331. *The Nonadrides. Part III.*[1] *The Absolute Configuration of Glauconic and Glaucanic Acids*

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The oxidation of glauconic acid to furnish *meso*-diethylsuccinic acid and two C_{15}-dicarboxylic acids has been investigated. The ozonolysis of glaucanic acid gave propane-1,2,2-tricarboxylic acid and (+)-αβ-*erythro*-diethylglutaric acid. The monodimethylamide of *meso*-diethylsuccinic acid has been resolved and the (+)-isomer has been indirectly homologated to furnish the (−)-enantiomer of the above mentioned glutaric acid derivative. The same monodimethylamide has been further transformed into (+)-α-ethylvaleric acid, whose absolute configuration has been confirmed by a synthesis of its enantiomer from (+)-diethylsuccinic acid of known absolute configuration. The absolute configurations of glaucanic acid, and hence of glauconic acid, have thus been determined.

The correlations reported have been made possible by the discovery that dimethylamides can be monodemethylated under specific oxidation conditions. The *N*-formyl-*N*-methylamides have been shown to be intermediates.

The constitution and relative stereochemistry of glauconic acid have been established as (I; R = OH) from chemical [2,3] and *X*-ray crystallographic [4] evidence. We now show that glauconic acid has the absolute configuration which is also depicted in (I; R = OH).

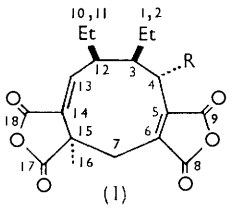
The oxidation of glauconic acid to the corresponding ketone has been described.[1] Further oxidation of this ketone, or oxidation of glauconic acid itself, with N-chromium trioxide at room temperature gave three dicarboxylic acids which could be separated by a combination of chromatography and fractional crystallisation. One of these acids was readily identified as *meso*-diethylsuccinic acid (IV; $R^1 = R^2 = OH$). The other two acids, of composition $C_{15}H_{20}O_7$, were assigned constitutions (II; R = OH) and (III; R = OH) on the basis of the following evidence. The infrared spectra of both acids showed the presence of the anhydride ring which, further, was shown to be of the itaconic type by the ultraviolet spectra. Both acids gave crystalline dimethyl esters. The nuclear magnetic resonance (n.m.r.) spectra of these esters permitted a stereochemical distinction between them. The ester (II; R = OMe) had a vinyl proton doublet (J = 11 c./sec.) at 3·28 τ just as in glauconic acid and its derivatives.[1,2] It also showed a peak at 8·37 for the quaternary methyl group and a broad singlet (two protons) at 6·77 for the isolated methylene absorption. The ester (III; R = OMe) showed vinyl absorption at 4·00 τ (J = 12 c./sec.), a position which indicates that the vinyl proton is no longer deshielded by the carbonyl group of the itaconic anhydride residue. The position of the quaternary methyl group at 8·50 was also changed, whilst the isolated methylene group now appeared as a pair of doublets at 6·84 and 7·26 (J = 12). The *cis*-relationship of the two ethyl groups in (II; R = OH) was confirmed by its oxidation with chromic acid to *meso*-diethylsuccinic acid (IV; $R^1 = R^2 = OH$). The formation of the two geometrical isomers (II; R = OH) and (III; R = OH) can be understood as addition of the 4-carboxyl group to the 13,14-ethylenic linkage followed by the elimination of the resultant γ-lactone to re-form (II; R = OH) or, alternatively, (III; R = OH). The exact position in the oxidation and isolation sequence where this change takes place was not determined.

The isolation of *meso*-diethylsuccinic acid has, of course, no bearing on the absolute

[1] Part II, D. H. R. Barton, L. M. Jackman, L. Rodriguez-Hahn, and J. K. Sutherland, preceding Paper.
[2] J. E. Baldwin, D. H. R. Barton, J. L. Bloomer, L. M. Jackman, L. Rodriguez-Hahn, and J. K. Sutherland, *Experientia*, 1962, **18**, 345.
[3] Part I, D. H. R. Barton and J. K. Sutherland, *J.*, 1965, 1769.
[4] G. Ferguson, G. A. Sim, and J. M. Robertson, *Proc. Chem. Soc.*, 1962, 385.

