

379. Wool Wax. Part I. Synthesis of Some anteiso-Acids.

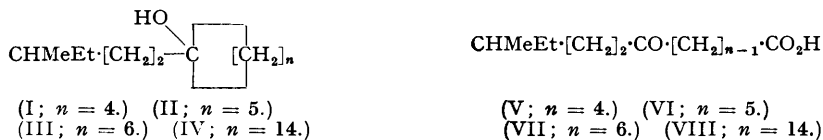
By J. R. NUNN.

8-Methyldecanoic,* 9-methylundecanoic, 10-methyldodecanoic, 12-methyltetradecanoic, 14-methylhexadecanoic, and 18-methyleicosanoic acids have been synthesised in their racemic forms. The long *X*-ray crystal spacings of the amides and solid acids have been recorded.

WEITKAMP (*J. Amer. Chem. Soc.*, 1945, **67**, 447) isolated from wool wax a series of dextro-rotatory fatty acids containing an odd number of carbon atoms, having the *anteiso*-structure (*i.e.*, the methyl side chain in the antepenultimate position). Velick and English (*J. Biol. Chem.*, 1945, **160**, 473) synthesised (+)-14-methylhexadecanoic acid, identical with the naturally derived acid, thereby confirming the structure assigned to this series of acids.

* Geneva nomenclature ($\text{CO}_2\text{H} = 1$) is used throughout this paper.

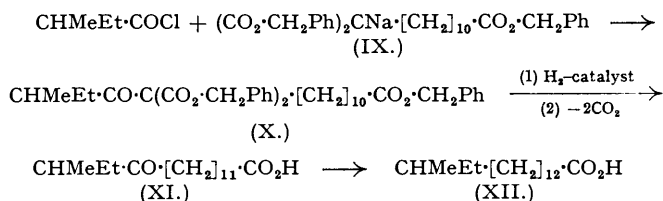
Studies of wool wax in progress in this Laboratory made it necessary to have available a number of these acids in either the racemic or the dextrorotatory form. A recent method of synthesis for fatty acids (Fieser and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1948, **70**, 3352) appeared to be useful for this purpose. It involves oxidative fission of the ring of an alkyl-substituted *tert.*-cycloalkanol, giving a keto-acid which is then reduced to the hydrocarbon-carboxylic acid. By this method (\pm)-8-methyldecanoic acid, (\pm)-9-methylundecanoic acid, (\pm)-10-methyldodecanoic acid, and (\pm)-18-methyleicosanoic acid have been prepared.



The *cycloalkanol*s (I—IV), obtained by the action of the appropriate *cycloalkanon*e on the Grignard reagent from 1-bromo-3-methylpentane, were oxidised in acetic acid with chromium trioxide to the keto-acids (V—VIII), which without purification were then reduced by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487).

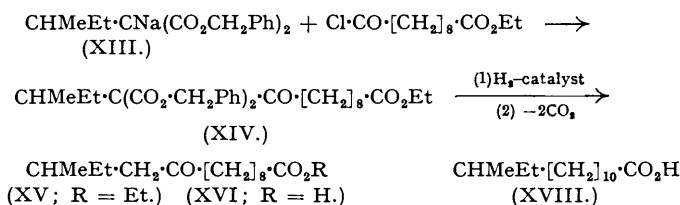
The yields of crude keto-acids were in no instance above 50%. The neutral material remaining after oxidation always contained some unchanged starting material, but the amount was difficult to assess on account of the presence of other oxidation products. Fieser and Szmuszkovicz (*loc. cit.*) reported yields of from 60—80% of keto-acids in most cases where the side chain of the *cycloalkanol* was unsubstituted.

14-Methylhexadecanoic acid was synthesised by a method recently elaborated by Ames, Bowman, and Mason (*J.*, 1950, 174), as follows:



The tribenzyl sodio-ester (IX) was formed in benzene by the trans-esterification of ethyl sodio-*n*-undecane-1 : 1 : 11-tricarboxylate with benzyl alcohol, and then condensed with α -methylbutyryl chloride to furnish (X). Hydrogenolysis of (X) and decarboxylation of the product gave 13-keto-14-methylhexadecanoic acid (XI), which was subsequently reduced to 14-methylhexadecanoic acid (XII).

