143. *Synthetical Experiments relating to Carpaine. Part III. Some Derivatives of Tetrahydrofuran and Intermediates of the Aliphatic Series.*

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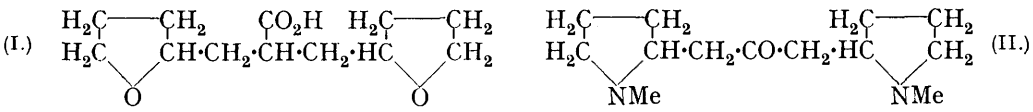
This interim report on a research in progress is now submitted because one of us has withdrawn from the investigation and also because the intermediates described may be found of value in other connections.

In view of the accessibility of tetrahydrofurfuryl alcohol experiments have been undertaken with the object of lengthening the side chain and so arriving at possible cyclic ether analogues of carpamic acid or one of its degradation products.

There was good reason to believe that the tetramethylene oxide system could be converted into the pyrrolidine group, relevant observations on the opening of the tetrahydrofuran ring being those of Hamonet (*Ann. Chim.*, 1918, **10**, 24), Paul (*Bull. Soc. chim.*, 1933, **53**, 417), and Starr and Hixon (*J. Amer. Chem. Soc.*, 1934, **56**, 1595) (cf. Hollins, "Synthesis of Nitrogen Ring Compounds," Benn, 1924, pp. 65 *et seq.*).

Tetrahydrofurfuryl chloride (Kirner, *J. Amer. Chem. Soc.*, 1930, **52**, 3251) is surprisingly inert towards such substances as potassium cyanide or ethyl sodioacetoacetate, and even tetrahydrofurfuryl bromide (Dox and Jones, *J. Amer. Chem. Soc.*, 1928, **50**, 2033; Gilman and Brown, *Iowa State Coll. J.*, 1931, **6**, 11; Paul, *loc. cit.*; Robinson and Hart Smith, J., 1936, 196) could not be condensed with the latter reagent in ether, alcohol, dioxan, benzene or toluene as solvent, with or without sodium iodide. Nevertheless, tetrahydrofurfuryl bromide enters into facile reaction with ethyl sodiomalonate in alcoholic solution and *ethyl tetrahydrofurfurylmalonate*, $(C_5H_9O)CH(CO_2Et)_2$, is obtained in good yield. The usual series of processes affords β-tetrahydrofurylpropionic acid, previously obtained by Adams and Kauffman (*J. Amer. Chem. Soc.*, 1923, **45**, 3042) by reduction of furylacrylic acid; the process now described is the more convenient. *Ethyl β-tetrahydrofurylpropionate* is readily reduced by the Bouveault–Blanc method to 3-tetrahydrofurylpropan-1-ol, previously obtained by catalytic reduction of furylacraldehyde (Bray and Adams, *J. Amer. Chem. Soc.*, 1927, **49**, 2105). The alcohol is convertible into *γ-tetrahydrofurylpropyl bromide*, $(C_4H_7O)CH_2{\cdot}CH_2{\cdot}CH_2Br$. Ethyl sodiotetrahydrofurfurylmalonate and tetrahydrofurfuryl bromide afford *ethyl bistetrahydrofurfurylmalonate*, which can be hydrolysed and decarboxylated to *ββ′-bistetrahydrofurylisobutyric acid* (I), a compound structurally related to cuskhygrine (II).



Although Paul (*Bull. Soc. chim.*, 1935, **55**, 747) has stated that tetrahydrofurfuryl bromide was not transformed into a nitrile by interaction with potassium cyanide at 150°, or in alcoholic solution, we have obtained fair results (47—52%) by prolonged refluxing of an aqueous alcoholic solution of the reactants. An alternative method is to make use of tetrahydrofurfuryl *p*-toluenesulphonate, obtained by Gilman and Brown (*loc. cit.*) as an oil and now crystallised. On hydrolysis of the *nitrile, tetrahydrofurylacetic acid*, $(C_4H_7O)CH_2{\cdot}CO_2H$, is produced and it may be noted that this substance must be prepared in this way because a satisfactory method of preparation of furylacetic acid has not yet come to light.

Details of a highly satisfactory method for the preparation of ethyl 2-furoylacetate are given in the experimental section. We hoped to condense the sodio-derivative of this ester with ω-halogeno-fatty acid esters and to apply similar methods to 2-pyrroylacetic ester. This led to a more prolonged investigation of the aliphatic intermediates than had been anticipated.

Ethyl ω-hydroxy-valerate, -hexoate, and -heptoate are obtainable by a modification of Baeyer and Villiger's process of oxidation of cyclic ketones by means of Caro's acid in the presence of alcohol (*Ber.*, 1899, **32**, 3625; 1900, **33**, 863; Robinson and Hart Smith, this vol., p. 371) and the hydroxyl groups of these esters have been replaced by chlorine and bromine. Careful attention to the conditions is requisite and when hydrogen bromide is used as the reagent there is even some dubiety in regard to the homogeneity of the product. Isomerisation may occur by way of an ethylene derivative and with this in mind we carried out the reaction in the case of ethyl 6-hydroxyhexoate in the presence of oxygen and a " peroxide " catalyst. This should have prevented isomerisation by the mechanism contemplated, because the olefin group would add the bromine terminally if it were formed (cf. Ashton and J. C. Smith, J., 1934, 435, 1308). In point of fact the ethyl bromoheptoate obtained in this way had a higher b. p. than that produced without this precaution and, as the primary bromide ought to have a higher b. p. than the secondary, we think that this and all similar reactions should be effected in the presence of oxygen and peroxide catalysts in order to obtain a homogeneous product.

