515. *Synthesis and Configuration of* (+)-6-*Methyloctanoic Acid, a Degradation Product of the Polymyxins.*

By Leslie Crombie and Stanley H. Harper.

Hydrolytic degradation of the polymyxins, a series of related antibiotics from *B. polymyxa*, gives a dextrorotatory nitrogen-free acid, $C_9H_{18}O_2$, together with amino-acids. By oxidative degradation earlier workers have identified this acid as 6-methyloctanoic acid.

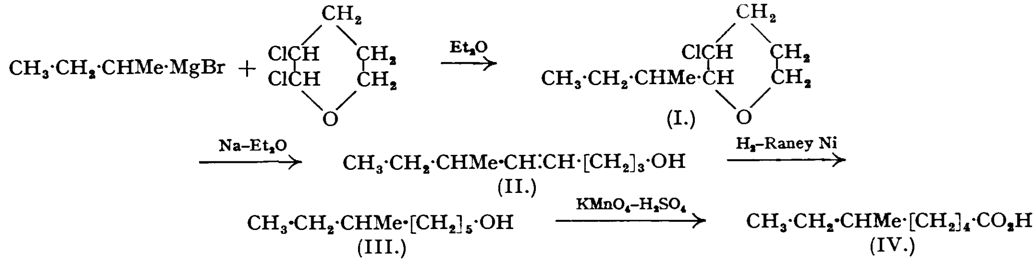
By the method, devised by us, of chain extension by four methylene groups at a time, (−)-2-methylbutanol is converted in four stages into (+)-6-methyloctanol, which on oxidation yields (+)-6-methyloctanoic acid, identical with the naturally derived acid. This synthesis relates 6-methyloctanoic acid configurationally, through 2-methylbutanol, to glyceraldehyde. The deduction that the (+)-acid has the L-configuration is criticised and a new configurational series based on 2-methylbutanol is proposed.

A similar synthesis, utilising the method of chain extension by five methylene groups at a time, yields (±)-6-methyloctanoic acid in four stages from (±)-*sec.*-butyl bromide.

The culture media of strains of *B. polymyxa* contain a series of related antibiotics which are now designated as polymyxins A, B, C, D, and E (Brownlee and Jones, *Biochem. J.*, 1948, **43**, xxv; various authors, Proc. of a Conference on Antibiotics derived from *B. polymyxa*, *Ann. New York Acad. Sci.*, 1949, **51**, 855 *et seq.*). They are considered to be cyclic peptides and on degradation all give threonine, αγ-diaminobutyric acid, and a dextrorotatory nitrogen-free acid, $C_9H_{18}O_2$, together with one or more of leucine, phenylalanine, and serine (Jones, *Biochem. J.*, 1948, **43**, xxvi; Catch, Wilkinson, and Jones, *ibid.*, p. xxvii). Comparison of the infra-red absorption spectrum of the C_9 acid with that of pelargonic (*n*-nonanoic) acid suggested a branched-chain structure for the former (Gore and Petersen, *Ann. New York Acad. Sci.*, 1949, **51**, 924), and Wilkinson (*Nature*, 1949, **164**, 622) has recently degraded this acid to (+)-3-methylpentanoic acid by the Miescher extension of the Barbier–Wieland degradation (*Helv. Chim. Acta*, 1944, **27**, 1815; 1945, **28**, 1252). The C_9 acid from the polymyxins is thus (+)-6-methyloctanoic acid, an acid which has previously been stated to occur in degras (wool fat) (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447). This communication is concerned with the synthesis of (±)- and (+)-6-methyloctanoic acid and the deduction of the configuration of the latter relative to glyceraldehyde.