12-Methyltetradecanoic acid (XVIII) was prepared by a variation of this route:



9-Carboethoxynonanoyl chloride was condensed with benzyl sodio-*sec*-butylmalonate (XIII) to give (XIV), which was converted into the keto-ester (XV). Reduction then yielded 12-methyltetradecanoic acid.

Despite all precautions, a certain amount of ketonic hydrolysis of the β -keto-esters (X) and (XIV) took place and the products, in the cases of the syntheses of the keto-acids (XI and XVI), had boiling points similar to those of the keto-esters themselves. The yields of the desired keto-acids were low because of the resultant difficulties in their separation.

The long crystal spacings for the amides and the solid acids are recorded in the Table. The values for the amides are slightly lower in all cases than those recorded by Velick (*J. Amer. Chem. Soc.*, 1947, **69**, 2317) for the corresponding (+)-amides. They do, however, fall on a straight line when plotted against the carbon content of the molecules. The value for (\pm)-18-methyleicosanoic acid is abnormally low when compared with that for (\pm)-14-methylhexadecanoic acid.

Furthermore whereas the value for (+)-14-methylhexadecanoic acid is nearly the same as that for the racemic acid, the value for (+)-methylheicosanoic acid is 2.5 A. higher than that for the corresponding racemic compound. The value 33.4 A. (Velick, *loc. cit.*) for (+)-methylhexadecanoic acid could not be confirmed. It is possible that the method of preparation of the samples (for X-ray examination) used by us gave crystals in a metastable state.

Substance.	Long crystal spacing (A.).		Substance.	Long crystal spacing (A.).	
	Amide.	Acid.		Amide.	Acid.
(±)-8-Methyldecanoic	22.3	—	(+)-12-Methyltetradecanoic	29.2 *	—
(+)-8-Methyldecanoic	23.2 *	—	(±)-14-Methylhexadecanoic	32.1	29.7
(±)-9-Methylundecanoic ...	23.15	—	(+)-14-Methylhexadecanoic	32.8 *	29.9
(±)-10-Methyl dodecanoic ...	24.9	—	(±)-18-Methylheicosanoic ...	38.0	30.0
(+)-10-Methyl dodecanoic ...	25.9 *	—	(+)-18-Methylheicosanoic ...	—	32.5
(±)-12-Methyltetradecanoic	28.0	—			

* These values were obtained by Velick (*loc. cit.*).

Attempts to resolve (±)-14-methylhexadecanoic acid by means of the brucine and quinine salts failed because the salts separated only as gums.

EXPERIMENTAL.

M. p.s are corrected.

3-Methylpentanol.—β-Methylvaleric acid was made by distilling *sec.*-butylmalonic acid slowly, and had b. p. 190—192°/656 mm. The ethyl ester, distilled through a 22-plate column, had b. p. 155.5°/660 mm., n_D^{25} 1.4035.

The ester (144 g., 1 mol.) was reduced with lithium aluminium hydride (22 g., 0.58 mol.) in anhydrous ether in the usual manner; the product, distilled through a 22-plate column, had b. p. 150°/654 mm., n_D^{25} 1.4159, n_D^{23} 1.4164 (98 g., 96%).

1-Bromo-3-methylpentane.—This material, made by the action of anhydrous hydrogen bromide on the above alcohol at 100° and distilled through the 22-plate column, had b. p. 145°/655 mm., n_D^{25} 1.4461 (89%).

1-3'-Methylpentylcycloheptan-1-ol (III).—To a Grignard reagent, formed from 1-bromo-3-methylpentane (29.7 g., 0.18 mol.) and magnesium (4.38 g., 0.18 atom) in anhydrous ether and cooled to -20°, there was added cycloheptanone (b. p. 176.6°/653 mm., n_D^{25} 1.4585; 16.8 g., 0.15 mol.) in ether (100 c.c.) with stirring. After being kept overnight at room temperature the reaction mixture was poured into crushed ice (*ca.* 100 g.) and hydrochloric acid (15 c.c.). The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed with 10% sodium carbonate solution and then with water. Evaporation of the ether from the dried (Na₂SO₄) solution and distillation of the residue afforded 1-3'-methylpentylcycloheptan-1-ol (18.5 g.), b. p. 145—147°/19 mm., n_D^{25} 1.4710 (Found: C, 79.2; H, 13.0. C₁₃H₂₆O requires C, 78.7; H, 13.2%).