By condensation of the appropriate bromo-esters with ethyl sodioacetoacetate, followed by hydrolysis, we have prepared 8-*ketononoic acid* and 9-ketodecoic acid. Godchot and Coquil (*Compt. rend.*, 1931, **192**, 962) state that 8-ketononoic acid is obtained by the oxidation of α-methyl*cyclo*octanone with permanganate, but they do not describe the acid (they give m. p. 116—117° for the semicarbazone; we find m. p. 136°). Van Romburgh (*Akad. Amsterdam Versl.*, 1911, **20**, 195) obtained 9-ketodecoic acid by the oxidation of 2-keto-Δ^{10}-undecene and the melting point is given as 49°, which tallies with our observation.

At this stage further results on the degradation of carpaine came to hand (Barger, Robinson, and Work, this vol., p. 711). One of the products is a hydroxy-acid, $C_{13}H_{26}(OH)\cdot CO_2H$, which most likely has the constitution of 9-hydroxy-9-methyltridecoic acid ($CO_2H = 1$) and experiments on the synthesis of this acid are in progress. In the meantime we have prepared an isomeride, p-*phenylphenacyl* 8-*hydroxy*-8-*methyltridecoate*, $CH_3\cdot[CH_2]_4\cdot CMe(OH)\cdot[CH_2]_6\cdot CO\cdot O\cdot CH_2\cdot CO\cdot C_6H_4Ph$ (III), by interaction of ethyl 8-ketononoate with *n*-amylmagnesium bromide and eventual formation of the ester in the usual way. This substance does not appear to be identical with the specimen derived from carpaine. A synthesis of *ethyl* 8-*phenoxyoctoate* is described, but the yield is far from satisfactory. An attempt to improve the method by hydrolysing the product of condensation of 5-phenoxyvaleryl chloride and ethyl sodioacetosuccinate (cf. G. M. Robinson, J., 1930, 745) was unsuccessful and is not mentioned in the experimental section.

Experimental.

Ethyl Tetrahydrofurfurylmalonate.—Ethyl malonate (160 g.) and tetrahydrofurfuryl bromide (165 g.) were successively added to a solution of sodium ethoxide (23 g. of sodium) in absolute alcohol (300 c.c.), and the mixture refluxed (bath at 100—105°) for 16 hours. The alcohol was distilled, and the product isolated by means of ether. Unchanged bromide and ethyl malonate (total, 36 g.) were collected below 110°/1 mm., and *ethyl tetrahydrofurfurylmalonate* passed over at 123°/1 mm. as a colourless pleasant-smelling oil (Found : C, 59·5; H, 8·5. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2%) (yield, 170 g. or 70%).

β-*Tetrahydrofurylpropionic Acid.*—A mixture of potassium hydroxide (80 g.), water (80 c.c.), alcohol (320 c.c.), and ethyl tetrahydrofurfurylmalonate (122 g.) was refluxed on the steam-bath for 6 hours. The alcohol was removed, the cooled residue diluted with water and washed with ether, and concentrated hydrochloric acid added with cooling in ice. The precipitated tetrahydrofurfurylmalonic acid was collected by means of ether as a pale yellow viscous oil, which would not crystallise even at − 20°. When the acid was heated at 140—160°, carbon dioxide was smoothly evolved, giving β-tetrahydrofurylpropionic acid as a pale brown oil (70 g.). On redistillation, the pure acid was obtained as a colourless, sharp-smelling, viscous oil, b. p. 119°/0·2

mm., $n_D^{15°}$ 1·4591 (Found : C, 58·3; H, 8·3. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%). Kauffman and Adams (*loc. cit.*) record b. p. 135—137°/4 mm.

Ethyl β-Tetrahydrofurylpropionate.—The crude product from the above experiment was heated with alcohol (130 c.c.) and concentrated sulphuric acid (5 c.c.) on the steam-bath for 5 hours. Isolated in the customary manner, *ethyl β-tetrahydrofurylpropionate* was obtained as a colourless oil of pleasant pine-apple odour (58·5 g.), b. p. 105°/11 mm., $n_D^{15°}$ 1·4425 (Found : C, 62·5; H, 9·5. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%).

3-Tetrahydrofurylpropan-1-ol.—Ethyl tetrahydrofurylpropionate (64·5 g.), dissolved in absolute alcohol (625 c.c.), was added during 4 minutes to sodium (54·5 g.) in a flask heated in a bath at 145°. After 20 minutes, more alcohol (100 c.c.) was added, followed after 15 minutes by 50% alcohol (100 c.c.). The alcohol was removed by passing a current of steam for a short period, and the product isolated from the residue by means of ether. After drying of the extract and removal of the solvent, the residual oil was fractionated, 3-tetrahydrofurylpropan-1-ol being obtained as a colourless oil of faint odour, b. p. 111·5°/11 mm., $n_D^{13°}$ 1·4597 (yield, 36 g. or 75%). Bray and Adams (*J. Amer. Chem. Soc.*, 1927, **49**, 2105) give the b. p. 106—107°/2 mm. and Burdick and Adkins (*ibid.*, 1934, **56**, 441) record b. p. 106°/10 mm.

