37. *The Preparation of Phenyl* (*α-Ethyl-α*-n-*decyl*)-n-*tridecyl Ketone* (*ω-Ethyl-ω*-n-*decyl-ω*-n-*dodecylacetophenone*) *and Related Substances.*

By C. L. CARTER and S. N. SLATER.

The preparation of ethyldecyldodecylacetophenone and a number of trialkylacetic acids by Haller's sodamide method is described. A small alkyl group is introduced into the aliphatic chain of one of the higher homologues of acetophenone, and the product alkylated with a long-chain alkyl iodide.

WITHIN recent years the isolation of physiologically active fatty acids containing branched chains has stimulated work in this field. In particular the suggestion that phthioic acid, isolated by Anderson and co-workers from *M. Tuberculosis*, might be a trialkylacetic acid (Stenhagen and Stallberg, *J. Biol. Chem.*, **1941**, **139**, 345) has led to the exploration of methods for preparing such substances (see especially Robinson *et al.*, *J.*, **1942**, 488; **1943**, 615; **1944**, 152). One of the few earlier methods was that of Haller and Bauer (*Ann. Chim.*, 1914, **1**, 5) in which a phenyl alkyl ketone is alkylated in the α-position by means of sodamide and an alkyl iodide to give an ω-trialkylacetophenone which is then decomposed by sodamide into a trialkylacetamide, from which the acid is obtained by nitrous acid.

Haller's method gives good yields of the simpler acids of this series, but difficulty has been experienced in preparing the higher members. Thus Birch and Robinson (*J.*, 1942, 490) were unable to prepare ω-methyl-ωω-di-*n*-decylacetophenone by methylation of ωω-di-*n*-decylacetophenone and state that " all attempts to alkylate acetophenones substituted in the ω-position by two long-chain alkyls were unsuccessful." Buu-Hoï and Cagniant (*Ber.*, 1943, **76**, 689) attempted to prepare ω-ethyl-ω-*n*-decylacetophenone by condensation of α-ethyl-lauryl chloride with benzene and aluminium chloride but obtained a viscous inseparable mixture, richer in carbon, of several ketone-like compounds. In preparing such ω-trialkylacetophenones it would appear to be more reasonable to introduce a small alkyl group into one of the higher homologues of acetophenone and then alkylate with a long-chain alkyl iodide. By this method, *phenyl (α-ethyl-α-*n*-decyl)-*n*-tridecyl ketone (ω-ethyl-ω-*n*-decyl-ω-*n*-dodecylacetophenone)* was prepared without difficulty by acting upon *phenyl (α-ethyl)-*n*-undecyl ketone (ω-ethyl-ω-*n*-decylacetophenone)* with sodamide and *n*-dodecyl iodide. The corresponding acid, however, was not obtained, except possibly in small amount in an impure state, by heating the ketone with sodamide and treating the product with nitrous acid. The main acidic product isolated was benzoic acid.