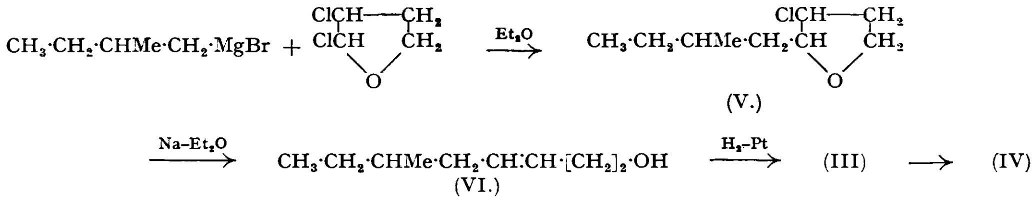
Levene and Marker (*J. Biol. Chem.*, 1932, **95**, 153; 1933, **103**, 299) prepared an active 6-methyloctanoic acid from *sec.*-butyl bromide by an eleven-stage synthesis and resolution. This lengthy route was clearly not intended as a preparative method, interest being centred on the optical rotations of the intermediates. A preparative method for the (±)-acid was described by Cason and Prout (*J. Amer. Chem. Soc.*, 1944, **66**, 46) who used a five-stage synthesis starting from adipic acid, in which ethyl 6-ketoheptanoate was prepared by the action of dimethylcadmium on δ-carbethoxyvaleryl chloride. Reaction of ethyl 6-ketoheptanoate with ethylmagnesium iodide, dehydration of the resulting hydroxy-ester, and catalytic hydrogenation yielded ethyl 6-methyloctanoate. The dehydration, by distillation with iodine, caused difficulty and the overall yield from ethyl 6-ketoheptanoate was only 20%, other reagents being even less satisfactory. Another method (Cason and Prout, *loc cit.*), based on the reaction of β-carbomethoxypropionyl chloride with di-2-methylbutylcadmium and subsequent Clemmensen reduction, yielded only an impure product, although this was attributed to the presence of *iso*amyl alcohol in the starting material.

The methods of chain extension by four and five methylene groups devised by us recently (Crombie and Harper, *J.*, 1950, 1707, 1714), based on the ring scission of 2-alkyl-3-chlorotetrahydro-furans and -pyrans respectively, appeared to offer more attractive routes to the racemic, and particularly to an optically active, acid whose configuration could be related to that of known substances. For (±)-6-methyloctanoic acid we have employed the second of these methods, as follows :



The mixed *cis*- and *trans*-2-*sec*.-butyl-3-chlorotetrahydropyrans (I), from the interaction of *sec*.-butylmagnesium bromide and 2 : 3-dichlorotetrahydropyran, were not separated but were subjected to ring scission to give, what is almost certainly in the light of our earlier experience, pure (±)-*trans*-6-methyloct-4-en-1-ol (II). Both this alcohol and the (±)-6-methyloctanol (III) obtained on reduction were characterised by crystalline 4-diphenylylurethanes. Unexpectedly, oxidation of (±)-6-methyloctanol with alkaline potassium permanganate failed (cf. Fournier, *Bull. Soc. chim.*, 1909, [iv], **5**, 920). However, oxidation in acid solution readily gave (±)-6-methyloctanoic acid (IV), which was characterised as the amide, the *p*-bromophenacyl ester, and the *S*-benzylthiuronium salt (see Table). Incidentally, this method provides a much improved route to (±)-6-methyloctanol which was used by Cason and Prout (*loc. cit.*) as an intermediate for the synthesis of (±)-16-methyloctadecanoic acid.

For the synthesis of an optically active 6-methyloctanoic acid we selected the first of the above methods of chain extension, for this permitted starting from the more accessible optically pure (—)-2-methylbutanol (" active " amyl alcohol from fusel oil) rather than an active *sec*.-butyl alcohol. Furthermore formation and reaction of the primary Grignard reagent should be possible with little, if any, racemisation. It is relevant that Whitmore and Olewine (*J. Amer. Chem. Soc.*, 1938, **60**, 2570) were able to convert (—)-2-methylbutanol into (+)-2-methylbutyl bromide, and thence through the Grignard reagent back into the alcohol with less than 10% racemisation. The method is as follows :



Again the mixed *cis*- and *trans*-3-chloro-2-2′-methylbutyltetrahydrofurans (V), from the interaction of (+)-2-methylbutylmagnesium bromide and 2 : 3-dichlorotetrahydrofuran, were subjected directly to ring scission to give 6-methyloct-3-en-1-ol (VI), which in the light of our previous experience may be a *cis–trans*-mixture in which the latter predominates. When this optically active 6-methyloct-3-en-1-ol was hydrogenated overnight in ether in presence of palladium on barium sulphate, a substantial amount of (+)-3-methyloctane was obtained. Hydrocarbon formation under these conditions, either by dehydration and subsequent further reduction or by direct hydrogenolysis, is unusual. Brief hydrogenation in presence of pre-reduced platinum oxide catalyst without a solvent gave (+)-6-methyloctanol in high yield. Again oxidation with alkaline potassium permanganate failed, but (+)-6-methyloctanol was smoothly oxidised in acid solution to (+)-6-methyloctanoic acid. The optical rotation of this acid (see Table) was identical, within the limit of experimental error, with that recorded for the naturally derived acid from the polymyxins. Through the kindness of Dr. W. G. Malcolm of the Lederle Laboratories Division of the American Cyanamid Company we have been able to make a direct comparison of these two acids. The *S*-benzylthiuronium salt and the *p*-bromophenacyl ester of the synthetic acid failed to depress the melting points of the corresponding derivatives prepared from the naturally derived acid. The structure of the latter is thus confirmed synthetically.†