γ-Tetrahydrofurylpropyl chloride was prepared by the method of Gilman and Hewlett (*loc. cit.*). These authors give b. p. 75°/4 mm., but we have found b. p. 78°/11 mm., representing a considerable divergence (Found : C, 56·6; H, 8·7; Cl, 23·6. Calc. for $C_7H_{13}OCl$: C, 56·6; H, 8·8; Cl, 24·0%).

γ-Tetrahydrofurylpropyl Bromide.—A mixture of tetrahydrofurylpropyl alcohol (16·5 g.) and dry pyridine (1 c.c.) was added during ½ hour to a mixture of phosphorus tribromide (11·3 g.) and dry pyridine (1·5 c.c.) which was well stirred and maintained at 0°. After 4 hours, the product was distilled under diminished pressure. When the distillate was redistilled, the desired *bromide* was obtained as a colourless oil of characteristic odour, b. p. 100—101°/16 mm. On keeping, the liquid became cloudy, and it was therefore washed with water and taken up in ether, and the residue from the dried extract redistilled; b. p. unchanged (Found : Br, 41·1. $C_7H_{13}OBr$ requires Br, 41·5%) (yield, 16·5 g.). A copious precipitate of silver bromide was obtained when the bromide was gently heated with alcoholic silver nitrate.

Ethyl Bistetrahydrofurfurylmalonate.—Ethyl tetrahydrofurfurylmalonate (31 g.) and then tetrahydrofurfuryl bromide (21 g.) were added to a solution of sodium ethoxide (2·9 g. of sodium) in absolute alcohol (60 c.c.). The mixture was refluxed for 30 hours, the alcohol distilled, and the product isolated by means of ether. Fractionation gave unchanged bromide (3·5 g.) and ethyl tetrahydrofurfurylmalonate (17 g.), after which *ethyl bistetrahydrofurfurylmalonate* distilled as a colourless, very viscous oil (14 g.), b. p. 165°/0·5 mm. (Found : C, 62·1; H, 8·6. $C_{17}H_{28}O_6$ requires C, 62·2; H, 8·5%).

ββ'-Bistetrahydrofurylisobutyric Acid (I).—The above ester was heated on the steam-bath with potassium hydroxide (15 g.), water (15 c.c.), and alcohol (60 c.c.) for 10 hours. After dilution with water and washing with ether, the alkaline solution was acidified with hydrochloric acid. The bistetrahydrofurfurylmalonic acid was extracted with ether, the extract dried, and the ether removed. The residual pale brown oil solidified incompletely at — 20°, and without further purification was heated to 120—140°; carbon dioxide was then smoothly evolved. On distillation *ββ'-bistetrahydrofurylisobutyric acid* was obtained as a colourless viscous oil (6·3 g.), b. p. 173°/0·35 mm. (Found : C, 63·2; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

Tetrahydrofurfuryl p-Toluenesulphonate.—A mixture of *p*-toluenesulphonyl chloride (96 g.), tetrahydrofurfuryl alcohol (51 g.), and dry ether was well stirred and cooled to — 5° to — 10° whilst finely powdered potassium hydroxide (56 g.) was added in small portions, the temperature being kept below 0°. Stirring was continued for ½ hour longer and the flask was then corked and kept, with frequent shaking, in the freezing mixture. After 2 hours, the mixture was poured into ice-water (800 c.c.), and after mechanical stirring for ½ hour the ethereal layer was separated, and the aqueous layer again extracted with ether (2 × 100 c.c.). The combined extracts were dried, and the ether removed, leaving a pale yellow oil (83—85 g.), which solidified, on cooling, in pale lemon crystals. A small portion, after several crystallisations from benzene and light petroleum, gave white needles, m. p. 38·7—39·1° (Found : S, 12·2. Calc. for $C_{12}H_{16}O_4S$: S, 12·5%).

Tetrahydrofurylacetonitrile.—A mixture of tetrahydrofurfuryl bromide (30 g.), potassium cyanide (20 g.), sodium iodide (1 g.), water (20 c.c.), and alcohol (35 c.c.) was refluxed for 35 hours. The product was isolated by means of ether and gave unchanged bromide (10 g.), b. p. 60—86°/17 mm., and then *tetrahydrofurylacetonitrile* (7 g.), b. p. 90—95°/15 mm., on distillation. In another experiment, using the same quantities as above, but no sodium iodide, the products were

4 g. of unchanged bromide and 8·1 g. of the nitrile. On redistillation the nitrile was obtained as a colourless oil of characteristic odour, b. p. 92·4°/13 mm., $n_D^{13°}$ 1·4476 (Found : N, 12·9. C_6H_9ON requires N, 12·6%).

