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The Monomethyldecoic Acids

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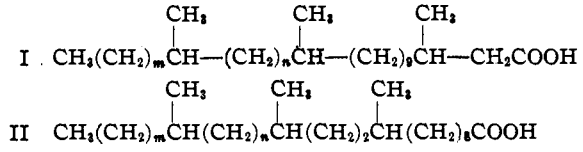
Phthioic acid, an optically active, saturated monobasic acid, $C_{26}H_{52}O_2$, isomeric with cerotic acid, was first isolated by Anderson.[1] Upon oxidation he isolated a C_{11}-acid, not *n*-undecoic acid, which he characterized as the *p*-bromophenacyl ester and tribromoanilide. Wagner-Jauregg,[2] by use of the Kuhn–Roth method, showed that there were three or four methyl groups on the chain; he also isolated azelaic acid. These results indicated that phthioic acid was probably a branched, long-chain acid with methyl groups as side chains. If this assumption is correct, only two structures can be written (where $m + n = 8$)



Of these I is preferred because of the observed high molecular rotation, which indicates the proximity of one methyl to the carboxyl group.[3] Structure I is in accord with the facts cited. The problem thus resolves itself into the identification of the C_{11}-acid.

The synthesis of the monomethyldecoic acids was undertaken. The 2-methyl,[4] 4-methyl,[5] 5-methyl,[6] and 9-methyl[7] decoic acids have been described in the literature, the 2- and 5-acids being optically active, but neither of the pertinent derivatives was made. Therefore, these acids, the 3- and 6-methyl isomers, and the reference compounds were all synthesized. It seemed obvious (see melting points in Table I) that the 6-methyldecoic acid was the C_{11}-acid isolated by Anderson, even though the synthetic acids are *dl*, whereas his was probably *d* or *l*.

At this point an excellent paper by Polgar and Robinson[8] appeared in which is reported not only the synthesis of the 3-, 4-, 5-, 6-, and 7-methyldecoic acids, but also the synthesis of a C_{26}-acid corresponding to formula I in which $m = 3$ and $n = 5$. The C_{11}-acid was identified as either the 5- or 6-methyldecoic acid, the latter being preferred. The C_{26}-acid exhibited all the characteristic properties of phthioic acid.

Since our work has been anticipated by Polgar and Robinson,[8] we merely wish to record our methods of syntheses of the methyldecoic acids, together with the melting points of the *p*-bromophenacyl esters and tribromoanilides. The latter are summarized in the table, with Polgar and Robinson's data (in parentheses) being included for comparison. The methods of syntheses of the acids differ in every instance from those previously recorded and are usually superior.

(1) (a) Anderson, *J. Biol. Chem.*, **85**, 77 (1929–1930); (b) **112**, 759 (1936).

(2) Wagner-Jauregg, *Z. physiol. Chem.*, **247**, 135 (1937).

(3) Levene, Rothen and Marker, *J. Chem. Phys.*, **1**, 662 (1933).

(4) Levene and Kuna, *J. Biol. Chem.*, **110**, 323 (1935).

(5) Ruzicka and Staudinger, *Helv. Chim. Acta*, **7**, 245 (1924).

(6) Levene and Marker, *J. Biol. Chem.*, **95**, 153 (1932).

(7) Levene and Allen, *ibid.*, **27**, 433 (1916).

(8) Polgar and Robinson, *J. Chem. Soc.*, 389 (1945).

Experimental

2-Methyldecoic Acid.[9]—This was prepared from sodioethyl methylmalonate and excess octyl chloride in butanol solution followed by hydrolysis and decarboxylation. The sodium was dissolved in butanol, the ester and the excess octyl chloride were added, and the mixture was heated with stirring for several hours. The butanol was then removed by distillation until the temperature of the vapor reached 150°. The residue was then heated under reflux for four hours. The ester was isolated in the usual manner; the subsequent hydrolysis showed that there had been some ester interchange during the reaction. The over-all yield was 65%. The 2-methyldecoic acid boiled under 4 mm. at 135–137°. The *d*-compound has been mentioned by Levene and Kuna[4] but its preparation is not described. The *p*-bromophenacyl ester and tribromoanilide were prepared in the usual way. Their melting points and analyses are recorded in Table I.