configuration of the precursors. It was clear, however, that if carboxylic acid derivatives of (II; R = OH) or (III; R = OH) could be oxidised then an asymmetric derivative of *meso*-diethylsuccinic acid would result, the absolute configuration of which could be determined. To this end the bis-*NN*-dimethylamide (III; R = NMe_2) was prepared and its oxidation studied. Before this approach could be successfully concluded, it became clear from work on byssochlamic acid (following Paper) that an ozonolytic degradation of glaucanic acid (I; R = H) might, after all, be possible. In the event, controlled ozonolysis of glaucanic acid gave the tricarboxylic acid (V) and (+)-αβ-*erythro*-diethylglutaric acid (VI; $R^1 = R^2 = OH$). Although the latter was a viscous oil it gave a crystalline bis-*p*-phenylphenacyl ester. Its constitution and relative stereochemistry were established by a synthesis of the racemate by the following procedure. *meso*-Diethylsuccinic acid anhydride with one mol. of sodium methoxide gave the monomethyl ester monosodium salt. Treatment of the latter with excess of oxalyl chloride [5] afforded the acid chloride which on Arndt–Eistert homologation furnished the monomethyl ester of the desired racemate. Alkaline hydrolysis gave (±)-αβ-*erythro*-diethylglutaric acid. Infrared comparison of the (±)-isomer with the (+)-isomer was made as the bis-*p*-phenylphenacyl esters.

In preliminary experiments we had shown that the *NN*-dimethylamide (IV; R^1 = OH, $R^2 = NMe_2$), prepared by treatment of *meso*-diethylsuccinic anhydride with dimethylamine, could be resolved easily to furnish the (+)-isomer in crystalline form. If, therefore, this compound could, on the one hand, be correlated with the αβ-diethylglutaric acid obtained from glaucanic acid (see above) and, on the other, be degraded to a substance of



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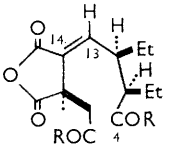

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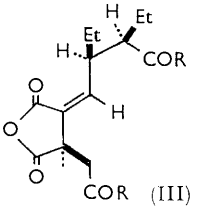

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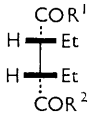

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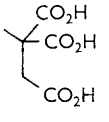

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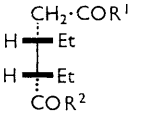

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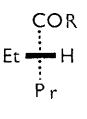

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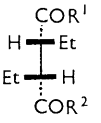

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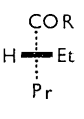

(IX)

known absolute configuration, then our stereochemical problem would be solved. We describe first the correlation with glaucanic acid.

The (+)-*NN*-dimethylamide (IV; $R^1 = OH$, $R^2 = NMe_2$) was methylated with diazomethane to give the ester (IV; $R^1 = OMe$, $R^2 = NMe_2$). Now, in other preliminary experiments we had discovered tht dialkylamides could be monodealkylated with oxidising agents, suitably ozone (see further below). This finding was of critical significance because it enabled the dimethylamide grouping to be removed under mild conditions without hydrolysing the sensitive methyl ester grouping. The (+)-dimethylamide (IV; $R^1 = OMe$, $R^2 = NMe_2$) was ozonised in acetic acid to furnish the (+)-monomethyl derivative (IV; $R^1 = OMe$, $R^2 = NHMe$). This amide in acetic acid–acetic anhydride was nitrosated and the resultant nitroso-amide at once hydrolysed with aqueous sodium hydrogen carbonate to give the desired (−)-monomethyl ester (IV; $R^1 = OMe$, $R^2 = OH$). To confirm that no inversion or racemisation had occurred during the reaction sequence the following transformations were effected. First, the (−)-monomethyl ester (IV;

[5] A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.*, 1950, **72**, 2388.