Tetrahydrofurylacetic Acid.—A mixture of tetrahydrofurylacetonitrile (10 g.), alcohol (100 c.c.), potassium hydroxide (12 g.), and water (25 c.c.) was refluxed (10 hours) until ammonia was no longer evolved. The alcohol was distilled, the residue carefully acidified with concentrated hydrochloric acid, the mixture shaken several times with ether, the combined extracts dried, and the solvent removed. The residue, on distillation in a vacuum, gave *tetrahydrofurylacetic acid* as a colourless, extremely viscous oil (7·7 g.), b. p. 144—146°/16 mm., 140°/11 mm. (Found : C, 55·6; H, 7·8. $C_6H_{10}O_3$ requires C, 55·4; H, 7·7%). The substance did not solidify at − 20°.

12 : 12-*Dicarboxy*-13-*tetrahydrofuryltridecan*-1-*ol*.—A mixture of ethyl tetrahydrofurfurylmalonate (6·1 g.), 11-bromoundecanyl acetate (7·3 g.), and sodium ethoxide (0·58 g. of sodium) in absolute alcohol (20 c.c.) was refluxed for 5 hours. The product was isolated in the usual manner and heated to 170°/40 mm. in order to remove traces of volatile matter. Subsequently, a portion was heated to 330°/0·165 mm., but it did not distil. The substance (7 g.) was therefore heated on the steam-bath during 2½ hours with a mixture of water (4 c.c.), alcohol (16 c.c.), and potassium hydroxide (4 g.). The *acid* was isolated after removal of the alcohol, dried, triturated with benzene to free it from an insoluble gum, and crystallised several times from alcohol; ultimately, it crystallised from aqueous alcohol in small white needles, m. p. 108—109° (Found : C, 64·0; H, 9·5. $C_{19}H_{34}O_6$ requires C, 63·8; H, 9·5%).

Ethyl 2-*Furoylacetate*.—The following modification of Sandelin's method (*Ber.*, 1900, **33**, 492, 1176) gives this substance in a yield amounting to 93%.

Ethyl furoate was prepared by refluxing furoic acid (" Organic Syntheses," **6**, 44) with alcohol containing 10% of its volume of concentrated sulphuric acid for 4 hours. The high concentration of sulphuric acid (60% of the volume of alcohol used) recommended by Jackson and Hill (*J. Amer. Chem. Soc.*, 1890, **12**, 24) is unnecessary. The ester, isolated in the customary manner, crystallised in very pale brown prisms, m. p. 33—34°; Hill (*J. Amer. Chem. Soc.*, 1881, **3**, 38) gives the same m. p.

Ethyl furoate (24·8 g.) was heated at 80° and mechanically stirred, finely cut sodium (2 g.) added, and pure ethyl acetate (8·8 g., 9·8 c.c.) gradually introduced. When all the sodium had disappeared, the temperature of the bath was raised to 95°, and further sodium wire (2 g.) was introduced, followed by the dropwise addition of 8·8 g. of ethyl acetate. The mass soon became almost solid and dry benzene (50—60 c.c.) was then added. The addition of sodium wire (2 g.), followed by ethyl acetate (8·8 g.), was continued until a total of 12 g. of sodium and 57 g. of ethyl acetate had been used. After the fifth addition of sodium, it was necessary to add about 50 c.c. of dry benzene, and 1 hour after the final addition of sodium a further 20 c.c. of benzene were introduced in order to promote efficient stirring. After 12 hours' stirring, only a small amount of sodium remained and the mixture was cooled in ice, decomposed by the addition of ice-water, and poured into a well-stirred solution of hydrochloric acid (50 c.c.) in water (200 c.c.), a further 15 c.c. of the acid being added subsequently. After ½ hour's stirring, the benzene layer was separated, the aqueous layer extracted twice with ether, and the combined extracts dried. After removal of the solvents, the residue was fractionated: ethyl acetoacetate and ethyl furoate (total, 9 g.), b. p. up to 90°/20 mm., were first obtained and then the main fraction of ethyl furoylacetate, b. p. 110—115°/1 mm., was collected (32 g.). On redistillation, pure ethyl furoylacetate was obtained, b. p. 113—114°/1 mm., $n_D^{16°}$ 1·5055 (Found : C, 59·2; H, 5·6. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%).

Ethyl 6-*Chlorohexoate*.—Thionyl chloride (7·5 g.) was added dropwise during 10 minutes to a mixture of ethyl 6-hydroxyhexoate (10 g.) and dry pyridine (5 c.c.), well stirred and maintained at 0°. After being stirred for 2 hours at 0° and 2 hours at room temperature, the liquid was decanted from the white crystals, which were then triturated several times with dry ether. The combined extracts were washed in turn with aqueous sodium carbonate, dilute hydrochloric acid, and water. It is essential to remove all the sulphur dioxide. When the residue from the dried extract was distilled, *ethyl* 6-*chlorohexoate* (9·1 g.) was obtained, b. p. 106—110°/15 mm., mostly 107—108°/15 mm. A redistilled specimen had b. p. 106°/14 mm., $n_D^{18°}$ 1·4398 (Found : Cl, 19·4. $C_8H_{15}O_2Cl$ requires Cl, 19·9%). Very similar results were obtained by using 40 g. of the hydroxyester.

