87. *Lipids. Part IV.* Synthesis of Branched-chain Fatty Acids.*

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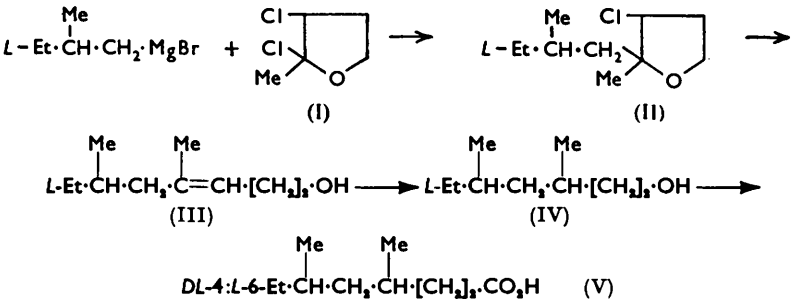
Preparative methods for 2 : 3-dichlorotetrahydro-2-methylfuran are examined. A general route using this substance, to acids with methyl branching at C_4 and higher positions is set out, and 4 : 5-, 4 : 6-, and 4 : 7-dimethyloctanoic and 4 : 10-dimethyldodecanoic acid are prepared. 4 : 6-Dimethyloctanoic acid is obtained in the *DL*-4 : *L*-6 configuration and found to be identical with a natural acid isolated by degrading the mould product, sclerotiorin.

Current interest in natural branched-chain fatty acids has led us to investigate their preparation from methyl-branched tetrahydrofuran derivatives. We have previously used the reaction between branched-chain Grignard reagents and 2 : 3-dichlorotetrahydrofuran or -pyran for this purpose : the 2-alkyl-3-chloro-derivative formed is readily converted into a branched-chain alk-2- or alk-3-en-1-ol which, by hydrogenation and oxidation, gives a branched-chain acid.[1] In this way *DL*- and *L*-6-methyloctanoic acid,[1] † and, by a modified procedure, 8-methylnonanoic [2,3] and 8-methylnon-6-enoic acid [3] have been prepared. These methods are limited to acids in which branching occurs at position 5 or higher-numbered positions. In the present investigation we were interested in synthesising *DL*-4 : *L*-6-dimethyloctanoic acid, a degradation product of sclerotiorin which has been isolated from *Penicillium multicolor* and related moulds.[4,5] The synthesis was carried out as follows :



First, we discuss the preparation of 2 : 3-dichlorotetrahydro-2-methylfuran. The substance was initially prepared by Paul and Tchelitcheff's method [6] in which tetrahydrofurfuryl bromide is dehydrohalogenated and isomerised to 4 : 5-dihydro-2-methylfuran; chlorine is then added to the latter at low temperature. Paul and Tchelitcheff have used the product in β-halogeno-ether syntheses of two unsaturated alcohols.[6] A modified route employs 4 : 5-dihydro-2-methylfuran obtained by cyclising 5-hydroxypentan-2-one with phosphoric acid.[7] Earlier, in the patent literature,[8] other methods were described for preparing the dichloride (I), and one of these, treatment of α-acetyl-α-chlorobutyrolactone (IX) with concentrated hydrochloric acid followed by gaseous hydrogen chloride,

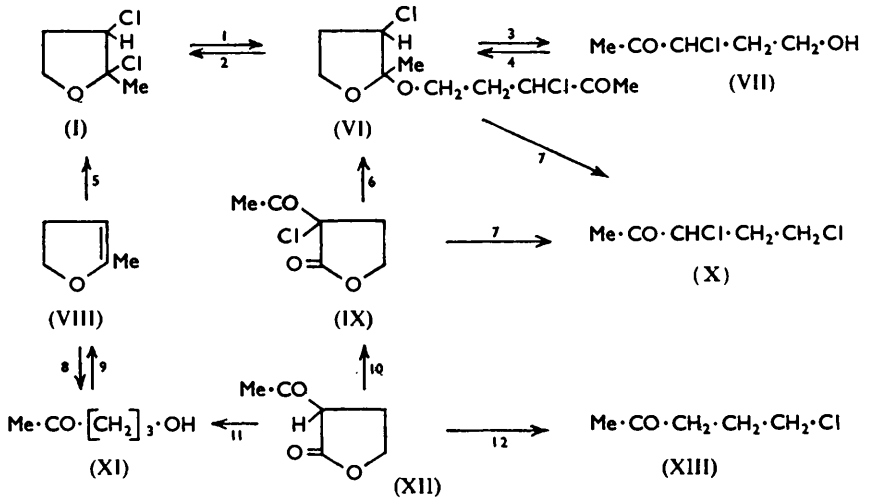
* Part III, *J.*, 1955, 3510.

† For the significance of the notation *L* and *D* see Linstead, Lunt, and Weedon, *J.*, 1950, 3333; Klyne, *Chem. and Ind.*, 1951, 1022.

[1] Crombie and Harper, *J.*, 1950, 2685.
[2] Hougen, Ilse, Sutton, and de Villiers, *J.*, 1953, 98.
[3] Crombie, Dandegaonker, and Simpson, *J.*, 1955, 1025
[4] Birkinshaw, *Biochem. J.*, 1952, **52**, 283.
[5] Watanabe, *J. Pharm. Soc. Japan*, 1952, **72**, 807.
[6] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1950, 520.
[7] Londergan, Hause, and Schmitz, *J. Amer. Chem. Soc.*, 1953, **75**, 4456.
[8] Kereszty and Wolf, B.P. 609,803; König, Gerecs, and Földi, U.S.P. 2,356,594.