(±)-Methyl 10-Methyl dodecanoate.—1-3'-Methylpentylcycloheptan-1-ol (9.9 g.) in acetic acid (375 c.c.) was treated with finely powdered chromium trioxide (3 g.) with rapid stirring. The solution darkened after a few minutes and the temperature started to rise. The temperature was kept between 27° and 30° while the remainder of the chromium trioxide (27 g.) was added in small portions during 45 minutes. After a total period of 1 hour the reaction mixture was poured into an equal volume of water and thoroughly extracted with a large volume of ether. The ethereal solution, having been washed with water thoroughly to free it from most of the acetic acid, was extracted with 5% sodium hydroxide solution. The latter solution was acidified and extracted with ether. Evaporation of the ether from the dried (Na₂SO₄) ethereal solution afforded crude 7-keto-10-methyl dodecanoic acid (6.0 g., 52%). The *semicarbazone* crystallised from aqueous methanol in small prisms, m. p. 115—116° (Found: C, 59.4; H, 9.5. C₁₄H₂₇O₃N₃ requires C, 58.9; H, 9.5%).

This keto-acid (10.9 g.) was dissolved in a solution of potassium hydroxide (9.0 g.) in diethylene glycol (64.5 c.c.) and treated with 85% hydrazine hydrate (6.5 c.c.). The mixture was refluxed for 1.5 hours. Sufficient water was distilled off to raise the temperature to 190—200° and refluxing continued for a further 4 hours. This mixture was cooled, diluted with water, and acidified with dilute hydrochloric acid. The acid was isolated in ether. Evaporation of the ether from the dried (Na₂SO₄) extract gave crude (±)-10-methyl dodecanoic acid (8.9 g.). This was treated with a dry ethereal solution of diazomethane (4 g. in 150 c.c.; 100% excess). The ether and excess of diazomethane were removed in a vacuum and the residue was distilled through a vacuum-jacketed Vigreux column, affording (±)-methyl 10-methyl dodecanoate (5.2 g.), b. p. 156—158°/22 mm., n_D^{25} 1.4351 (Found: C, 73.7; H, 12.4. C₁₄H₂₈O₂ requires C, 73.6; H, 12.4%).

(±)-10-Methyl dodecanoic Acid.—The above ester (4.8 g.) was saponified in 20% alcoholic potassium hydroxide (35 c.c.); 10-methyl dodecanoic acid (3.93 g.), isolated in the normal manner, had b. p. 124—126°/0.3 mm., m. p. 5.6°, n_D^{25} 1.4432 (Found: C, 73.0; H, 12.4. C₁₃H₂₆O₂ requires C, 72.9; H, 12.2%). The overall yield calc. on 1-bromo-3-methylpentane was 18%.

The acid chloride was prepared by refluxing the acid (0.36 g.) with pure thionyl chloride (0.8 c.c.) for 1 hour. The excess of thionyl chloride was removed in a vacuum and the residue dissolved in dioxan (3—4 c.c.). This solution was added dropwise, with agitation, to ice-cold ammonia solution (*d* 0.88; 30 c.c.). The *amide*, filtered off after 1 hour and recrystallised from aqueous methanol, had m. p. 91.6—92.1° (Found: C, 73.3; H, 12.7. C₁₃H₂₇ON requires C, 73.2; H, 12.8%).

1-3'-Methylpentylcyclopentan-1-ol (I).—The Grignard reagent from 1-bromo-3-methylpentane (32.5 g., 0.197 mol.) and magnesium (4.8 g., 0.2 atom) in ether was treated with cyclopentanone (b. p. 127°/653 mm., 33.1 g., 0.394 mol.) as described for the previous case. The product was isolated as usual and distilled through a vacuum-jacketed Vigreux column, affording an alcohol (5.7 g.), b. p. 122—124°/23 mm., n_D^{25} 1.4638 (Found: C, 77.4; H, 12.6. $C_{11}H_{22}O$ requires C, 77.6; H, 13.0%).

A high-boiling fraction (b. p. 135—155°/23 mm.) from this distillation solidified on cooling. Crystallisation from methanol afforded yellow plates, m. p. 81—82° (Found: C, 83.7; H, 9.55. Calc. for $C_{15}H_{30}O$: C, 83.3; H, 9.3%). This probably was 1:3-dicyclopentylidene-cyclopentanone and would account for the low yield of desired product. Wallach (*Ber.*, 1896, 29, 2964) gives m. p. 76—77° for this substance.