6-Methyloctanoic acid.	B. p./mm.	n_D^{20}.	$[\alpha]_{5461}$ in Et_2O.	Amide, m. p.	*p*-Bromophenacyl ester, m. p.	*S*-Benzylthiuronium salt, m. p.
Synthetic (±)- ...	148—150°/23	1·4337	—	91°	57—58°	150·5°
Synthetic (+)- ...	148—149°/21	1·4330	+8·9°	90—91	58—59	149·5
Natural (+)-	—	1·4325	+8·6 *	93 *	57·0—57·5	148—149

* Catch, Jones, and Wilkinson, *Biochem. J.*, 1948, **43**, xxvii.

The above synthesis, which does not affect the asymmetric carbon atom and thus avoids inversion, relates (+)-6-methyloctanoic acid configurationally to (—)-2-methylbutanol.

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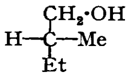
† Dr. S. Wilkinson (private communication) informs us that he has prepared (±)-6-methyloctanoic acid and resolved it to give the (+)-acid, which likewise proved to be identical with the naturally derived acid.

Furthermore the specific rotation of the product indicates that little, if any, racemisation occurred. (—)-2-Methylbutanol (" active " amyl alcohol) has long been described as the *d*-form and this is still persisted in. The prefix *d*- merely indicates that on oxidation the alcohol gives dextrorotatory valeric acid [(+)-2-methylbutanoic acid] (Marckwald, *Ber.*, 1902, **35**, 1595; Whitmore, " Organic Chemistry," Chapman and Hall, London, 1937, p. 125) and it is desirable to discontinue the use of this prefix since it is being confused with the real configuration [*e.g.*, *Chem. Abs.*, 1948, **42**, 9840, lists an entry referring to (—)-2-methylbutanol from fusel oil under D-(—)]. On the contrary the following argument can be developed relating (—)-2-methylbutanol, and hence (+)-6-methyloctanoic acid, to L-(—)-glyceraldehyde. First, (—)-2-methylbutanol has the same configuration as (—)-methylsuccinic acid. This follows from the argument of Freudenberg (" Stereochemie," F. Deuticke, Leipzig, 1933, p. 680), which has since been confirmed by interconversions through 3-methyladipic acid. Brown, Kharasch, and Chao (*J. Amer. Chem. Soc.*, 1940, **62**, 3435) converted (—)-2-methylbutanol through (+)-1-chloro-2-methylbutane into (—)-1 : 4-dichloro-2-methylbutane, the enantiomorph of which had earlier been obtained by von Braun and Jostes (*Ber.*, 1926, **59**, 1091) from the degradation of (+)-3-methyladipic acid. von Braun and Jostes later (*ibid.*, p. 1444) degraded (+)-3-methyladipic acid in the same manner to (+)-1 : 4-dibromo-2-methylbutane and converted this into (+)-2-methylbutane-1 : 4-diol and by further oxidative degradation into (+)-methylsuccinic acid. This configurational relationship is further supported by Ställberg-Stenhagen (*Arkiv Kemi Min., Geol.*, 1946, **23**, *A*, No. 15) who converted (+)-2-methylpent-4-enoic acid into (+)-2-methylpentanoic acid by hydrogenation, into (+)-2-methyldecanoic and (+)-2-methylhexacosanoic acids by chain extension from the vinyl group, and subsequently (Ställberg-Stenhagen and Stenhagen, *ibid.*, 1947, **24**, *B*, No. 9) by direct oxidation into (—)-methylsuccinic acid. By analogy these authors assigned (+)-2-methylbutanoic acid and hence (—)-2-methylbutanol the same configuration as (—)-methylsuccinic acid. Secondly, (—)-methylsuccinic acid has the same configuration as (—)-malic acid. This follows from the work of Fredga, who made use of the method of " quasi-racemic compound " formation (cf. " The Svedberg Commemorative Volume," Uppsala, 1944, p. 261). (—)-Methylsuccinic acid was related to (—)-mercaptosuccinic acid through the formation of a quasi-racemic compound between the former and (+)-mercaptosuccinic acid (Fredga, *Arkiv Kemi Min., Geol.*, 1942, **15**, *B*, No. 23), while (—)-" ethylxanthogenosuccinic acid " was related to (+)-" dithiocarbethoxyoxysuccinic acid " through formation of a quasi-racemic compound between the latter and (+)-" ethylxanthogenosuccinic acid " (Fredga, *ibid.*, 1941, **14**, *B*, No. 27). Holmberg (*ibid.*, 1916, **6**, No. 1) had converted (—)-" ethylxanthogenosuccinic acid " into (—)-mercaptosuccinic acid and subsequently (*Ber.*, 1925, **58**, 1822) prepared (+)-" dithiocarbethoxyoxysuccinic acid " from (—)-malic acid. In neither chemical transformation is the bond to the asymmetric carbon atom broken, hence (—)-malic acid is related to (—)-mercaptosuccinic acid and thence to (—)-methylsuccinic acid. Thirdly, (—)-malic acid has the same configuration as L-(—)-glyceraldehyde. This follows from the argument of Freudenberg and Lux (*ibid.*, 1928, **61**, 1083) relating (—)-malic acid to (+)-lactic acid, which Freudenberg (*ibid.*, 1914, **47**, 2027) had earlier converted into (+)-glyceric acid; and (—)-glyceric acid had been obtained by oxidation of D-(+)-glyceraldehyde (Wohl and Schellenberg, *ibid.*, 1922, **55**, 1404). Further support for the configurational relationship of (+)-lactic acid to L-(—)-glyceraldehyde has recently been provided by Wolfrom, Lemieux, Olin, and Weisblat (*J. Amer. Chem. Soc.*, 1949, **71**, 4057). This relationship, however, involves the convention that the carboxyl group of the lactic acid arises from the aldehyde group of glyceraldehyde and not from the primary alcohol group (cf. Freudenberg, " Sterochemie," p. 679; Wolfrom, Lemieux, and Olin, *J. Amer. Chem. Soc.*, 1949, **71**, 2870). Similar conventions arise in the inter-relationship of 2-methylbutanol and methylsuccinic acid, where the primary alcohol group is converted into carboxyl, and with 3-methyladipic acid. Furthermore the correlation of methylsuccinic acid with malic acid, in which a methyl group takes the place of hydroxyl, raises doubt as to the significance of configurational relationships involving such contrasting change at the asymmetric centre; for it should be noted that the methyl group of 2-methylbutanol corresponds, not with the methyl group of lactic acid, but with the hydroxyl group of the latter.