Ethyl 6-*Bromohexoate*.—(A) A mixture of ethyl 6-hydroxyhexoate (20 g.) and pyridine (4 c.c.) was added during 45 minutes to phosphorus tribromide (12 g.) and pyridine (2 c.c.), well stirred and maintained at 0°. Stirring was continued for 2½ hours, and the mixture kept over-night.

After the addition of ice-water, the product was extracted with ether, the extract being washed with aqueous sodium carbonate and water. The residue from the dried extract, on distillation, gave a pleasant-smelling colourless oil (13 g.), b. p. 126—127°/20—21 mm. (Found : Br, 32·0. $C_8H_{15}O_2Br$ requires Br, 35·9%). In addition, there was obtained a residue (4—5 g.), b. p. 215—220°/1 mm.

(B) A more satisfactory method was the following : Ethyl 6-hydroxyhexoate (30 g.) was added to a cooled mixture of hydrobromic acid (250 c.c., *d* 1·5) and sulphuric acid (60 c.c.) and kept at room temperature for 2 hours with occasional shaking. After being heated on the steam-bath for 4 hours, the mixture was cooled, diluted with water, and saturated with ammonium sulphate and the bromo-acid was collected by means of ether and esterified by refluxing with alcohol (50 c.c.) and sulphuric acid (2·5 c.c.) for 8 hours. The *ester* was isolated in the usual manner, there being obtained 31 g., b. p. 122—125°/12 mm. (Found : Br, 33·0%), and not more than 1 c.c. of residue.

The above result has been duplicated on several occasions; but from one experiment, on the same scale as above, there was obtained a liquid (31 g.), b. p. 132—134°/14 mm. When ethyl 6-hydroxyhexoate (14·5 g.) was allowed to react with a mixture of hydrobromic acid (110 c.c.) and sulphuric acid (20 c.c.) containing 0·2 c.c. of α-heptenylheptaldehyde, first at room temperature for 1 hour and then on the water-bath for 4 hours, a slow stream of oxygen being passed continuously through the liquid, the bromo-ester (13·0 g.) finally obtained had b. p. 134—145°/22 mm. In another experiment, the hydroxy-ester (40 g.) was treated with hydrobromic acid (320 c.c.) and sulphuric acid (60 c.c.) in the presence of α-heptenylheptaldehyde and oxygen, under precisely the same conditions as the above; the bromo-ester (36·5 g.) finally isolated had b. p. 127—130°/19 mm.

Ethyl 7-Bromoheptoate.—(A) To a mixture of phosphorus tribromide (2·9 g.) and dry pyridine (0·5 c.c.), well stirred and maintained at 0°, ethyl 7-hydroxyheptoate (5 g.) was added dropwise during 20 minutes. The mixture was subsequently stirred for 2 hours at 0° and for 3 hours at 15°. The product was isolated in the usual manner and refluxed with alcohol (10 c.c.) and sulphuric acid (0·5 c.c.) during 4 hours. The *ester* was obtained as a pleasant-smelling oil (4·8 g.), b. p. 135—139°/17 mm., mostly 135°/17 mm. (Found : C, 47·4; H, 7·3. $C_9H_{17}O_2Br$ requires C, 45·5; H, 7·2%. $C_9H_{18}O_3$ requires C, 62·2; H, 10·4%). Obviously the bromo-ester is contaminated with a little of the hydroxy-ester.

(B) Ethyl 7-hydroxyheptoate (25 g.) was allowed to react with a mixture of hydrobromic acid (200 c.c., *d* 1·7) and sulphuric acid (50 c.c.) during 1 hour at room temperature and 3 hours on the steam-bath. The crude bromo-acid was isolated as above and refluxed with alcohol (50 c.c.) and sulphuric acid (2·5 c.c.) during 7 hours. The bromo-ester had b. p. 129—136°/12 mm., mostly 132°/12 mm.; yield, 20 g.

Ethyl α-Acetylsuberate.—Ethyl acetoacetate (17·5 g.) and ethyl 6-bromohexoate (31 g.) were added in turn to a solution of sodium ethoxide (3·1 g. of sodium) in absolute alcohol (100 c.c.), and the mixture refluxed for 9 hours. The product was isolated in the known manner and on distillation gave *ethyl α-acetylsuberate* (18 g.), b. p. 148—165°/0·28 mm., mostly 154—158°/0·28 mm., and a residue of about 10 g.

When ethyl sodioacetoacetate (sodium, 2·1 g.; ethyl acetoacetate, 12 g.) and ethyl 6-chlorohexoate (16 g.) were allowed to react in alcohol in the presence of a little anhydrous sodium iodide during 14 hours at 110—120°, and the product isolated as usual, there was obtained a liquid, b. p. 140—160°/0·7 mm., mostly 156—160°/0·7 mm. Redistillation gave ethyl α-acetylsuberate, b. p. 158°/0·7 mm. (Found : C, 61·9; H, 9·0. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%). The crude ethyl α-acetylsuberate is always contaminated by a small amount of ethyl suberate.