(±)-Methyl 8-Methyldecanoate.—1-3'-Methylpentylcyclopentan-1-ol (3.3 g.) was oxidised in acetic acid (130 c.c.) with chromium trioxide (10 g.) at 25°.

The keto-acid (2.0 g., 51%) was reduced in diethylene glycol (10 c.c.) containing potassium hydroxide (2.2 g.) and 85% hydrazine hydrate (2 c.c.). The reduced acid (1.63 g.) was esterified with methanol (15 c.c.) and sulphuric acid (0.2 c.c.). Distillation of the product afforded (±)-methyl 8-methyldecanoate (0.81 g.), b. p. 129—132°/22 mm., n_D^{25} 1.4275 (Found: C, 71.7; H, 12.1. $C_{12}H_{24}O_2$ requires C, 72.0; H, 12.1%).

(±)-8-Methyldecanoic Acid.—The above ester (0.78 g.) was saponified in 20% alcoholic potassium hydroxide (8 c.c.), and the acid isolated and distilled (0.54 g.), b. p. 111—112°/0.5 mm., m. p. —11.6°, n_D^{25} 1.4380 (Found: C, 70.8; H, 11.8. $C_{11}H_{22}O_2$ requires C, 70.9; H, 11.9%). The amide, crystallised from aqueous methanol, had m. p. 86.8—87.2° (Found: C, 71.3; H, 12.45. $C_{11}H_{23}ON$ requires C, 71.3; H, 12.5%).

1-3'-Methylpentylcyclohexan-1-ol (II).—cycloHexanone (b. p. 152°/653 mm.; 49.0 g., 0.5 mol.) in ether (200 c.c.) was added to the Grignard reagent from 1-bromo-3-methylpentane (82.5 g., 0.5 mol.) and magnesium (12.4 g., 0.51 mol.) in ether. Distillation of the product afforded 1-3'-methylpentylcyclohexan-1-ol (63 g.), b. p. 129—131°/19 mm., n_D^{25} 1.4657 (Found: C, 78.0; H, 12.7. $C_{12}H_{24}O$ requires C, 78.2; H, 13.1%).

(±)-9-Methylundecanoic Acid.—1-3'-Methylpentylcyclohexan-1-ol (25 g.) in acetic acid (800 c.c.) was oxidised at 25° with chromium trioxide (75 g.) and the keto-acid (6.3 g.) isolated. The keto-acid (15 g.) was reduced with potassium hydroxide (14 g.), 85% hydrazine hydrate (9.5 c.c.), and diethylene glycol (95 c.c.). Distillation of the product through a vacuum-jacketed Vigreux column afforded (±)-9-methylundecanoic acid (10.8 g.), b. p. 121—122°/0.5 mm., m. p. —1.8°, n_D^{25} 1.4420 (Found: C, 71.6; H, 12.05. $C_{13}H_{26}O_2$ requires C, 72.0; H, 12.1%). The amide, recrystallised from aqueous methanol, had m. p. 80.8—81.1° (Found: C, 72.6; H, 12.8. $C_{13}H_{25}ON$ requires C, 72.3; H, 12.6%).

1-3'-Methylpentylcyclopentadecan-1-ol (IV).—cycloPentadecanone (Firmenich et Cie, Genève, m. p. 64—65°; 28.1 g., 0.125 mol.) in ether (100 c.c.) was added to the Grignard reagent from 1-bromo-3-methylpentane (26.4 g., 0.16 mol.) in ether. The reaction mixture was worked up and 1-3'-methylpentylcyclopentadecan-1-ol distilled as a very viscous liquid (31 g.), b. p. 165—166°/0.3 mm., n_D^{25} 1.4845 (Found: C, 81.5; H, 13.7. $C_{21}H_{42}O$ requires C, 81.2; H, 13.6%).