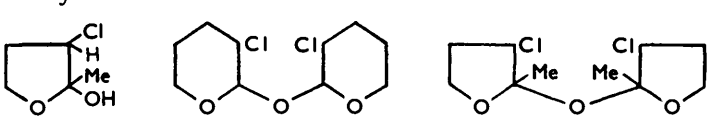
has previously been observed to yield 3 : 5-dichloropentan-2-one.[9] There is no mention of this substance in the patents.

If acetylchlorobutyrolactone is heated with *ca.* 1% aqueous hydrochloric acid, the main product, even before distillation which promotes dehydration and cyclisation, is, according to Stevens and Stein,[10] 3-chloro-2-(3-chloro-4-oxopentyloxy)tetrahydro-2-methylfuran (VI). When the product is distilled, small amounts of 3-chloro-5-hydroxypentan-2-one are eliminated as a low-boiling fraction : when the whole distilled product is used for synthetic purposes we shall refer to it as acetylchloropropanol. We find that infrared data for the product (VI) in carbon tetrachloride solution agree with the proposed structure. The ketone extinction coefficient (max. 1724 cm.$^{-1}$) for 3 : 5-dichloropentan-2-one (X) is 286 and that for the furan derivative (VI) is 256 (max. 1724 cm.$^{-1}$) if the molecular weight of the dehydrated dimer is employed [if the molecular weight for the pentanone



Reagents: 1, H_2O, 20°. 2, Dry HCl. 3, H_2O, 60°. 4, Heat. 5, Cl_2. 6, 1·1% aq. HCl, 100°. 7, 38% aq. HCl, 100°. 8, H_3O^+. 9, H_3PO_4. 10, SO_2Cl_2. 11, 5% aq. HCl, 100°. 12, 20% aq. HCl, 100°.

(VII) is used the extinction coefficient is only 134]. This result could alternatively be explained by postulating a mixture of (VII) and (XIV) but the interpretation is ruled out as the intensity of the hydroxyl band is less than 2. Boiling point, analytical, and molecular-weight evidence is also against it.[10] Paul records[11] that the substance (XV) * is formed when 2 : 3-dichlorotetrahydropyran is treated with water and a similar ether is reported in the tetrahydrofuran series,[12] but there is at present no evidence for an analogous structure in this case; perhaps (VI) is preferred for steric reasons, as models show that (XVI) is a much more crowded structure than (XV) or (VI) because of interactions caused by the two 2-methyl substituents.



Other clauses in the patents referred to above state that acetylchloropropanol is converted into 2 : 3-dichlorotetrahydro-2-methylfuran by thionyl chloride or anhydrous

* In agreement with this structure, we find no ketonic band in the infrared spectrum (paraffin mull).

[9] Crombie, Harper, and Stokes, *J.*, 1955, 4488.
[10] Stevens and Stein, *J. Amer. Chem. Soc.*, 1940, **62**, 1045.
[11] Paul, *Compt. rend.*, 1944, **218**, 122; see also Woods and Temin, *J. Amer. Chem. Soc.*, 1950, **72**, 139.
[12] Normant, *Compt. rend.*, 1948, **226**, 185.

hydrogen chloride and further details have recently been given by König, Gerecs, and Földi.[13] In our hands the thionyl chloride procedure yields 2 : 3-dichlorotetrahydro-2-methylfuran but it is contaminated with about 15% of 3 : 5-dichloropentan-2-one (identified and estimated by infrared techniques). The hydrogen chloride procedure is, however, an excellent one and gives 2 : 3-dichlorotetrahydro-2-methylfuran containing only about 2% of ketonic contaminant : this is comparable in purity with material from Paul's procedure and this material was used in all synthetic work reported here.

The failure of the one-step conversion of acetylchlorobutyrolactone into 2 : 3-dichlorotetrahydro-2-methylfuran [8] probably arises from the initial treatment with warm concentrated hydrochloric acid. We find that, once formed, 3 : 5-dichloropentan-2-one survives unchanged when treated with hydrogen chloride. Dilute acid cannot be employed as the dichloride (I) formed in the next stage is readily hydrolysed to acetylchloropropanol. In an attempt to adjust conditions, the treatment with concentrated hydrochloric acid was carried out at 30—35° but the final product was a mixture of 3 : 5-dichloropentan-2-one and 2 : 3-dichlorotetrahydro-2-methylfuran, together with lactonic material. Separation of the two stages from acetylchlorobutyrolactone seems inevitable. As reported,[8] 4-amino-2-methyl-5-thioformamidomethylpyrimidine condenses with 2 : 3-dichlorotetrahydro-2-methylfuran to give vitamin B_1 : since replacement of the 5-chlorine atom of 3 : 5-dichloropentan-2-one is conceivable under the reaction conditions [13] (see Experimental section), the condensation was also checked with this ketone but it does not lead to vitamin B_1 directly.

The mechanism of the conversion (VI) ⟶ (I) is not known, but it might proceed by a direct replacement reaction on (VI) or by formation of 3-chloro-4 : 5-dihydro-2-methylfuran, followed by addition of hydrogen chloride. If *trans*-addition is presumed for this latter reaction, and there is *trans*-addition of chlorine to 2 : 3-dihydro-2-methylfuran, then the samples obtained by the two synthetic methods described above should be stereoisomeric. In fact, their infrared spectra are almost identical : the configuration of the substance remains unsettled though the *trans*-dichloride is probably the stable structure since, though steric effects in the two isomers are somewhat similar, the mutual effect of the carbon–chlorine dipoles is minimised.