In order to gain some idea of the scope of the Haller method a number of lower trialkylacetic acids* were prepared. One alkyl group was restricted to one or two carbon atoms, and the other two were successively lengthened. No difficulty was experienced in preparing all the acids of this series up to $C_{10}H_{20}O_2$. In the $C_{11}H_{22}O_2$ group the formation of benzoic acid instead of the required fatty acid became noticeable. Thus α-methyl-α-ethyl-*n*-octoic acid was not obtained pure, and an attempted preparation of αα-diethyl-*n*-heptoic acid yielded mainly benzoic acid. On the other hand α-methyl-α-butyl-*n*-hexoic acid and *α-ethyl-α-propyl-*n*-hexoic acid* were prepared satisfactorily, and Grunfeld (*Ann. Chim.*, 1933, **20**, 304) has synthesised αα-dimethyl-*n*-nonoic acid by Haller's method. In the $C_{12}H_{24}O_2$ group, αα-dimethyl-*n*-decoic acid was prepared, but much benzoic acid was formed in the preparation of αα-diethyl-*n*-octoic acid, and an attempted preparation of α-ethyl-α-propyl-*n*-heptoic acid gave mainly benzoic acid. In the $C_{13}H_{26}O_2$ group, *α-methyl-α-butyl-*n*-octoic acid* and *αα-diethyl-*n*-nonoic acid* were prepared, but the attempted preparation of α-ethyl-α-propyl-*n*-octoic acid and α-ethyl-α-butyl-*n*-heptoic acid gave mainly benzoic acid. In the $C_{14}H_{28}O_2$ group, αα-dimethyl-*n*-dodecoic acid has been prepared (Haller and Bauer, *loc. cit.*; Birch and Robinson, *loc. cit.*), but an attempted preparation of α-ethyl-α-butyl-*n*-octoic acid gave mainly benzoic acid. In the $C_{15}H_{30}O_2$ group, *α-ethyl-α-butyl-*n*-nonoic acid*, accompanied by much benzoic acid, was obtained, and the main product of an attempted preparation of α-ethyl-α-amyl-*n*-octoic acid was benzoic acid. In the $C_{16}H_{32}O_2$ group, a small yield of *α-ethyl-α-butyl-*n*-decoic acid* was obtained. In the $C_{17}H_{34}O_2$ group, attempted preparations of α-methyl-α-butyl-*n*-dodecoic acid and α-ethyl-α-amyl-*n*-decoic acid gave mainly benzoic acid. A similar result was obtained in the case of α-ethyl-α-butyl-*n*-dodecoic acid in the $C_{18}H_{36}O_2$ group. Higher in the series, αα-dimethyl-*n*-tetradecoic acid (Buu-Hoï and Cagniant, *Z. physiol. Chem.*, 1943, **279**, 76), αα-dimethylpalmitic acid (*idem, ibid.*), αα-dimethylstearic acid (Birch and Robinson, *loc. cit.*), and αα-dimethylarachidic acid (Buu-Hoï and Cagniant, *loc. cit.*) have been prepared.

It appears therefore that while dimethylalkylacetic acids can be successfully prepared, even when the alkyl group attains to a length of eighteen carbon atoms, the Haller method may fail with acids of much lower molecular weight but greater complexity as measured by the length of all three substituent groups.

EXPERIMENTAL.

Haller's preparations of dimethylethylacetic acid (αα-dimethyl-*n*-butyric acid), b. p. 184—186° (184—185°), dimethylpropylacetic acid (αα-dimethyl-*n*-valeric acid), b. p. 199—205° (199—200°; Tafel and Emmert, *Z. Elektrochem.*, 1911, **17**, 571, 200—205°), methyldiethylacetic acid (α-methyl-α-ethyl-*n*-butyric acid), b. p. 202—206° (203—204°; Schdanow, *Annalen*, 1877, **185**, 120, 207—208°), methylethylpropylacetic acid (α-methyl-α-ethyl-*n*-valeric acid), b. p. 215—224° (215—220°), and triethylacetic acid, b. p. 211—215° (220—222°) were repeated. Except where otherwise indicated the figures in parenthesis are the b. ps. given by Haller.

*αα-Dimethyl-*n*-hexoic acid.* This and the following acid have not previously been made by Haller's method. Propiophenone (27 g.) was successively methylated (sodamide, 8 g., methyl iodide, 29 g., in benzene) and butylated (sodamide, 8 g., butyl iodide, 38 g.) and worked up to give a product, b. p. 140—153°/28 mm. (total distillate collected, 20·5 g.). Treated with sodamide (6·0 g.) in boiling benzene this gave the amide (8·0 g.), b. p. 140—145°, m. p. (from benzene–ligroin) 88—89°. The amide in concentrated sulphuric acid was cooled in a freezing mixture while excess of a cold, saturated solution of sodium nitrite was slowly stirred in; the product was warmed, diluted with water, and extracted with ether. The ethereal extract was shaken with three successive portions of 2N-sodium hydroxide and the combined alkaline extracts acidified. The liberated acid was extracted with chloroform and distilled (1·6 g., b. p. 210—218°).