(±)-18-Methyleicosanoic Acid.—The foregoing material (10.3 g.) in acetic acid (360 c.c.) was oxidised with chromium trioxide (30 g.) to crude 15-keto-18-methyleicosanoic acid (3.4 g.). This acid (4.2 g.) was reduced with potassium hydroxide (2.3 g.), 85% hydrazine hydrate (1.7 c.c.), and diethylene glycol (17 c.c.). The neutralisation equivalent of the reduced acid (3.7 g.) indicated that it probably was contaminated with some dibasic acid. It was assumed that the impurity was pentadecanedioic acid and hence the amount of (±)-18-methyleicosanoic acid in the mixture could be calculated. The crude acid (2.137 g.) in a little ethanol was neutralised (phenolphthalein) with dilute potassium hydroxide solution, and treated with the volume of standard hydrochloric acid needed to liberate the 18-methyleicosanoic acid. The acid was extracted from this mixture with ether, and the ethereal solution washed with water and dried (Na_2SO_4). Evaporation of the ether left a colourless solid (1.14 g.) which gave (±)-18-methyleicosanoic acid, colourless needles, m. p. 57.2—57.6°, on crystallisation from acetone (Found: C, 77.2; H, 12.9. $C_{21}H_{42}O_2$ requires C, 77.25; H, 13.0%). The amide, crystallised from methanol, had m. p. 93.2—93.4° (Found: C, 77.7; H, 13.4. $C_{21}H_{43}ON$ requires C, 77.5; H, 13.5%).

The aqueous solution remaining after the extraction of the above acid was acidified further with dilute hydrochloric acid, and the precipitated pentadecanedioic acid filtered off. This crystallised from acetone as colourless needles, m. p. 114.5—115° (lit., 115°) (Found: C, 66.1; H, 10.5. Calc. for $C_{15}H_{28}O_4$: C, 66.1; H, 10.4%).

Ethyl *n*-Undecane-1:1:11-tricarboxylate.—The ethyl ω -bromoundecanoate was made by esterification of ω -bromoundecanoic acid (Ashton and Smith, *J.*, 1934, 438; m. p. 52—53°) in the usual manner. Sodimalonic ester (0.13 mol.) in absolute ethanol (125 c.c.) was treated with ethyl ω -bromoundecanoate (38 g., 0.13 mol.), and the solution refluxed for 2 hours. Next morning the triester was isolated and distilled (34 g.), having b. p. 175°/0.3 mm., n_D^{25} 1.4423 (Found: C, 64.2; H, 9.6. Calc. for $C_{26}H_{38}O_6$: C, 64.5; H, 9.7%).

Benzyl Sodio-*n*-undecane-1:1:11-tricarboxylate (IX).—The benzyl alcohol for this experiment was refluxed with sodium hydroxide, washed with water, dried, and distilled twice *in vacuo*. Powdered sodium (2.05 g., 0.089 atom) in thiophen-free, dry benzene (180 c.c.) was treated with ethyl *n*-undecane-1:1:11-tricarboxylate (33.5 g., 0.09 mol.). When all the sodium had dissolved, benzyl alcohol (29.1 g., 0.27 mol.) was added and the reflux condenser replaced by a 30-cm. column packed with Fenske helices. The ethanol from the trans-esterification was distilled off very slowly as the benzene-ethanol azeotrope (b. p. 64°/650 mm.), the ethanol in it being estimated by means of the refractive index. The temperature tended to rise rapidly towards the end of ester interchange. After 5 hours the temperature was

74.5°/650 mm. (the b. p. of pure benzene) and the theoretical amount of ethanol had been collected. The volume of the reaction mixture was kept fairly constant by the periodic addition of pure benzene.

Condensation of α -Methylbutyryl Chloride with the Above Sodio-ester.—The α -methylbutyryl chloride was made by treating α -methylbutanoic acid (*Org. Synth.*, Coll. Vol. I, 1941, p. 361) with pure thionyl chloride. It was obtained as a colourless oil, b. p. 111–112°/653 mm. The solution of sodio-ester described above was cooled and to it was added α -methylbutyryl chloride (10.6 g., 0.085 mol.) slowly with efficient stirring. The solution was refluxed for 1 hour and then cooled to 5° while ice-water (150 c.c.) containing sulphuric acid (1.5 c.c.), was run in with rapid stirring. The organic layer was separated, washed with water, and dried (Na_2SO_4). The solvent was removed in a vacuum at room temperature and finally at 50°.