We now return to our main theme. *L*-2-Methylbutylmagnesium bromide, derived from natural (—)-*L*-2-methylbutanol, gave 3-chlorotetrahydro-2-methyl-2-2′-methylbutylfuran (II) when treated with 2 : 3-dichlorotetrahydro-2-methylfuran, and ring fission with sodium produced 4 : *L*-6-dimethyloct-3-en-1-ol. The overall yield was 35%. Catalytic hydrogenation gave *DL*-4 : *L*-6-dimethyloctanol (IV). In this reaction, there may be some asymmetric induction so that equal amounts of the *D*-4 : *L*-6 and *L*-4 : *L*-6 are not necessarily formed : the same remark applies to the acid produced by degradation of sclerotiorin (below). Oxidation of the alcohol (IV) with acidic permanganate below 30° gave *DL*-4 : *L*-6-dimethyloctanoic acid (V).

DL-4 : *L*-6-Dimethyloctanoic acid from sclerotiorin is obtained by alkali treatment [which gives an acid formulated as (XVII) by both Birkinshaw [4] and Watanabe [5]], followed by hydrogenation. Birkinshaw isolated the acid (V) and its *p*-bromophenacyl ester, and Watanabe gave further data. Professor Birkinshaw has kindly provided us with 100 mg. of the acid (XVII) and we find that spectral data agree with the proposed chromophore.

$$\mathrm{Et{\cdot}CHMe{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}CO_2H} \quad \text{(XVII)}$$
$$\mathrm{Pr^n{\cdot}CHMe{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H} \quad \text{(XVIII)}$$
$$\mathrm{Me_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H} \quad \text{(XIX)}$$
$$\mathrm{Et{\cdot}CHMe{\cdot}[CH_2]_5{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H} \quad \text{(XX)}$$

The acid was catalytically hydrogenated and the natural acid (V) further characterised by its infrared spectrum, rotation, and *S*-benzylthiuronium salt. The synthetic acid (V)

[13] König, Gerecs, and Földi, *Acta Chim. Acad. Sci. Hung.*, 1953, **3**, 157.

was identical with the natural substance. The diene acid (XVII) is therefore related to natural active amyl alcohol and must have the *L*- or (L_a) configuration like other natural (+)-*anteiso*-acids.[14, 15]

The general synthetic method was used to afford two isomeric acids, 4 : 5- and 4 : 7-dimethyloctanoic acid, which were appropriately characterised : the infrared spectra of the three acids are different, but not widely so. Preparation of the 4 : 5-dimethyl acid was of interest because branching on adjacent carbon atoms involves the reaction of the dichloride (I) with an α-branched Grignard reagent. Although the yield was reduced, 3-chlorotetrahydro-2-methyl-2-1'-methylbutylfuran was readily isolated. Reaction with a di-α-branched Grignard reagent as exemplified by *tert.*-butylmagnesium bromide gave poor results, presumably because of the high steric compression involved, or else instability of the product on distillation.[16] Finally the method was extended to a longer-chain acid, 4 : 10-dimethyldodecanoic acid. Its preparation involved two ring fissions, the first using 2 : 3-dichlorotetrahydropyran to give 6-methyloctanol,[1] and the second involving chain extension with 2 : 3-dichlorotetrahydro-2-methylfuran. Difficulty was encountered in the final oxidation as the usual permanganate oxidation at 30° was very slow, but a temperature of 70° was satisfactory. To ascertain that this treatment caused no carbon–carbon cleavage, the 4 : 10-dimethyldodecanoic acid was examined by reversed-phase chromatography [17, 18] but no impurity was found.

Further development of this approach to branched-chain acids with methyl groups in the 2- and the 3-position requires other appropriately substituted dichlorofuran or dichloropyran units. Parham and Holmquist [19] have prepared 3 : 4-dihydro-4-methyl-2*H*-pyran and 2 : 3-dihydro-3-methylfuran, and have recently shown [20] that, after addition of chlorine, they can be used in the β-halogeno-ether synthesis of unsaturated alcohols. By using these furans and pyrans in the above route, it should be possible to build the terminal residues $\cdot CH_2 \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CO_2H$ and $\cdot CH_2 \cdot CH_2 \cdot CHMe \cdot CO_2H$ on to branched or unbranched alkyl chains.

Experimental

Analyses were carried out in the Microanalytical (Miss J. Cuckney) and infrared measurements in the Spectroscopic Laboratories (Mr. R. L. Erskine, B. Sc., A.R.C.S.) of this Department. A Grubb–Parsons double-beam instrument with rock-salt optics was used.

Acetylchloropropanol.—Acetylbutyrolactone (XII) was prepared on a 5-mole scale in 48% yield according to the method of Knunjanz *et al.*[21] and had b. p. 123—125°/10—12 mm., n_D^{20} 1·4608. It was chlorinated by Buchman's procedure [22] to give acetylchlorobutyrolactone (IX) (89%), b. p. 93—95°/5 mm., n_D^{20} 1·4730. The latter was hydrolysed by Steven and Stein's procedure [10] to acetylchloropropanol (71%), b. p. 90—110°/2 mm. In another run the b. p. was 85—120°/2 mm., n_D^{21} 1·4721—1·4752. The infrared spectrum (liquid film) had bands as follows (cm.$^{-1}$) : 3420m, 2937m, 2882m, 1715s, 1479mw, 1440m, 1420m, 1379m, 1356m, 1303m, 1283w, 1258i, 1232m, 1196m, 1159s, 1096s, 1077s, 1047m, 1021s, 1005s, 980w, 954i, 942i, 928m, 877i, 864w, 834w, 811i, 744w (s = strong, m = medium, w = weak, i = inflexion). Redistillation of acetylchloropropanol gave the dominant product, 3-chloro-2-(3-chloro-4-oxopentyloxy)tetrahydro-2-methylfuran (VI), b. p. 110—112°/2 mm., n_D^{21} 1·4748. Stevens and Stein [10] give b. p. 111—112°/1 mm., n_D^{25} 1·4748. The eliminated fore-run is presumed to be 3-chloro-5-hydroxypentan-2-one. When distilled at 50 mm., it is reported [13] that the cyclodehydration product, 3-chloro-4 : 5-dihydro-2-methylfuran, is obtained. The infrared spectrum of (VI) was determined in CCl_4 (*c* 1·19%). For comparison in the hydroxyl region, the spectrum