8-*Ketononoic Acid.*—The crude ethyl α-acetylsuberate (8 g.) was shaken during 3 hours with aqueous (300 c.c.) potassium hydroxide (7·5 g.) at room temperature. The solution was extracted with ether, acidified with dilute hydrochloric acid, and saturated with ammonium sulphate, and the product extracted with ether. The ether was removed without drying, and the residue heated with 5% sulphuric acid (50—100 c.c.) for ½ hour. The keto-acid was taken up in ether, the extract dried, and the ether removed. The residues from several such experiments were united and purified as follows. The keto-acid is freely soluble in hot light petroleum, whereas suberic acid is insoluble. The crude acid was therefore warmed with light petroleum (b. p. 40—60°), the solvent decanted, and the process repeated until no more could be extracted. The residue from the combined extracts was the pure *keto-acid*, white needles, m. p. 40—41°; after one crystallisation, m. p. 40·5—42° (Found : C, 62·9; H, 9·1. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). The 2 : 4-*dinitrophenylhydrazone* was readily obtained and formed small yellow needles from methyl alcohol, m. p. 88—89° (Found : N, 15·4. $C_{15}H_{20}O_6N_4$ requires N, 15·9%).

The *semicarbazone* formed short thick prisms, m. p. 136°, from methyl alcohol–light petroleum (Found : N, 18·1. $C_{10}H_{19}O_3N_3$ requires N, 18·3%).

Ethyl 8-Ketononoate.—8-Ketononoic acid (17·5 g.) was refluxed with alcohol (30 c.c.) containing sulphuric acid (1·5 c.c.) during 6 hours. The ester was isolated in the usual manner, b. p. 141—142°/11 mm. (Found : C, 65·9; H, 10·2. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%); yield, 18·3 g. The *semicarbazone* was readily obtained, and after recrystallisation from aqueous alcohol, was again crystallised from benzene and light petroleum; it formed silky needles, m. p. 108° (Found : N, 16·3. $C_{12}H_{23}O_3N_3$ requires N, 16·3%).

p-*Phenylphenacyl 8-Ketononoate.*—8-Ketononoic acid (0·34 g.) was suspended in water (5 c.c.) and not quite neutralised with *N*-sodium hydroxide; alcohol (10 c.c.) was then added, followed by *p*-phenylphenacyl bromide (0·55 g.) (Drake and Bronitsky, *J. Amer. Chem. Soc.*, 1930, **52**, 3715), and the mixture refluxed for 1 hour. When the product was cooled, an almost quantitative yield of white crystals was obtained, which after recrystallisation from ethyl alcohol formed colourless prisms, m. p. 93·5—95° (Found : C, 75·6; H, 7·3. $C_{23}H_{26}O_4$ requires C, 75·4; H, 7·1%).

9-*Ketodecoic Acid.*—To a solution of sodium (2·4 g.) in absolute alcohol (100 c.c.), ethyl acetoacetate (13·7 g.) and ethyl 7-bromoheptoate (25 g.) were added in turn, and the mixture heated at 100—110° for 5½ hours. The product was isolated in the usual manner. Distillation gave 18 g. of a liquid, b. p. 145—160°/0·27 mm., mostly 151—152°/0·27 mm., and 5 g. of a residual dark oil. The crude ethyl α-acetylazelate (18 g.) was shaken during 3·5 hours at room temperature with potassium hydroxide (12·5 g.) in water (500 c.c.). After washing with ether, the alkaline solution was acidified with dilute hydrochloric acid, and the mixture heated on the water-bath for ½ hour. The liquid was cooled, saturated with ammonium sulphate, and extracted with ether, the extract dried, and the solvent removed entirely (crude product, 10·7 g. or 91·5%). The keto-acid was purified in the same manner as 8-ketononoic acid. 9-Ketodecoic acid crystallised from light petroleum in white needles, m. p. 47·5—48·5° (Found : C, 64·5; H, 9·7. Calc. for $C_{10}H_{18}O_3$: C, 64·6; H, 9·7%). The *semicarbazone* was readily prepared, and after crystallisation from ethyl acetate formed hard white crystals, m. p. 127° (Found : N, 15·2; loss at 80° in a vacuum, 11·7. $C_{11}H_{21}O_3N_3,2H_2O$ requires N, 15·1; H_2O, 12·9%). Curiously enough, the semicarbazone crystallised from aqueous methyl alcohol in glistening plates, m. p. 115—116°, which were anhydrous (Found : no loss at 100° in a vacuum; N, 17·1. $C_{11}H_{21}O_3N_3$ requires N, 17·3%).