Hence although a formal relationship between (—)-2-methylbutanol and L-(—)-glyceraldehyde can be deduced it appears so tenuous as to be devoid of significance. Instead, we suggest that compounds containing the asymmetric carbon atom, ·C′·CHMe·C″·, should constitute a new configurational series, designated by D_a- and L_a-, with D_a-(+)-2-methylbutanol (subscript " a " indicating " active " amyl alcohol; similar designations for the glyceraldehyde and the amino-acid series have been suggested, see *Chem. Eng. News*, 1947, **25**, 1364) as the



$$\begin{array}{c} \mathrm{CH_2{\cdot}OH} \\ | \\ \mathrm{H{-}C{-}Me} \\ | \\ \mathrm{Et} \end{array}$$

(VII.)

standard of reference, written on the Fischer convention as (VII). For determining unambiguously configurational relationships within this series for the compounds discussed above, three conventions appear necessary. First, that the hydrogen and methyl attached to the asymmetric atom remain unchanged. Second, that in monocarboxylic acids (or other monofunctional compounds) the carboxyl group be derived by oxidation of, or by chain extension from, the primary alcohol group. Third, that in dicarboxylic acids (or other difunctional compounds) the carboxyl group nearer to the asymmetric atom be derived from the primary alcohol group.* On this scheme (−)-2-methylbutanol and hence (+)-6-methyloctanoic acid have the $\mathrm{L_a}$-configuration.

EXPERIMENTAL.

Microanalyses and determinations of optical rotation are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorr.