[14] Crombie and Harper, *Chem. and Ind.*, 1950, 757.
[15] Klyne, *Biochem. J.*, 1953, **53**, 378.
[16] Crombie, Gold, Harper, and Stokes, *J.*, 1956, 136.
[17] Howard and Martin, *Biochem. J.*, 1950, **46**, 532.
[18] Crombie, *J.*, 1955, 3510.
[19] Parham and Holmquist, *J. Amer. Chem. Soc.*, 1951, **73**, 913.
[20] *Idem, ibid.*, 1954, **76**, 1173.
[21] Knunjanz, Celincev, and Osetrova, *Doklady Acad. Sci. U.R.S.S.*, 1934, **1**, 315.
[22] Buchman, *J. Amer. Chem. Soc.*, 1936, **58**, 1803.

of *n*-pentyl alcohol was measured (*c* 1·19%) and had bands at 3625 (ε 27·9, sharp, free OH), 3460 (ε 11·6, single bridge), and 3333 cm.$^{-1}$ (ε 12·6, polymeric OH).

5-Hydroxypentan-2-one.—This substance was prepared from acetylbutyrolactone in 63% yield by Knunjanz's[21] procedure and had b. p. 87—90°/4 mm., n_D^{22} 1·4382 (lit.,[21] b. p. 115—116°/30 mm., n_D^{20} 1·439). Its infrared spectrum (liquid film) shows a broad hydroxyl (3400 cm.$^{-1}$) and a keto-band (1712 cm.$^{-1}$) having inflexions at both sides; all the bands are unsharp. In CCl_4 (*c* 1·04%) there were OH bands at 3600 (ε 7·0) and 3460 cm.$^{-1}$ (ε 8·7): the ketone absorption was at 1717 cm.$^{-1}$ (ε 160) and there was a second maximum on the side of this band at 1740 cm.$^{-1}$. 5-Chloropentan-2-one has a ketone band at 1715 cm.$^{-1}$ (ε 304) in CCl_4 (*c* 1·03%) which suggests that this solution of 5-hydroxypentanone contains open-chain and cyclic material. Lüttke[23] has found physical evidence for keto-lactol tautomerism in this system, the keto-form predominating. Stevens and Stein have demonstrated that repeated distillation in the presence of a trace of acid gives an ether analogous to (VI).

5-Chloropentan-2-one.—Prepared in the usual way, this had b. p. 106°/110 mm., n_D^{19} 1·4334 (lit.,[24] b. p. 70—72°/20 mm., n_D^{25} 1·4371), and a ketone band at 1715 cm.$^{-1}$ (liquid film) (Found: C, 50·0; H, 7·8. Calc. for C_5H_9OCl: C, 49·8; H, 7·5%).

3 : 5-*Dichloropentan-2-one.*—The procedure of Kõnig *et al.*[13] gave the ketone (78% yield) from acetylchlorobutyrolactone. It had b. p. 44°/0·8 mm., n_D^{19} 1·4638, and is characterised by infrared bands (liquid film) as follows (cm.$^{-1}$): 2935m, 2905w, 1720s, 1441m, 1419m, 1358s, 1310m, 1287m, 1245m, 1238m, 1202m, 1164m, 1151m, 1093w, 1074w, 1027w, 979w, 930m, 856i, 845w, 817m, 782w, 731w, 695w, 681w. Lit.: [13,25] b. p. 58°/3 mm., 72—73°/11 mm. Dry hydrogen chloride was passed through the substance for 2½ hr. On redistillation it was completely recovered (b. p. 45°/0·4 mm., n_D^{30} 1·4588: infrared spectrum unchanged).

2 : 3-*Dichlorotetrahydro-2-methylfuran.*—*Method* 1.[8,13] Acetylchloropropanol (9·9 g.) was cooled in ice–salt, and dry hydrogen chloride passed in until an increase of 3·2 g. was recorded. A reddish aqueous phase floated on the product which was shaken with a little anhydrous sodium sulphate to bind the water, and then poured off, and distilled (b. p. 35—37°/3 mm.; n_D^{17} 1·4803; 7·0 g., 63%). Before distilling large batches, it is desirable to remove excess of hydrogen chloride with a stream of dried nitrogen. The infrared bands (liquid film) are (cm.$^{-1}$): 2965m, 2911m, (1721w), 1478m, 1441s, 1381s, 1362m, 1301m, 1278m, 1241m, 1226w, 1196m, 1163s, 1090m, 1062s, 1014s, 961w, 928m, 915w, 900m, 866m, 817w, 769w, 743w, 686m. The spectrum was recorded promptly after distillation and the substance must be protected from moisture. The ketone band at 1721 cm.$^{-1}$ indicates slight contamination and this was estimated as 1·8% (calc. as 3 : 5-dichloropentan-2-one). A second batch contained 3·4%.

