methylhept-*1*-yne and* 1*-chloro-*5*-iodopentane.* 6-Methylhept-1-yne (44 g., 0·4 mole) was added to sodamide (from 10 g., 0·435 g.-atom of sodium) in liquid ammonia and 1-chloro-5-iodopentane (93 g., 0·32 mole) was subsequently added (cf. Strong *et al.*, *loc. cit.*). After 24 hours the product was worked up, to yield 1-chloro-11-methyldodec-6-yne, b. p. 80°/1 mm. (24 g., 35% based on the 1-chloro-5-iodopentane), which was refluxed with ethanol (95%; 300 c.c.) for 72 hours with sodium cyanide (15 g., 0·31 mole); the precipitated sodium chloride was filtered off and the filtrate refluxed for 120 hours with sodium hydroxide (9·5 g., 0·24 mole) in water (50 c.c.). The 12-*methyltridec*-7-*ynoic acid* so produced was freed from non-acids by extraction of its alkaline solution (in 20% aqueous ethanol) with ether in the usual way and distilled, having b. p. 150—151°/1 mm. (11·8 g., 48% based on the 11-methyl-1-chlorododec-6-yne) [Found: C, 74·6; H, 10·6%; equiv., 219; 0·2598 g. took up 52·7 c.c. of H_2 (N.T.P.). $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%; equiv., 224·3; 0·2598 g. is equivalent to 52·0 c.c. of H_2]; the acid had n_D^{30} 1·4556, d_4^{30} 0·91604, $[R_L]_D$ 66·5. (Calc. 66·4). Its p-*bromophenacyl* ester had m. p. 51° (from aqueous ethanol) (Found: C, 62·5; H, 6·95; Br, 19·0. $C_{22}H_{29}BrO_3$ requires C, 62·7; H, 6·9; Br, 19·0%). The acetylenic acid was smoothly hydrogenated in ethyl acetate in the presence of Adams's catalyst, to yield 12-methyltridecanoic acid, recrystallised from acetone and then hexane to m. p. 53·4—53·6°, b. p. 158°/2 mm. (Found: C, 73·6; H, 12·5%; equiv., 226. Calc. for $C_{14}H_{28}O_2$: C, 73·6; H, 12·4%; equiv., 228·4), characterised as its amide, m. p. 108·1—108·3° (from hexane) (Found: C, 74·0; H, 12·6. $C_{14}H_{29}ON$ requires C, 73·9; H, 12·85%).

(b) *From* 4-*methylpentanoic acid and ethyl hydrogen sebacate*. The anodic method was used: 4-methylpentanoic acid (23 g., 0·2 mole), ethyl hydrogen sebacate (46 g., 0·2 mole), and sodium (0·2 g., 0·009 g.-atom) were electrolysed, to yield 12-methyltridecanoic acid, recrystallised as above to give m. p. 53·3—53·6° (12 g., 27%) (Found: equiv., 225·5. Calc. for $C_{14}H_{28}O_2$: equiv., 228·4).

16-*Methylheptadecanoic Acid* (V).—12-Methyltridecanoic acid (5 g., 0·022 mole), ethyl hydrogen adipate (16·8 g., 0·1 mole), and sodium (0·1 g., 0·004 g.-atom) were electrolysed, to yield 16-methylheptadecanoic acid (3 g., 47% based on the 12-methyltridecanoic acid) contaminated with sebacic acid. The latter was removed by counter-current distribution in a Craig apparatus with the two-phase solvent system detailed above; after 11 transfers the last two tubes contained the bulk of the 16-methylheptadecanoic acid, showing its preferential partition in the hydrocarbon layer; the acid had m. p. 68·0—68·7° and was recrystallised from acetone and then from hexane to m. p. 69·5—69·7° (Found: C, 75·8; H, 12·7%; equiv., 286. Calc. for $C_{18}H_{36}O_2$: C, 76·0; H, 12·6%; equiv., 284·5). The amide had m. p. 107·8—107·9° (from acetone and hexane) (Found: N, 4·7. Calc. for $C_{18}H_{37}ON$: N, 4·9%).

18-*Methylnonadecanoic Acid* (VI).—10-Methylundecanoic acid (34 g., 0·17 mole), ethyl hydrogen sebacate (113 g., 0·49 mole), and sodium (0·3 g., 0·01 g.-atom) were electrolysed, to yield 18-methylnonadecanoic acid (19 g., 36% based on the 10-methylundecanoic acid) (Found: C, 76·6; H, 12·9%; equiv., 312. Calc. for $C_{20}H_{40}O_2$: C, 76·7; H, 12·9%; equiv., 312·5), recrystallised from 96% ethanol to m. p. 75·3—75·6°, alone or mixed with the specimen supplied by Dr. Weitkamp. The amide had m. p. 105·9—106·1° (from acetone) (Found: N, 4·5. Calc. for $C_{20}H_{41}ON$: N, 4·5%).

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