Ethyl 9-Ketodecoate.—The keto-acid was refluxed with alcohol (20 c.c.) and sulphuric acid (1·5 c.c.) during 7 hours, and the ester (8·4 g.) isolated as usual, b. p. 154—156°/13 mm.; Ruzicka and Stoll (*Helv. Chim. Acta*, 1927, **10**, 691) record b. p. 151—153°/11 mm. The semicarbazone formed glistening plates from alcohol, m. p. 97—98° (Found : N, 15·4. Calc. for $C_{13}H_{25}O_3N_3$: N, 15·5%). Ruzicka and Stoll (*loc. cit.*) record m. p. 102—103°.

p-*Phenylphenacyl 9-ketodecoate*, prepared from 9-ketodecoate (0·2 g.) and *p*-phenylphenacyl bromide (0·2 g.) precisely as for the similar compound above, and twice crystallised from methyl alcohol, was obtained in almost colourless prisms, m. p. 68—70° (Found : C, 76·0; H, 7·4. $C_{24}H_{28}O_4$ requires C, 75·8; H, 7·4%).

p-*Phenylphenacyl 8-Hydroxy-8-methyltridecoate* (III).—A Grignard reagent prepared from fresh magnesium turnings (0·7 g.), *n*-amyl bromide (4·85 g.), and dry ether (30 c.c.) with the help of a trace of iodine was slowly added to a well-stirred solution of ethyl 8-ketononoate (5·0 g.) in ether (100 c.c.). The addition caused the formation of a white precipitate and stirring was continued for 6 hours at room temperature and next day the mixture was heated at 70—80° for 3 hours, with stirring. The product was cooled in ice and mixed with water and ammonium chloride; the ethereal layer was separated, and the aqueous portion extracted several times with small amounts of ether. The residue from the dried extracts, after being exposed in a vacuum, weighed 6·7 g. This was shaken with semicarbazide hydrochloride (3 g.), sodium acetate (5 g.), alcohol (20 c.c.), and water (15 c.c.) for 6 hours. The semicarbazone (1 g.) which separated was collected, and the oil extracted from the filtrate. The ether was removed, and the residue allowed to remain with a solution of potassium hydroxide (2 g.) in water (5 c.c.) and alcohol (10 c.c.). After 3½ hours, the product was diluted with water, extracted several times with small amounts of ether, and the aqueous portion then acidified with dilute hydrochloric acid at 0°. The white precipitate was collected in ether, the residue from the dried extract being an oil (3 g.) which would not solidify. It was therefore added to an ethereal solution (40 c.c.) of diazomethane (from 10 g. of nitrosomethylurea) and after 3 hours the excess of diazomethane was decomposed with a little acetic acid, and after the addition of alkali, the ethereal layer was separated; the aqueous portion was again extracted, and the combined extract dried. After removal of

the ether, the residue was distilled : fraction (1) had b. p. 90—122°/0·03 mm., and fraction (2) (0·8 g.) had b. p. 123—130°/0·03 mm., mostly 126—130°/0·03 mm. Analysis of fraction (2) (Found : C, 69·0; H, 11·3. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%. $C_{15}H_{30}O_3$ requires C, 69·8; H, 11·6%) showed it to be a mixture of the desired hydroxy-ester and unchanged keto-ester. The oil was saturated to permanganate, it being necessary to warm gently before the colour was discharged. The ester was hydrolysed during 3 hours with potassium hydroxide (0·2 g.) dissolved in 70% alcohol (7 c.c.); the product was diluted with water and extracted with ether. The alkaline solution was acidified, and the precipitated acid extracted with ether, the residue (0·58 g.) from the dried extract being a viscous oil which did not solidify at low temperatures. It was therefore treated with *p*-phenylphenacyl bromide (0·45 g.) precisely as described above for another such derivative. A yellow oil was thus obtained which did not solidify on cooling. It was therefore treated with ether, washed with water, a little alkali, and finally water, and the ethereal solution was then dried. The resultant pale yellow oil gave a sticky solid when cooled in ice; but after being rubbed with a drop of alcohol, and standing for 5 days, it had formed a mass of white needles. These were collected, washed with a drop of cold alcohol, dried on a porous tile, and recrystallised from light petroleum (m. p. 62—69° at this stage) and finally from alcohol. As crystallisation was delayed (3 days), the concentrated solution was triturated with a little light petroleum, whereby white crystals were obtained, m. p. 68—71° (Found : C, 77·1; H, 8·7. $C_{28}H_{38}O_4$ requires C, 76·8; H, 8·7%). This is obviously the p-*phenylphenacyl* ester of 8-*hydroxy*-8-*methyltridecoic acid*.

A similar experiment with *n*-butylmagnesium bromide and ethyl 9-ketodecoate was unsuccessful, because at the final stage *p*-phenylphenacyl 9-ketodecoate was isolated, m. p. 66—68° alone or mixed with an authentic specimen. Doubtless the desired hydroxy-acid was present, but instead of purifying it by the preparation of the derivative we unfortunately purified and isolated the unchanged starting material.

Ethyl γ-Phenoxypropylacetoacetate.—Ethyl acetoacetate (70 g.) and γ-phenoxypropyl bromide (108 g.) were added to a solution of sodium ethoxide (11·6 g. of sodium) in absolute alcohol (200 c.c.), and the mixture refluxed on the steam-bath for 30 hours. The alcohol was distilled and, after the addition of water, the *product* was isolated by means of ether as a colourless liquid of faint fruity odour, b. p. 164°/1 mm., $n_D^{18°}$ 1·5018 (Found : C, 68·4; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·5%) (yield, 93·5 g. or 71%).