Method 2.[8,13] Thionyl chloride (10 g.) was added to acetylchloropropanol (10 g., the same batch as used in method 1), with cooling to moderate reaction. The mixture was warmed to 50° (1 hr.) and then distilled, to give a product (6·1 g.), b. p. 30—40°/0·4 mm. The latter was redistilled, giving two fractions: (*a*) b. p. 26—28·5°/0·2 mm., $n_D^{20\cdot5}$ 1·4778 (4·3 g.), and (*b*) b. p. 28·5—30°/0·2 mm., $n_D^{20\cdot5}$ 1·4764 (0·5 g.). Both showed ketonic absorption at 1721 cm.$^{-1}$: intensity measurements showed 13% for (*a*), and 33% for (*b*), of 3 : 5-dichloropentan-2-one. In a second experiment, acetylchloropropanol (15 g.) and thionyl chloride (15 g.) gave a product (9·0 g.), b. p. mainly 32—33°/1 mm., containing 16·5% of 3 : 5-dichloropentan-2-one. Identification of the impurity as the latter substance is made by the presence of a band at 1419 cm.$^{-1}$ and increases in the intensity of certain bands particularly at 1361 and 930 cm.$^{-1}$. The presence of acetylchloropropanol formed by hydrolysis would have been revealed by disturbances in the spectral region 1000—1110 cm.$^{-1}$, but none was observed.

Method 3. 2 : 3-Dihydro-5-methylfuran, prepared by dehydrohalogenation of tetrahydrofurfuryl bromide and isomerisation of the initial product,[6] had b. p. 78—81°, n_D^{20} 1·4334. Prepared by cyclodehydration of 5-hydroxypentanone,[7] it had b. p. 80—81°, n_D^{20} 1·4336 (lit.,[6] b. p. 80—81° $n_D^{18\cdot5}$ 1·4328). The spectra of the two were identical, and contained the bands listed by Meakins.[26] Methylene chloride (48 g.) was cooled to −68° and a slow stream of dried chlorine passed in whilst 2 : 3-dihydro-5-methylfuran (12 g.) was added dropwise to keep the solution decolorised. Passage of chlorine was halted when approx. 12 g. had been absorbed.

[23] Lüttke, *Chem. Ber.*, 1950, **83**, 571; see also Wiemann and Maitte, *Bull. Soc. chim. France*, 1947, 764.
[24] *Org. Synth.*, 1951, **31**, 74.
[25] Yoshida and Unoki, *J. Pharm. Soc. Japan*, 1952, **72**, 1431.
[26] Meakins, *J.*, 1953, 4170.

The solution was allowed to warm to room temperature and the solvent evaporated *in vacuo*. The residue was fractionated, to give 2 : 3-dichlorotetrahydro-2-methylfuran, b. p. 55°/10 mm., n_D^{19} 1·4778 (9 g.). A higher-boiling material, b. p. 64—87°/10 mm., n_D^{18} 1·4871—1·4974, was also isolated. The infrared spectrum of the main product was almost identical with material from method 1. Ketonic contaminant, estimated on the usual basis at 1721 cm.$^{-1}$, was 1·6%.

Paul and Tchelitcheff [6] give b. p. 56—58°/20 mm., n_D^{18} 1·4812; Londergan *et al.*,[7] b. p. 49—51°/15 mm., n_D^{20} 1·4780; and Kõnig *et al.*,[13] b. p. 42—43°/1 mm., for 2 : 3-dichlorotetrahydro-2-methylfuran.

Condensations with 4-Amino-2-methyl-5-thioformamidomethylpyrimidine.[8]—Dry potassium formate (0·85 g.), 4-amino-2-methyl-5-thioformamidomethylpyrimidine (1 g.), formic acid (2 ml.), and 2 : 3-dichlorotetrahydro-2-methylfuran (1·5 g.) were mixed and kept at 50° for 65 hr. Absolute ethanol (9 ml.) and dry ethanol containing 30% of hydrogen chloride (1 ml.) were added and the mixture refluxed for a few minutes and cooled to 0°. The crystals were filtered off, and washed with ethanol (3·5 ml.). They were dissolved in a minimum of hot water and a hot solution of ammonium picrate (1·7 g.) in water (20 ml.) added: the picrate (1·82 g.), m. p. 203°, was gradually obtained. The dry picrate was heated under reflux with dry ethanol (20 ml.) and 30% ethanolic hydrogen chloride (5 ml.). On cooling, vitamin B_1 hydrochloride, m. p. and mixed m. p. 249—250°, was isolated. Under identical conditions, no vitamin B_1 was obtained directly from 3 : 5-dichloropentan-2-one, indicating that replacement of the 5-chlorine, followed by hydrolysis, does not occur.

Acid Treatment of Acetylchlorobutyrolactone at 30—35°.—Acetylchlorobutyrolactone (25 g.) was stirred with concentrated hydrochloric acid (12·5 ml.) at 30—35° for 4 hr. The dark product was cooled in ice–salt, and dry hydrogen chloride passed in (3 hr.). The product was extracted with chloroform and the extract dried (Na_2SO_4), evaporated, and distilled. Four groups of fractions were taken: (*a*) b. p. 32°/1 mm., n_D^{20} 1·4774—1·4735, (*b*) b. p. 32—57°/1 mm., n_D^{20} 1·4692, (*c*) b. p. 57—72°/1 mm., n_D^{20} 1·4692; (*d*) b. p. 72—73°/1 mm., n_D^{20} 1·4748. Infrared spectra showed that (*a*) was a mixture of 3 : 5-dichloropentan-2-one and 2 : 3-dichlorotetrahydro-2-methylfuran, (*b*) was mainly 3 : 5-dichloropentan-2-one containing a little contaminant with a lactonic ketone band (1776 cm.$^{-1}$), and (*d*) was the same but containing much more of the latter substance (presumably acetylchlorobutyrolactone).