*αα-Dimethyl-*n*-heptoic acid.* Phenyl *n*-hexyl ketone (14 g.) was methylated twice to phenyl αα-dimethylhexyl ketone (15 g.), b. p. 148—150°/18 mm., which was split with sodamide to the amide (8 g.), b. p. 147—149°/19 mm., which solidified readily. A sample crystallised from benzene had m. p. 101°. The amide (7 g.) was converted to the acid (3·0 g.), b. p. 124—127°/21 mm., together with a small residue of benzoic acid (Leers, *Bull. Soc. chim.*, 1926, **39**, 651, gives 101—102° as the m. p. of the amide, but the b. p. given for the acid, 130°/12 mm., appears to be too high for a C_9 trialkylacetic acid judged by the b. ps. of the other isomers).

*α-Methyl-α-ethyl-*n*-hexoic Acid.*—Phenyl *sec.*-butyl ketone (9·7 g.) was alkylated with sodamide (2·4 g.) and butyl iodide (12 g.) and the total distillate (11·1 g.), b. p. 132—152°/18 mm., refluxed with sodamide in benzene to give the crude amide (7·8 g.), b. p. 124—144°/18 mm. On treatment with nitrous acid the *acid* (1·9 g.) was obtained, b. p. 123—125°/22 mm. (Found: C, 69·0; H, 11·4. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

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* These have been systematically named. The authors emphasised that the compounds are trialkyl substituted acetic acids; systematically, they are αα-di-*n*-alkyl substituted acids of the *n*-$C_nH_{2n+1}CO_2H$ series. (Temp. Editor.)

*α-Methyl-α-propyl-*n*-valeric acid.* This was made by Haller's method. Propiophenone was treated twice with sodamide and propyl iodide and the product, b. p. 144—152°/23 mm., split with sodamide to give the crude amide, b. p. 145—153°/25 mm. On treatment with nitrous acid the required acid was obtained, b. p. 126—129°/29 mm. Meerwein (*Annalen*, 1919, **419**, 141) gives b. p. 118—122°/14 mm.

*αα-Diethyl-*n*-valeric Acid.*—Butyrophenone was successively ethylated and propylated and the product (34·8 g.), b. p. 147—155°/27 mm., split with sodamide to give the crude amide (10·5 g.), b. p. 144—153°/26 mm. On treatment with nitrous acid the required *acid* (3·9 g.) was obtained, b. p. 128°/29 mm. (Found : C, 67·6; H, 11·1. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

*αα-Dimethyl-*n*-octoic Acid.*—Phenyl *n*-heptyl ketone (30 g.) was methylated twice and the product (14 g.), b. p. 165°/17 mm., split with sodamide to give the amide (8·8 g.), b. p. 162°/22 mm., which solidified on cooling; it had m. p. 103—104° (from benzene). Treatment of the amide (6 g.) with nitrous acid gave the required *acid* (3·0 g.), b. p. 135—138°/21 mm. (Found : C, 69·9; H, 11·9. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-ethyl-*n*-heptoic Acid.*—Phenyl *n*-hexyl ketone (14 g.) was successively methylated and ethylated and the product (14 g.), b. p. 179—182°/26 mm., split with sodamide to give the crude amide (8 g.), b. p. 147—153°/19 mm. On treatment with nitrous acid this furnished the required *acid* (2·9 g.), b. p. 131—135°/21 mm. (Found : C, 69·1; H, 11·1. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-propyl-*n*-hexoic Acid.*—Phenyl *n*-amyl ketone (35 g.) was successively methylated and propylated and the product (37 g.), b. p. 149—155°/18 mm., split with sodamide to give the crude amide (25·7 g.), b. p. 145—152°/20 mm. On treatment with nitrous acid this furnished the required *acid* (2·8 g. from 10 g. of crude amide), b. p. 141—143°/29 mm. (Found : C, 69·4; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*αα-Diethyl-*n*-hexoic Acid.*—Butyrophenone (25 g.) was successively ethylated and butylated and the product (26·2 g.), b. p. 160—170°/29 mm., split with sodamide to give the crude amide (10 g.), b. p. 153—164°/26 mm. Treatment of this with nitrous acid gave the *acid* (2·4 g.), b. p. 137—141°/21 mm. On redistillation, it had b. p. 135°/25 mm. (Found : C, 69·4; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