(+)-2-sec.-*Butyl-3-chlorotetrahydropyran.*—By the procedure used for the preparation of 3-chloro-2-methyltetrahydropyran (Crombie and Harper, *J.*, 1950, 1707), dihydropyran (84 g., 1·0 mol.) was chlorinated at 0—5° in dry ether (200 ml.), and the resulting solution of 2 : 3-dichlorotetrahydropyran added slowly to the well-stirred Grignard reagent prepared from *sec.*-butyl bromide (205 g., 1·5 mols.) and magnesium (36 g.) in dry ether (250 ml.). When one-fifth of the dichlorotetrahydropyran remained to be added solid separated and stirring became impossible, so that the remainder was added with vigorous shaking. Next day the product was isolated as described previously. Distillation of the product gave a considerable lower-boiling fraction (17·5 g.), b. p. <60°/15 mm., n_D^{20} 1·4389, followed by the crude mixed cis–trans-(±)-2-sec.-*butyl*-3-*chlorotetrahydropyrans* (81 g.), b. p. 60—94°/15 mm. On redistillation a portion of the main fraction had b. p. 86—88°/17 mm., n_D^{20} 1·4594 (Found : Cl, 20·6. $C_9H_{17}OCl$ requires Cl, 20·1%). On the assumption that the lower-boiling fraction eliminated at the next stage was present in this crude product, the yield was only 37% (on the dihydropyran), noticeably lower than with the isomeric primary bromide (Crombie and Harper, *loc. cit.*).

(±)-trans-6-*Methyloct*-4-*en*-1-*ol.*—By the procedure used for the ring scission of 3-chloro-2-methyltetrahydropyran (Crombie and Harper, *loc. cit.*) the crude mixed *cis–trans*-(±)-2-*sec.*-butyl-3-chlorotetrahydropyrans (76 g.) were added dropwise to a stirred suspension of powdered sodium (22 g.) in dry ether (200 ml.). Next day the product was isolated and distilled. to give a fraction (15 g.), b. p. 52—80°/10 mm., n_D^{20} 1·4363 (which from its odour and refractive index was probably the lower-boiling impurity not eliminated at the previous stage), followed by an intermediate fraction (6·5 g.), b. p. 80—94°/10 mm., n_D^{20} 1·4416, and then pure (±)-trans-6-*methyloct*-4-*en*-1-*ol* (42 g., 85% on pure alkylchlorotetrahydropyran), b. p. 94—95°/10 mm., n_D^{20} 1·4463 (Found : C, 75·4; H, 12·65. $C_9H_{18}O$ requires C, 76·0; H, 12·75%). The 4-*diphenylylurethane* crystallised from light petroleum (b. p. 80—100°) in prisms, m. p. 85·5° (Found : C, 78·55; H, 8·0; N, 4·2. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·05; N, 4·15%).

(±)-6-*Methyloctan*-1-*ol.*—(±)-*trans*-6-Methyloct-4-en-1-ol (22·7 g.) was hydrogenated without a solvent in the presence of Raney nickel (*ca.* 1 g., damp with ethanol) until absorption of hydrogen ceased (uptake : 3·64 l. at N.T.P. Calc. for 1 $\models$ 3·57 l.). Filter cel was added and the catalyst filtered off and rinsed with ether. Distillation of the filtrate gave (±)-6-methyloctan-1-ol (22·3 g., 95%), b. p. 112—114°/23 mm., n_D^{0} 1·4350 (Found : C, 74·0; H, 13·35. Calc. for $C_9H_{20}O$: C, 74·9; H, 13·95%). The 4-*diphenylylurethane* formed crystals, m. p. 99·5°, of ill-defined shape from light petroleum (b. p. 80—100°) (Found : C, 77·7; H, 8·45; N, 4·3. $C_{22}H_{29}O_2N$ requires C, 77·8; H, 8·6; N, 4·15%).