3-Methyldecoic Acid.—Methylheptylcarbinol (54 g., obtained from octaldehyde by the Grignard reaction with methylmagnesium iodide), b. p. 192–194°, $n^{24}D$ 1.4300, was converted with phosphorus tribromide to 2-bromononane (65 g., 80%; b. p. 102–103° (22 mm.), $n^{25}D$ 1.4529). By use of the malonic ester synthesis the latter was converted to ethyl (1-methyloctyl)-malonate which was isolated and hydrolyzed with alcoholic potassium hydroxide without purification. The 1-methyloctylmalonic acid (m. p. 76°) obtained on acidification was decarboxylated to give 3-methyldecoic acid (30 g.), b. p. 155–157° (12 mm.). Polgar and Robinson[8] give 153–154° (14 mm.).

4-Methyldecoic Acid.—Methylhexylcarbinol was converted to the bromide by treatment with phosphorus tribromide in the usual way. The bromide was used in a malonic ester synthesis and the resulting ester hydrolyzed and decarboxylated to 3-methylpelargonic acid (b. p. 109–111° (3 mm.)); Polgar and Robinson[8] give 136–137° (10 mm.). The acid was converted to the ethyl ester, b. p. 104–106° (8 mm.), and the latter (72 g.) reduced with sodium (65 g.) and ethyl alcohol (700 cc.) to 3-methylnonanol-1 (39 g., 68%; b. p. 105–106° (8 mm.); Polgar and Robinson[8] give 117–118° (14 mm.). This was converted successively to the bromide (41 g., 75%; b. p. 98–99° (8 mm.)) and the nitrile (27 g., 82%; b. p. 113–115° (8 mm.)), and the latter was hydrolyzed with 20% potassium hydroxide to 4-methyldecoic acid (16 g., 54%; b. p. 152–153° (10 mm.)). Polgar and Robinson[8] give b. p. 98–99° (10 mm.) for the bromide, 121–122° (13 mm.) for the nitrile, and 150–151° (10 mm.) for the acid. Ruzicka and Staudinger[5] give b. p. 150–152° (12 mm.) for 4-methyldecoic acid.

5-Methyldecoic Acid.—Ethyl *s*-heptylmalonate, prepared from *s*-heptyl bromide and ethyl malonate, was converted in the usual manner to 3-methyloctoic (caprylic) acid, b. p. 96–98° (2 mm.). The ethyl ester (50 g., b. p. 105–106° (17 mm.)) of this acid was reduced with sodium (48 g.) and alcohol (450 cc.) to 3-methyl-octanol-1 (28 g., 72%; b. p. 92–95° (8 mm.)). This alcohol was converted to the bromide (31 g., 78%; b. p. 103–104° (21 mm.)) with phosphorus tribromide. The malonic ester synthesis

(9) The carboxyl group is numbered 1.

TABLE I

C_{11}-acid	Derivatives: *p*-Bromophenacyl ester M. p., °C.	*Anal.* for Br (calcd. 20.9), %	Tribromoanilide M. p., °C.	*Anal.* for Br (calcd. 48.2), %
2-Methyldecoic	66-67	20.8	110-110.5	48.0
3-Methyldecoic	39-40 (39)	20.8	117-117.5 (111.5)	48.0
4-Methyldecoic	45-46 (42)	21.0	96-97 (89.5)	48.4
5-Methyldecoic	48-49 (50)	20.8	96-96.5 (95.5)	48.2
6-Methyldecoic	51-51.5 (51)	21.2	104.5 (104.5)	48.6
7-Methyldecoic	(56)		(118.0)	
9-Methyldecoic	65-65.5	20.8	124.5	48.2
Undecoic	69	20.8	128-128.5	47.9
Oxidation product of phthioic acid.[1b]	49-50		111	

was then repeated on the bromide (31 g.) to give ethyl (3-methyloctyl)-malonate which was hydrolyzed and decarboxylated to 5-methyldecoic acid (8 g., 30%; b. p. 117-119° (2 mm.); Polgar and Robinson[8] using a different synthesis give b. p. 167-168° (20 mm.); Levene and Marker[8] give b. p. 135°(3 mm.) for the *l*-compound).