α-Ethyl-α-propylvaleric Acid.—Butyrophenone (30 g.) was propylated twice and the product (37·9 g.), b. p. 155—164°/27 mm., split with sodamide to give the crude amide (13·2 g.), b. p. 153—162°/27 mm. When treated with nitrous acid this gave the required *acid* (4·3 g.), b. p. 138—144°/25 mm. On redistillation, it had b. p. 132°/22 mm. (Found: C, 69·3; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-ethyl-*n*-octoic Acid.*—Phenyl *n*-heptyl ketone (15 g.) was successively methylated and ethylated and the product (16 g.), b. p. 167—169°/21 mm., refluxed with sodamide (9 g.) in benzene giving a product (12·3 g.), b. p. 152—162°/18 mm., which partly solidified. Treatment with nitrous acid yielded a mixture of acids distilling over a fairly wide range. On standing the product partly crystallised. It was redistilled giving a liquid acid (2·6 g.), b. p., 135—140°/19 mm. A portion, b. p. 135—137°/19 mm., was collected for analysis (Found : C, 68·0; H, 8·9. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%).

*α-Methyl-α-butyl-*n*-hexoic acid.* This has not previously been made by Haller's method. Propiophenone (16 g.) was butylated twice and the product (21·3 g.), b. p. 156—168°/18 mm., split with sodamide to give the crude amide (9·3 g.), b. p. 163—169°/25 mm. When this was treated with nitrous acid the required acid (3·2 g.) was obtained, b. p. 144—147°/20 mm. On redistillation, it had b. p. 144°/22 mm. (Found : C, 70·5; H, 11·9. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%). Meerwein, *loc. cit.*, gives b. p. 158—159°/18 mm. which appears to be high.

*α-Ethyl-α-propyl-*n*-hexoic Acid.*—Butyrophenone (16 g.) was successively propylated and butylated and the product (14 g.), b. p. 149—162°/22 mm., split with sodamide to give the crude amide (8·7 g.), b. p. 142—160°/22 mm. On treatment with nitrous acid this gave the required *acid* (1·4 g.), b. p. 135—137°/22 mm. (Found : C, 70·1; H, 12·0. $C_{11}H_{22}O_2$ requires C, 71·0; H, 11·8%).

*αα-Dimethyl-*n*-decoic acid.* This has not previously been made by Haller's method. *iso*Butyrophenone was alkylated with sodamide and *n*-octyl iodide and the product, b. p. 190°/25 mm., split with sodamide to give the amide, b. p. 191—193·5°/25 mm. When this was treated with nitrous acid the required acid, b. p. 153—158°/19 mm., was obtained.

*Attempted preparation of αα-diethyl-*n*-octoic acid.* (*a*) Phenyl *n*-heptyl ketone (14 g.) was treated with sodamide (3 g.) and ethyl iodide (12 g.) and the product (14 g.), b. p. 157—162°/19 mm., subjected to the same treatment giving 11 g. of an oily ketone, b. p. 167—173°/17 mm. This was split with sodamide (8 g.) to yield the crude amide (9 g.), b. p. 167—169°/18 mm. Treatment with nitrous acid furnished a liquid acid (2·4 g.) having the expected b. p. (156—163°/18 mm., portion b. p. 160—162° collected for analysis), but satisfactory analytical figures were not obtained (Found : C, 68·7, 68·8; H, 11·2, 11·1%).

(*b*) Phenyl α-ethylpropyl ketone was treated with sodamide and *n*-hexyl iodide in the usual manner and the product, boiling over a wide range, was heated with sodamide in benzene to give a mixture of amides which with nitrous acid furnished a mixture of much benzoic acid and liquid fatty acids boiling over a wide range (up to 174°/24 mm.). The material distilling at 140—158° solidified on cooling, while that distilling at 158—174° contained a greater proportion of liquid acid. It was filtered and the small quantity of filtrate redistilled. Analysis of a sample of the middle portion of this distillate gave figures well removed from the theoretical (Found : C, 73·2; H, 10·5%).