(±)-6-*Methyloctanoic Acid.*—(±)-6-Methyloctanol (6·0 g.) was dispersed in a cold solution of sulphuric acid (12·0 g.) in water (80 ml.) by vigorous stirring, and powdered potassium permanganate (9·0 g.) was added as fast as it was reduced, whilst the temperature was kept below 25°. Sufficient solid sodium hydrogen sulphite was then added to dissolve the manganese dioxide, and the solution thoroughly extracted with ether. The ethereal extracts were extracted with 20% sodium hydroxide. This alkaline extract was covered with light petroleum (b. p. 40—60°), and the acid liberated by acidification (Congo-red) with 30% sulphuric acid. Evaporation and distillation gave pure (±)-6-methyloctanoic acid (4·30 g., 66%), b. p. 148—150°/23 mm., n_D^{20} 1·4337 (Found : C, 68·4; H, 11·25. Calc. for $C_9H_{18}O_2$: C, 68·3; H, 11·45%). The amide, prepared by treatment of the acid chloride with aqueous ammonia (*d* 0·880), crystallised as plates, m. p. 91°, from ether–light petroleum (b. p. 40—60°). This acid was further characterised as the p-*bromophenacyl* ester, plates (from aqueous ethanol), m. p. 57—58° (Found : C, 57·65; H, 6·55. $C_{17}H_{23}O_3Br$ requires C, 57·45; H, 6·5%), and as the S-*benzylthiuronium* salt, plates (from aqueous ethanol), m. p. 150·5° (Found : C, 63·3; H, 8·55. $C_{17}H_{28}O_2N_2S$ requires C, 62·95; H, 8·7%).

(+)-2-*Methylbutyl Bromide.*—(−)-2-Methylbutanol, isolated from fusel oil by fractional distillation through a many-plate column, had α_D^{18} −9·44° (*l*, 2), which on the assumption of $d_4^{18} = 0{\cdot}818$ gives $[\alpha]_D^{18}$ −5·77°. Marckwald and McKenzie (*Ber.*, 1901, **34**, 485) recorded $[\alpha]_D^{20}$ −5·90° for pure (−)-2-methylbutanol isolated by fractional crystallisation of the 3-nitrophthalate, Marckwald (*ibid.*, 1902, **35**, 1595) recorded $[\alpha]_D$ −5·82° for pure alcohol obtained by fractional crystallisation of the barium alkyl sulphate, and Whitmore and Olewine (*J. Amer. Chem. Soc.*, 1938, **60**, 2569) have recorded $[\alpha]_D^{28}$ −6·04° for alcohol isolated by fractional distillation (100-plate column). We therefore regard this material as substantially optically pure ($\nless$98%) and are particularly indebted to Drs. M. P. Balfe and J. Kenyon for procuring it for us.

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* We are indebted to the Editor for the interest he has shown and the help he has given in the elucidation of this stereochemical problem.

Phosphorus tribromide (18·5 g.) was added slowly to a mixture of the above (−)-2-methylbutanol (15·0 g.) and pyridine (4·65 g.) kept at 0°. After a further 2 hours the crude bromide (24·2 g.) was isolated by distillation at 300 mm., heating being discontinued when the orange residue in the flask seethed. The distillate was diluted with light petroleum (b. p. 40—60°) and washed successively with 5% sodium hydroxide, 10% sulphuric acid, concentrated sulphuric acid, and water. After drying ($CaCl_2$), distillation gave (+)-2-methylbutyl bromide (17·0 g., 66%), b. p. 118—120°, n_D^{20} 1·4552, $[\alpha]_D^{20}$ +5·81° (*c*, 4·8 in chloroform) (Found: C, 39·75; H, 7·35; Br, 52·9. Calc. for $C_5H_{11}Br$: C, 40·05; H, 7·35; Br, 53·3%). Whitmore and Olewine (*ibid.*, p. 2570) isolated only a 29% yield, by a similar procedure, of bromide, n_D^{20} 1·4450.

"*Active*" 3-*Chloro*-2-2′-*methylbutyltetrahydrofuran*—By the procedure used for 3-chloro-2-methyltetrahydrofuran (Crombie and Harper, *J.*, 1950, 1714) freshly distilled 2 : 3-dichlorotetrahydrofuran (5·5 g., 1·0 ml.) was diluted with ether (5 ml.) and added slowly with stirring to the Grignard reagent prepared from magnesium (1·08 g.) and (+)-2-methylbutyl bromide (6·8 g., 1·15 mols.) in dry ether (25 ml.). After brief refluxing the product was isolated as described previously. Distillation eliminated a forerun (1·5 g.), b. p. 40—74°/21 mm., n_D^{20} 1·4280, and then gave mixed "active" cis–trans-3-*chloro*-2-2′-*methylbutyltetrahydrofuran* (3·56 g., 52%), b. p. 104—110°/21 mm., n_D^{20} 1·4580, which was used for the next stage without further purification. In another experiment, however, on redistillation the product had b. p. 85—90°/11 mm., n_D^{20} 1·4600 (Found: Cl, 19·6. $C_9H_{17}OCl$ requires Cl, 20·05%).