The pale yellow oil from the above experiment (61.5 g.) in ethanol–ethyl acetate (1:1; 200 c.c.) was shaken with hydrogen at 50 lbs./sq. in. in the presence of palladium–charcoal (8 g.; 5% of Pd). No absorption took place, hence the catalyst was filtered off and replaced with palladium–calcium carbonate (20 g.; 2% of Pd). Absorption of hydrogen was then complete in 20 minutes. The catalyst was filtered off and the solution refluxed for 30 minutes. A brisk evolution of carbon dioxide took place, after which the solvent was distilled off, leaving a pale yellow oil (28 g.). In order to decompose any β -keto-ester, this material was dissolved in acetic acid (140 c.c.), containing 20N-sulphuric acid (14 c.c.), and the solution refluxed for 45 minutes. It was diluted with water, and the product isolated in ether. Evaporation of the ether from the dried (Na_2SO_4) solution afforded a solid residue.

The acid thus obtained was esterified with ethanol (240 c.c.) containing sulphuric acid (6 c.c.), and the ester was distilled through a vacuum-jacketed Vigreux column as a colourless oil (16 g.), b. p. 130–145°/0.3 mm., a large amount of black tar being left. Repeated attempts to fractionate this ester did not yield a pure specimen of ethyl 13-keto-14-methylhexadecanoate. Analysis indicated that the product probably was contaminated with the ester of a dibasic acid. Hence it was saponified in ethanol (50 c.c.) containing potassium hydroxide (12 g.). The mixture was diluted with water and thoroughly extracted with ether. The aqueous layer was acidified with dilute sulphuric acid and the liberated acids isolated in ether. This ethereal solution was shaken with saturated sodium hydrogen carbonate solution (50 c.c.). The alkaline extract was separated, boiled to free it from ether, and acidified. The precipitated brassylic acid, when dried and recrystallised several times from ethyl acetate, had m. p. 113–114° (lit., 114°) (Found: C, 63.8; H, 10.0. Calc. for $\text{C}_{13}\text{H}_{24}\text{O}_4$: C, 63.9; H, 9.8%).

The ethereal solution which remained after sodium hydrogen carbonate extraction was washed with water and dried (Na_2SO_4). Evaporation left a solid residue (11 g.), which was reduced with diethylene glycol (53 c.c.), 85% hydrazine hydrate (5.3 c.c.), and potassium hydroxide (7.4 g.). The reaction mixture was worked up as usual and the acid (10.1 g.) recrystallised several times from acetone, giving colourless needles of (\pm)-14-methylhexadecanoic acid (7 g., 30% overall yield on α -methylbutyryl chloride), m. p. 39.5–40.1° (Found: C, 75.8; H, 12.7. $\text{C}_{17}\text{H}_{34}\text{O}_2$ requires C, 75.5; H, 12.7%). The *amide*, crystallised from methanol, had m. p. 89.4–90.6° (Found: C, 76.0; H, 13.0. $\text{C}_{17}\text{H}_{33}\text{ON}$ requires C, 75.75; H, 13.1%).

(\pm)-12-Methyltetradecanoamide.—Dibenzyl sodio-*sec.*-butylmalonate (0.047 mol.), formed from ethyl *sec.*-butylmalonate (10.02 g., 0.047 mol.), sodium (1.08 g., 0.047 atom), and benzyl alcohol (10.02 g., 0.094 mol.), was treated with 9-carbomethoxynonanoyl chloride [b. p. 178–180°/20 mm. (Robinson and Robinson, *J.*, 1925, 127, 178); 11.4 g., 0.045 mol.]. The product was isolated, debenzylated, and decarboxylated as described for the previous case (the debenzylation was more difficult). The product (12 g.) boiled over a wide range when it was distilled through a column, and after several fractionations a small amount of impure ethyl 10-keto-12-methyltetradecanoate was obtained, having b. p. 123–124.5°/0.1 mm., n_D^{25} 1.4439 (Found: C, 71.0; H, 11.3. Calc. for $\text{C}_{17}\text{H}_{32}\text{O}_3$: C, 71.8; H, 11.3%). These distillations resulted in large losses of material.

This ester (0.6 g.) was saponified and the acid was reduced with diethylene glycol (5 c.c.), 85% hydrazine hydrate (0.5 c.c.), and potassium hydroxide (0.4 g.). The acid (0.37 g.) was isolated and converted into the *amide* which was crystallised from methanol and had m. p. 84–85° (Found: C, 74.7; H, 12.8. $\text{C}_{16}\text{H}_{31}\text{ON}$ requires C, 74.6; H, 12.9%).

X-Ray Measurements.—These were carried out by using a copper target with a metal filter and recorded by a Geiger Counter Spectrophotometer.

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