Solvolysis of 2 : 3-Dichlorotetrahydro-2-methylfuran.—The chlorofuran (0·75 g.) was shaken with water (4. ml.) at 20° for 2 hr. and dissolved completely: it may therefore be present as (VII) at this stage. The solution was set aside (3 days), saturated with salt, and thoroughly extracted with ether. Evaporation and distillation of the extract gave acetylchloropropanol (0·35 g.), n_D^{18} 1·4761: its infrared spectrum was identical with that of the specimen prepared as above. A 2 : 4-*dinitrophenylhydrazone* was prepared by treating 2 : 3-dichlorotetrahydro-2-methylfuran in ethanol with 2 : 4-dinitrophenylhydrazine and a drop of hydrochloric acid in the usual way. It had m. p. 105—106° and analysed as expected for a derivative of 3-chloro-5-hydroxypentan-2-one (Found: C, 42·05; H, 4·45. $C_{11}H_{13}O_5N_4Cl$ requires C, 41·7; H, 4·15%).

3-Chlorotetrahydro-2-methyl-2-L-2′-methylbutylfuran (II).—*L*-2-Methylbutyl bromide, prepared by Crombie and Harper's procedure,[1] had b. p. 118°, n_D^{20} 1·4451 (the refractive index previously given,[1] n_D^{20} 1·4552, is an error for n_D^{20} 1·4452). The rotation, $\alpha_D^{19\cdot5}$ +4·31°(*l* 1), gives, with Milburn and Truter's value,[27] α_D +4·75° (*l* 1), an optical purity of 93%. A Grignard reagent was prepared from the bromide (4·0 g.) with magnesium (0·64 g.) in dry ether (20 ml.). 2 : 3-Dichlorotetrahydro-2-methylfuran (3·6 g.) in ether (5 ml.) was added dropwise and with stirring at such a rate that the ether did not reflux: the product was set aside for 1 hr. Water was cautiously added until there was no further reaction, and the ether layer was poured off, dried (Na_2SO_4), evaporated, and distilled. *3-Chlorotetrahydro-2-methyl-2-L-2′-methylbutylfuran* (2·12 g., 44%), b. p. 59—62°/0·3 mm., n_D^{17} 1·4587—1·4583, was isolated as a colourless odorous liquid (Found: Cl, 18·2. $C_{10}H_{19}OCl$ requires Cl, 18·55%). Yields in this, and the examples below, are calculated on the dichloromethylfuran used. A fraction of b. p. 62—98°/0·3 mm., n_D^{17} 1·477, and a little low-boiling material were rejected, and a black tar remained in the flask.

3-Chlorotetrahydro-2-methyl-2-1′-methylbutylfuran.—A Grignard reagent from 1-methylbutyl bromide (11·52 g.) and magnesium (1·85 g.) in ether (80 ml.) gave, when treated with 2 : 3-dichlorotetrahydro-2-methylfuran (9·4 g.) in ether (10 ml.), *3-chlorotetrahydro-2-methyl-2-1′-methylbutylfuran* (2·3 g., 20%), b. p. 51—53°/0·05 mm., n_D^{18} 1·4641 (Found: Cl, 19·25%).

3-Chlorotetrahydro-2-methyl-2-isopentylfuran.—A Grignard reagent from *iso*pentyl bromide

[27] Milburn and Truter, *J.*, 1954, 3344.

(15 g.) and magnesium (2·4 g.) in ether (85 ml.) gave, when treated with 2 : 3-dichlorotetrahydro-2-methylfuran (13·0 g.) in ether (25 ml.), *3-chlorotetrahydro-2-methyl-2-isopentylfuran* (9·0 g., 48%), b. p. 83—86°/5 mm., $n_D^{19\cdot5}$ 1·4569 (Found : C, 63·15; H, 10·3; Cl, 17·5. $C_{10}H_{19}OCl$ requires C, 63·0; H, 10·05; Cl, 18·55%).

3-Chlorotetrahydro-2-methyl-2-6′-methyloctylfuran.—6-Methyloctanol was prepared as previously described [1] and had b. p. 55°/0·1 mm., n_D^{21} 1·4356 (Found : C, 74·5; H, 13·8. Calc. for $C_9H_{20}O$: C, 74·9; H, 13·95%). Lit.,[1] b. p. 112—114°/23 mm., n_D^{20} 1·4350. It was converted into *6-methyloctyl bromide*, b. p. (approx.) 43—45°/0·05 mm. (Found : C, 52·6; H, 9·35. $C_9H_{19}Br$ requires C, 52·15; H, 9·28%), by refluxing 45% aqueous hydrogen bromide containing 5% sulphuric acid (yield 71%). A Grignard reagent from the bromide (5·1 g.) and magnesium (1·2 g.) in ether (40 ml.) was treated with 2 : 3-dichlorotetrahydro-2-methylfuran (3·1 g.) in ether (10 ml.) to give *3-chlorotetrahydro-2-methyl-2-6′-methyloctylfuran* (3·01 g., 61%), b. p. 92°/0·15 mm., n_D^{26} 1·4568 (Found : C, 67·85; H, 11·05. $C_{14}H_{27}OCl$ requires C, 68·15; H, 11·05%).