As a by-product, there were obtained 15—20 g. of a pale yellow, viscous oil, b. p. 240—250°/0·35 mm. (Found : C, 72·1; H, 7·6. $C_{24}H_{30}O_5$ requires C, 72·3; H, 7·5%). On redistillation this substance had b. p. 220°/0·06 mm., and solidified on cooling. After recrystallisation from light petroleum, it formed fine silky needles, m. p. 61—62° (Found : C, 72·4; H, 7·7%). The substance is therefore *ethyl di(phenoxypropyl)acetoacetate*.

Products of Hydrolysis of Methyl 4-Keto-5-acetyl-5-carbethoxy-8-phenoxyoctoate.—Ethyl phenoxypropylacetoacetate (98·5 g.) was added to pulverised sodium (8·65 g.) under dry benzene (200 c.c.) and when all the sodium had passed into a clear golden solution carbomethoxypropionyl chloride (62 g.) was added, and the mixture refluxed for 16 hours. The product was cooled and diluted with water, and the benzene layer separated. The aqueous phase was again extracted twice with ether, the combined extracts dried, and the solvent removed. The crude product was then shaken during 24 hours with potassium hydroxide (88 g.) dissolved in water (2640 c.c.). The alkaline solution was extracted with ether in order to remove unchanged ester. The alkaline solution was acidified with hydrochloric acid, the liberated acid being collected by means of ether. Examination of the two ethereal extracts showed that only one-fourth of the total ester had been hydrolysed. The residual ester was therefore shaken during 60 hours with 2 l. of 5% potassium hydroxide solution, which process reduced the amount of unchanged ester by 50%. This residue was shaken with 5% potassium hydroxide solution (800 c.c.) and an equal volume of acetone for 2 days. The still considerable amount of unchanged ester was shaken during 1 week with 5% potassium hydroxide solution (800 c.c.); only a small portion then remained undissolved. The various acid fractions were united and refluxed for 5 hours with 5% sulphuric acid (600 c.c.), the product being isolated by means of ether. It was then boiled for 12 hours with aqueous potash (70 g. in 3500 c.c.). The alkaline solution (A) was extracted with ether, the extract dried, and the solvent removed. Distillation of the residue gave *methyl δ-phenoxybutyl ketone* (22·5 g.) as a pale lemon oil of pleasant odour, b. p. 136—137°/1 mm., 102—103°/0·02 mm., $n_D^{13°}$ 1·5143 (Found : C, 75·2; H, 8·7. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The 2 : 4-*dinitrophenylhydrazone*, readily prepared and recrystallised from alcohol, formed small yellow needles, m. p. 97—98° (Found : N, 15·2. $C_{18}H_{20}O_5N_4$ requires N, 15·1%).

The alkaline solution (A) was acidified and extracted with ether, the extract dried, and the

ether removed. The residue (about 25 g.) was reduced by the method of Clemmensen, following precisely the directions of Le Sueur and Withers (J., 1915, **107**, 736). The reduction mixture was finally extracted with benzene, from which, in turn, the organic acids were extracted with sodium hydroxide. Acidification gave a dark brown oil, which solidified incompletely in ice. The whole was therefore refluxed with alcohol (40 c.c.) and sulphuric acid (1 c.c.) for 5 hours. The product was rendered alkaline with potassium carbonate, and extracted with ether. The residue from the dried extract was fractionally distilled, two fractions being obtained: (1) *ethyl 5-phenoxyvalerate*, b. p. 115—117°/0·42 mm. (Found: C, 70·8; H, 8·1. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%) (yield, 8·5 g.). A portion of this ester was hydrolysed by means of 10% aqueous potash at room temperature to 5-phenoxyvaleric acid, m. p. 64·5—65·5°, not lowered by admixture with an authentic sample. The fraction (2) was ethyl 8-phenoxyoctoate, b. p. 135—140°/0·42 mm. (3 g.). This was hydrolysed by means of aqueous alkali to *8-phenoxyoctoic acid*, which crystallised from light petroleum (b. p. 40—60°) in glistening white plates, m. p. 68—70°, unchanged after three recrystallisations (Found: C, 70·9; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

5-Phenoxyvaleric Acid and its Chloride.—Ethyl γ-phenoxypropylacetoacetate (69 g.) was heated on the steam-bath during 5 hours with potassium hydroxide (70 g.), water (50 c.c.), and alcohol (60 c.c.). After 12 hours at room temperature, water was added, and the mixture shaken with ether in order to remove alkali-insoluble matter (3 g. of methyl δ-phenoxybutyl ketone). The alkaline solution was acidified with hydrochloric acid and the precipitated 5-phenoxyvaleric acid, which solidified after cooling in ice, was collected, washed with water, and dried (44 g.). A small portion, recrystallised from light petroleum, formed white needles, m. p. 62·5—63·5°.

5-Phenoxyvaleric acid (47·5 g.) was heated at about 40° for 3 hours with purified thionyl chloride (40 g.). The excess of thionyl chloride was removed in a vacuum; the residue gave 5-phenoxyvaleryl chloride (34 g.), b. p. 142—144°/8 mm. After standing for 2 days in a sealed vessel, it solidified to a mass of white needles, m. p. 44·5—45·0°. The acid chloride was characterised through the *anilide*, which formed glistening white plates from light petroleum, m. p. 84·5—85·5° (Found: N, 5·2. $C_{17}H_{19}O_2N$ requires N, 5·2%).

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