*α-Methyl-α-butyl-*n*-octoic Acid.*—Phenyl *n*-heptyl ketone (15 g.) was successively methylated and butylated and the product (11 g.), b. p. 175—183°/17 mm., split with sodamide to give the amide (9 g.), b. p. 167—169°/18 mm. This was treated with nitrous acid to give the required *acid* (2·4 g.), b. p. 156—163°/18 mm. On redistillation, it had b. p. 160—162°/18 mm. (Found : C, 73·4; H, 12·3. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·2%).

*αα-Diethyl-*n*-nonoic Acid.*—Phenyl *n*-octyl ketone (12 g.) was ethylated twice and the product (11 g.), b. p. 175—185°/16 mm., split with sodamide to give the crude amide (8 g.), b. p. 180—185°/24 mm. This was treated with nitrous acid to furnish the required *acid* (1·9 g.), b. p. 158—163°/16 mm. (Found : C, 72·6; H, 12·2. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·2%).

*α-Ethyl-α-butyl-*n*-nonoic Acid.*—Phenyl *n*-octyl ketone (12 g.) was successively ethylated and butylated and the product (11 g.), b. p. mainly 190—195°/16 mm., refluxed with sodamide to give the crude amide (9 g.), b. p. mainly 175—182°/18 mm. When this was treated with nitrous acid a product was obtained which after distillation solidified in part and contained benzoic acid. It was redistilled and the required *acid* (1·4 g.) obtained as the fraction, b. p. 165—172°/16 mm. (Found : C, 74·1; H, 12·0. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%).

*α-Ethyl-α-butyl-*n*-decoic Acid.*—Phenyl *n*-amyl ketone (75 g.) was ethylated and the product (68 g.), b. p. 149—151°/19 mm., alkylated with sodamide (13·2 g.) and *n*-octyl iodide (82 g.) to give 50 g. of material, b. p. 204—210°/16 mm. This was refluxed with sodamide (20 g.) in xylene and the product worked up to furnish a small yield of an oil giving a positive test for nitrogen together with recovered material (29 g.). This was treated again in boiling xylene solution with sodamide to give an oil boiling over rather a wide range. All fractions gave a positive test for nitrogen and the total distillate was therefore treated with nitrous acid and worked up to give a small yield of *acid*, b. p. 175—195°/16 mm. This was redistilled and a portion of the middle distillate analysed (Found : C, 75·5; H, 12·3. $C_{16}H_{32}O_2$ requires C, 74·9; H, 12·6%).

*Phenyl (α-Ethyl-α-*n*-decyl)-*n*-tridecyl Ketone (Ethyl-*n*-decyl-*n*-dodecylacetophenone).*—Phenyl *n*-undecyl ketone (52 g.,)

b. p. 214—218°/24 mm., and sodamide (8 g.) were refluxed for 6 hours in benzene, and ethyl iodide (35 g.) added. After heating overnight the *phenyl* (*α-ethyl*)-n-*undecyl ketone* (*ethyl*-n-*decylacetophenone*) (47 g., b. p. mainly 211°/16 mm.) was obtained in the usual way (Found: C, 82·6; H, 11·5. $C_{20}H_{32}O$ requires C, 83·3; H, 11·1%). This ketone (47 g.) was treated with sodamide (6·5 g.) and *n*-dodecyl iodide (48·3 g.) in benzene to give *phenyl* (*α-ethyl-α*-n-*decyl*)-n-*tridecyl ketone* (*ethyl*-n-*decyl*-n-*dodecylacetophenone*) (33 g.), b. p. 240—252°/1 mm., and in a second preparation 240—246°/1 mm. A portion of the middle distillate was collected for analysis (Found: C, 84·4; H, 12·3. $C_{32}H_{56}O$ requires C, 84·2; H, 12·3%). Treatment of the ketone with sodamide gave a product boiling over a wide range (up to 285° under high vacuum), and interaction of this with nitrous acid yielded a mixture of benzoic and other acids from which a small amount of a liquid fatty acid was isolated whose composition approximated to that of the desired C_{26} acid (Found: C, 80·7; H, 11·7. Calc. for $C_{26}H_{52}O_2$: C, 78·8; H, 13·1%).

UNIVERSITY OF OTAGO.

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