Treatment of 2 : 3-*Dichlorotetrahydro-2-methylfuran with* tert.-*Butylmagnesium Bromide.*—*tert.*-Butyl bromide (4·44 g.) was converted into the Grignard reagent in dry ether (30 ml.) with magnesium (0·79 g.). 2 : 3-Dichlorotetrahydro-2-methylfuran (4·5 g.) in ether (10 ml.) was added slowly and with stirring. An oil separated which eventually solidified. When the addition was complete, water was added, and the ether layer separated, dried, and evaporated to give a viscous oil from which only 0·4 g. of distillable product, b. p. 52—88°/11 mm., n_D^{22} 1·4660—1·4778, was obtained. The lowest- and highest-boiling materials were examined spectroscopically and the former contained some hydroxylic impurity whilst the latter contained both hydroxylic (3390 cm.$^{-1}$) and ketonic (1717 cm.$^{-1}$) impurity. From the spectrum, the high-boiling fraction contains large amounts of acetylchloropropanol arising from unchanged 2 : 3-dichlorotetrahydro-2-methylfuran.

DL-4′: L-6-*Dimethyloctanol* (IV).—3-Chlorotetrahydro-2-methyl-2-*L*-2′-methylbutylfuran (1·92 g.) was added dropwise and with stirring to powdered sodium (0·5 g.) under anhydrous ether (10 ml.). The mixture became dark blue-grey soon after reaction began : when reaction ceased, the mixture was heated under reflux for 20 min., cooled, and decomposed with water. The ether layer was separated, dried, evaporated and distilled, to give *DL*-4 : *L*-6-dimethyloct-3-en-1-ol (1·25 g., 79%), b. p. 70—71°/0·25 mm., n_D^{19} 1·4557, $[\alpha]_D^{20}$ +0·91° (*c* 7·7% in MeOH). Hydrogenation of the alcohol (1·0 g.) in methanol (9 ml.) with Adams platinum catalyst (150 mg.), filtration, evaporation, and distillation gave DL-4 : L-6-*dimethyloctanol* (0·63 g., 62%), b. p. 68°/0·2 mm., n_D^{17} 1·4426, $[\alpha]_D^{20}$ +15° (*c* 4·45% in MeOH) (Found : C, 75·8; H, 13·75. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%).

4 : 5-*Dimethyloctanol.*—3-Chlorotetrahydro-2-methyl-2-1′-methylbutylfuran (1·73 g.) was treated with powdered sodium (0·46 g.) under ether (15 ml.) and worked up as above, to give 4 : 5-dimethyloct-3-en-1-ol (1·11 g., 78%), b. p. 51°/0·1 mm., n_D^{23} 1·4542. Hydrogenation of the alcohol (1·0 g.) in methanol (5 ml.) over 5% palladium–charcoal gave 4 : 5-*dimethyloctanol* (0·50 g., 49%), b. p. 78—79°/0·3 mm., n_D^{24} 1·4421 (Found : C, 75·8; H, 14·05%).

4 : 7-*Dimethyloctanol.*—3-Chlorotetrahydro-2-methyl-2-*iso*pentylfuran (9·0 g.) was treated with powdered sodium (1·2 g.) under ether (40 ml.), to give 4 : 7-dimethyloct-3-en-1-ol (4·7 g., 63·5%), b. p. 120°/50 mm., n_D^{22} 1·4526. Moroe *et al.*[28] prepared this alcohol by a different method and give b. p. 98—102°/10 mm., $n_D^{14\cdot5}$ 1·4560. Hydrogenation of the alcohol (4·5 g.) in ethanol (5 ml.) over Adams platinum catalyst gave 4 : 7-dimethyloctanol (4·0 g., 88%), b. p. 125°/50 mm., n_D^{23} 1·4390.

4 : 10-*Dimethyldodecanol.*—3-Chlorotetrahydro-2-methyl-2-6′-methyloctylfuran (2·71 g.) was treated with powdered sodium (0·51 g.) under ether (5 ml.) as above. Ring fission was rather sluggish : working up gave 4 : 10-*dimethyldodec-3-en-1-ol* (1·46 g., 63%), b. p. 92—93°/0·1 mm., n_D^{22} 1·4549 (Found : C, 78·50; H, 13·3. $C_{14}H_{28}O$ requires C, 79·2; H, 13·3%). [This, and the other alk-3-en-1-ols above, for which analytical data are not reported, gave satisfactory hydrogen but low carbon figures (0·7—1%) : it is not known whether this is due to unrecognised impurity or to difficulty in combustion.] 4 : 10-Dimethyldodec-3-en-1-ol (0·92 g.) in ethanol (5 ml.) was hydrogenated over 5% palladium–charcoal (100 mg.), to give 4 : 10-*dimethyldodecanol* (0·68 g., 67%), b. p. 92°/0·03 mm., $n_D^{21\cdot5}$ 1·4458 (Found : C, 78·7; H, 13·95. $C_{14}H_{30}O$ requires C, 78·45; H, 14·1%).