6-Methyldecoic Acid.—Butylmagnesium bromide was treated with ethyl levulinate, following the procedure of Cason, *et al.*,[10] to give α-methyl-α-*n*-butylbutyrolactone, (b. p. 120-123° (15 mm.)), which was converted by thionyl chloride in dry benzene, followed by treatment with hydrogen chloride and ethyl alcohol, to ethyl 4-methyl-3-octenoate (b. p. 113-115° (17 mm.)).[11] This unsaturated ester (41 g.) was reduced with sodium (40 g.) and ethyl alcohol (350 cc.) to 4-methyl-3-octenol-1 (22 g., 68%; b. p. 103-106° (17 mm.)) and the unsaturated alcohol (20 g.) hydrogenated in alcoholic solution with platinum oxide to 4 methyloctanol-1 (16 g., 80%; b. p. 103-106° (17 mm.)). The alcohol (15 g.) was converted to 1-bromo-4-methyloctane (15 g., 70%; b. p. 93-95° (16 mm.); $n^{30}D$ 1.4495; Levene and Marker[12] give b. p. 95° (17 mm.); $n^{25}D$ 1.4540). The bromide (15 g.) was converted to ethyl (4-methyloctyl)-malonate by the usual procedure and the hydrolysis carried out without isolation of the ester. The resulting alkaline solution was extracted with ether to remove any neutral products and then acidified. The 4-methyloctylmalonic acid was separated from the acid solution by extraction, and decarboxylated to 6-methyldecoic acid (10 g., 75%; b. p. 160-164° (17 mm.); $n^{21}D$ 1.4393; Polgar and Robinson[8] give b. p. 164-165° (18 mm.); $n^{20}D$ 1.4403).

9-Methyldecoic Acid.—The Grignard reagent from isoamyl bromide (137 g.) and magnesium (22 g.) in ether (600 cc.) was treated with dry cadmium chloride (89 g.). The ether was removed by distillation and replaced by dry benzene (350 cc.) and the resulting mixture treated with δ-carbomethoxyvaleryl chloride (130 g.)[13] in benzene (250 cc.). After the mixture was refluxed for an hour, it was decomposed with dilute hydrochloric acid and the methyl 6-keto-9-methyldecoate isolated and hydrolyzed to 6-keto-9-methyldecoic acid (65 g., m. p. about 34°). The semicarbazone (m. p. 123°) was prepared in the usual manner.

Anal. Calcd. for $C_{12}H_{23}O_3N_3$: N, 16.3. Found: N, 16.0.

The keto acid (48 g.) was reduced by the Clemmensen method as modified by Schneider and Spielman[14] to 9-methyldecoic acid (32 g., 71%; b. p. 122-124° (2 mm.); Levene and Allen[7] give b. p. 174-175° (23 mm.)). The use of cadmium alkyls for the preparation of simple ketones was introduced by Gilman[15] and developed by Cason.[16]

The *p*-bromophenacyl ester and tribromoanilide derivatives of all the above acids were prepared. Their melting points and analyses are shown in Table I.

Summary

1. The 2-, 3-, 4-, 5-, 6- and 9-methyldecoic acids, and their *p*-bromophenacyl esters and tribromoanilides, have been prepared.

2. In most instances, the syntheses differ somewhat from those previously recorded.

3. The possible relationship of 6-methyldecoic acid to the C_{11}-oxidation product of phthioic acid is pointed out.

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(10) Cason, Adams, Bennett and Register, THIS JOURNAL, **66**, 1764 (1944).

(11) This compound was prepared by Miss Eleanor R. Webster, of the Kodak Research Laboratories.

(12) Levene and Marker, *J. Biol. Chem.*, **91**, 77 (1931).

(13) Morgan and Walton, *J. Chem. Soc.*, 91 (1933).

(14) Schneider and Spielman, *J. Biol. Chem.*, **142**, 345 (1942).

(15) Gilman, *Rec. trav. chim.*, **55**, 518 (1936).

(16) Cason, *J. Org. Chem.*, **6**, 462 (1941); THIS JOURNAL, **64**, 1106 (1942).