"*Active*" 6-*Methyloct*-3-*en*-1-*ol*.—By the procedure used for the ring scission of 2-*sec.*-butyl-3-chlorotetrahydropyran, the mixed "active" *cis–trans*-3-chloro-2-2′-methylbutyltetrahydrofuran (3·56 g.) was added to powdered sodium (1·05 g.) suspended in dry ether (10 ml.). Isolation of the product as already described gave "active" cis–trans-6-*methyloct*-3-*en*-1-*ol* (2·22 g., 78%), b. p. 91—92°/10 mm., 109—110°/22 mm., n_D^{20} 1·4493 (Found: C, 75·8; H, 12·75. $C_9H_{18}O$ requires C, 76·0; H, 12·75%).

(+)-6-*Methyloctan*-1-*ol*.—The above 6-methyloct-3-en-1-ol (2·12 g.) was hydrogenated without a solvent over a platinum oxide catalyst (100 mg.) (uptake: 326 ml. at N.T.P. Calc. for 1⊧ 334 ml.). Isolation as described for the (±)-isomer gave (+)-6-*methyloctanol* (1·90 g., 89%), b. p. 111—113°/22 mm., n_D^{20} 1·4350, $[\alpha]_D^{16}$ +7·21° (*c*, 6·4 in chloroform) (Found: C, 75·0; H, 13·9. $C_9H_{20}O$ requires C, 74·9; H, 13·95%). The 4-*diphenylylurethane* had m. p. 100° (Found: C, 77·95; H, 8·5; N, 4·05. $C_{22}H_{29}O_2N$ requires C, 77·8; H, 8·6; N, 4·15%).

In another reduction of 6-methyloct-3-en-1-ol (2·59 g.) with palladium on barium sulphate (150 mg.; 5% Pd) in ether, hydrogenation was continued overnight until there was no further uptake (not measured). The product was heterogeneous and on distillation gave the fractions: (i) b. p. 32—42°/10 mm., n_D^{20} 1·4080 (610 mg.); (ii) b. p. 42—96°/10 mm., n_D^{20} 1·4350 (530 mg.); and (iii) b. p. 96°/10 mm., n_D^{20} 1·4355 (910 mg.). Redistillation of (ii) and (iii) gave pure (+)-6-methyloctanol, b. p. 97°/11 mm., n_D^{20} 1·4358. Redistillation of (i) gave (+)-3-methyloctane, b. p. 144°/760 mm. (Emich method), n_D^{20} 1·4081, $[\alpha]_{5461}^{19}$ +8·39°, $[\alpha]_{5896}^{19}$ +7·54° (*c*, 9·8 in chloroform) (Found: C, 83·95; H, 15·4. Calc. for C_9H_{20}: C, 84·3; H, 15·7%).

(+)-6-*Methyloctanoic Acid*.—(+)-6-Methyloctanol (1·0 g.) was oxidised with potassium permanganate (1·5 g.) in 20% sulphuric acid (15 ml.) as described for the (±)-isomer. Distillation of the product gave (+)-6-methyloctanoic acid (660 mg., 60%), b. p. 148—149°/21 mm., n_D^{20} 1·4330, $[\alpha]_{5461}^{19}$ +8·9°, $[\alpha]_{5896}^{19}$ +7·9° (*c*, 10·2 in ether). This acid was characterised as the amide, m. p. 90—91°, as the p-*bromophenacyl* ester, plates (from aqueous ethanol), m. p. 58—59° (Found: C, 57·8; H, 6·6. $C_{17}H_{23}O_3Br$ requires C, 57·45; H, 6·5%), and as the S-*benzylthiuronium* salt, glistening plates (from aqueous ethanol), m. p. 149·5° (Found: C, 63·0; H, 8·7. $C_{17}H_{28}O_2N_2S$ requires C, 62·95; H, 8·7%).

C_9 *Acid Derived from the Polymyxins*.—The sample of slightly impure naturally derived acid (0·2 ml.) was pale brown and had an odour somewhat different odour to that of the synthetic acid. It was characterised as the *p*-bromophenacyl ester, plates (from aqueous ethanol), m. p. 57·0—57·5° [mixed m. p. with the corresponding derivative of the synthetic (+)-acid, 57—58°], and as the *S*-benzylthiuronium salt, glistening plates (from aqueous ethanol), m. p. 148—149° [mixed m. p. with the corresponding derivative of the synthetic (+)-acid, 149·5°].

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