Naturally Derived DL-4 : L-6-*dimethyloctanoic Acid.*—The acid (XVII) obtained by alkaline

[28] Moroe, Hattori, and Ikegami, *J. Pharm. Soc. Japan*, 1952, **72**, 1147.

treatment of sclerotiorin had $\lambda_{max.}$ 263 mμ (ε 23,500 in EtOH) : this is consistent with mono-substitution at the 5-position, for 5-methylsorbic acid has $\lambda_{max.}$ 272 mμ (ε 24,000), whilst 2-methylsorbic acid has $\lambda_{max.}$ 260 mμ (ε 23,700), and 3-methylsorbic acid has $\lambda_{max.}$ 266 mμ (ε 14,000). The infrared spectrum (paraffin mull) shows a strong maximum at 1689 cm.$^{-1}$ consistent with an α-unsaturated acid, and a strong band at 1613 cm.$^{-1}$ attributed to the ·C:C·; it is not split as is usual, though the curve is not Gaussian. A medium band at 987 cm.$^{-1}$ indicates a *trans*-CH:CH grouping in conjugation. The acid (85 mg.) was hydrogenated in glacial acetic acid (3 ml.) over Adams platinum catalyst. Filtration, evaporation, and distillation gave *DL*-4 : *L*-6-dimethyloctanoic acid (48 mg.), n_D^{23} 1·4369, $[\alpha]_D^{22}$ +17·7° (*c* 3·28% in EtOH). The S-*benzylthiuronium* salt crystallised from aqueous ethanol in shining plates, m. p. 142—143° (Found : C, 63·6; H, 8·8. $C_{18}H_{30}O_2N_2S$ requires C, 63·95; H, 8·95%). Watanabe gives [5] b. p. 105—108°/3 mm., n_D^{20} 1·4339, $[\alpha]_D^{17}$ +16·3° (*c* 6·08% in EtOH), and states that its *p*-bromophenacyl ester could be obtained in two diastereoisomeric forms, m. p. 42—43° and 31—33°. Birkinshaw gives [4] $[\alpha]_{5461}$ +22·0° (*c* 0·5% in EtOH) (*p*-bromophenacyl ester, m. p. 41°).

Synthetic DL-4 : L-6-*dimethyloctanoic Acid* (V).—*DL*-4 : *L*-6-Dimethyloctanol (228 mg.) was suspended in water (2·5 ml.) and concentrated sulphuric acid (0·35 ml.), and cooled to 15°. Potassium permanganate (304 mg.) was added at <30° in portions with continuous shaking. Then excess of sodium metabisulphite was added. The clear solution was extracted with ether (3 times) and the acid purified through 2N-sodium hydroxide and collected in ether. The ethereal solution was dried, evaporated, and distilled, to give *DL*-4 : *L*-6-dimethyloctanoic acid (101 mg.), b. p. (approx.) 84°/0·15 mm., n_D^{22} 1·4370, $[\alpha]_D^{20}$ +16·1° (*c* 4·04% in EtOH) (Found : C, 69·65; H, 11·75. Calc. for $C_{10}H_{20}O_2$: C, 69·7; H, 11·7%). The *S*-benzylthiuronium salt crystallised in plates, m. p. 142—143°, undepressed on admixture with the above specimen. Crystallised from aqueous ethanol, the *p*-bromophenacyl ester was obtained in plates, m. p. 38—40° : there was insufficient material to continue crystallisations but its m. p. was undepressed by Professor Birkinshaw's specimen. The infrared spectra of the natural and the synthetic acid were identical.

4 : 5-*Dimethyloctanoic Acid* (XVIII).—4 : 5-Dimethyloctanol (0·49 g.) in water (5 ml.) containing concentrated sulphuric acid (0·7 ml.) was oxidised with potassium permanganate (650 mg.) at <30°. The solution was worked up and purified as above, to give 4 : 5-*dimethyloctanoic acid* (0·32 g.), b. p. 88°/0·1 mm., n_D^{24} 1·4409 (Found : C, 69·4; H, 11·75%). The p-*bromophenacyl ester*, crystallised from ethanol, had m. p. 31° (Found : C, 58·4; H, 6·7. $C_{18}H_{25}O_3Br$ requires C, 58·55; H, 6·8%). The S-*benzylthiuronium salt* had m. p. 138—139° (from ethyl acetate) (Found : C, 64·15; H, 9·15%).

4 : 7-*Dimethyloctanoic Acid* (XIX).—4 : 7-Dimethyloctanol (1·0 g.) in water (12·5 ml.) containing concentrated sulphuric acid (1·5 g.) was oxidised below 25° with potassium permanganate (1·5 g.). Working up and purification as above gave 4 : 7-*dimethyloctanoic acid* (0·4 g.), b. p. 94°/10 mm., n_D^{24} 1·4341 (Found : C, 69·0; H, 11·7%). The p-*bromophenacyl ester* crystallised from ethanol, had m. p. 41° (Found : C, 58·35; H, 7·0%), and the *S*-benzylthiuronium salt (from ethyl acetate), m. p. 139—140°.

4 : 10-*Dimethyldodecanoic Acid* (XX).—4 : 10-Dimethyldodecanol (220 mg.) in water (3 ml.) containing concentrated sulphuric acid (0·4 ml.) was oxidised with potassium permanganate (220 mg.) at 70°. Working up and purification as usual gave 4 : 10-*dimethyldodecanoic acid* (75 mg.), b. p. (approx.) 155°/0·8 mm., n_D^{20} 1·4488 (Found : C, 73·4; H, 12·2. $C_{14}H_{28}O_2$ requires C, 73·65; H, 12·35%). The acid was chromatographed on a paraffin-loaded kieselguhr column,[17, 18] elution being with 50, 55, and 65% acetone in water. It emerged in 60% acetone as one unresolved band. We thank Mr. S. E. Callander for carrying out the determination.

We are grateful to Professor Birkinshaw for samples of the degradation product (XVII) and the *p*-bromophenacyl ester of naturally derived *DL*-4 : *L*-6-dimethyloctanoic acid. One of us (M. M. K.) expresses his thanks for the award of a Royal Exhibition of 1851 Scholarship.

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