R^1 = OMe, R^2 = OH) was converted into the dimethyl ester with diazomethane. This diester had no optical activity and was pure dimethyl *meso*-diethylsuccinate as judged by gas chromatography. Secondly, the (−)-half-ester (IV; R^1 = OMe, R^2 = OH) was converted, through the acid chloride, back into the (+)-monomethylamide (IV; R^1 = OMe, R^2 = NHMe). The optical activity was identical for both specimens of this amide. The optically active (−)-half-ester (IV; R^1 = OMe, R^2 = OH) was then homologated as already described (see above) for the (±)-isomer to furnish (−)-αβ-*erythro*-diethylglutaric acid [enantiomer of (VI; $R^1 = R^2$ = OH)], characterised as the crystalline bis-*p*-phenylphenacyl ester. The enantiomeric relationship of the (−)-acid thus obtained with the (+)-isomer from glaucanic acid was established by all the usual criteria.

It now remained to determine the absolute configuration of the (+)-dimethylamide (IV; R^1 = OH, R^2 = NMe_2). Photochemical decarboxylation of this compound with the lead tetra-acetate–iodine reagent,[6] and reduction, without isolation, of the resultant iodide with zinc dust and acetic acid at room temperature afforded (+)-α-ethylvaleric acid *NN*-dimethylamide (VII; R = NMe_2). The absolute configuration of (+)-α-ethylvaleric acid had been determined,[7] but the optically pure acid had not hitherto been prepared. Resolution of α-ethylvaleric acid by fractionation of the cinchonidine salt [7] gave, at best, a mixture containing 65% of the (−)-isomer. A variety of derivatives was made from the partially resolved acid, and an enantiomeric relationship with the amide (VII; R = NMe_2) was strongly suggested. In order to settle the question beyond argument an alternative method for the preparation of α-ethylvaleric acid of determined absolute configuration was devised.

The preparation and determination of the absolute configuration of (+)-diethylsuccinic acid (VIII; $R^1 = R^2$ = OH) has been described [8] as well as its conversion into the optically pure anhydride. Treatment of the latter with dimethylamine afforded the half-amide (VIII; R^1 = NMe_2, R^2 = OH). Application of the photochemical decarboxylation procedure and further processing as above then furnished (−)-α-ethylvaleric acid dimethylamide (IX; R = NMe_2). Both the (+)- and the (−)-dimethylamides gave the corresponding monomethylamides (VII; R = NHMe) and (IX; R = NHMe), respectively, on oxidative demethylation. Each pair of amides afforded enantiomeric optical rotatory dispersion curves, and on mixing equal amounts of the enantiomeric monomethylamides the corresponding racemate was obtained. The (−)-amide (IX; R = NHMe) was nitrosated and thence converted into optically pure (−)-α-ethylvaleric acid, whose rotation was in good agreement with that calculated for the pure acid as a result of the earlier work.[7] The determination of the absolute configuration of glaucanic acid, and hence of the related glauconic acid,[1] was thus complete.

In the experiments reported above we made extensive use of the oxidative de-*N*-methylation reaction as applied to dimethylamides, and, indeed, the work could not have been completed without this reaction. Two oxidising agents, chromium trioxide and ozone, have been investigated. Chromic acid oxidation of *NN*-dimethylstearamide gave *N*-formyl-*N*-methylstearamide which had infrared bands at 1723 and 1670 $cm.^{-1}$ and gave *N*-methylstearamide when heated with aqueous acetic acid and stearic acid on more vigorous acid hydrolysis. From the similar oxidation of the half-amide (IV; R^1 = OH, R^2 = NMe_2) no *N*-formyl compound could be isolated. Instead the *N*-methylamide (IV; R^1 = OH, R^2 = NHMe) and *meso*-diethylsuccinic acid were obtained. The difference in products must be ascribed to a facilitation of hydrolysis of the formyl group by the neighbouring carboxyl group even though a seven- or nine-membered hydrogen-bonded ring appears to be involved. Analogous results were obtained on ozonolysis in acetic acid. The mono-*N*-methylamide (IV; R^1 = OH, R^2 = NHMe) was more stable to either of the two oxidants. Ozonolysis of the amides (VII; R = NMe_2), (IX; R = NMe_2), and of the

[6] D. H. R. Barton and E. P. Serebryakov, *Proc. Chem. Soc.*, 1962, **309**.
[7] P. A. Levene, A. Rothen, and C. M. Meyer, *J. Biol. Chem.*, 1936, **115**, 401.
[8] K. Nagarajan, C. Weissmann, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1963, **46**, 1212.

ester amide (IV; R^1 = OMe, R^2 = NMe_2) gave, in each case, the corresponding *N*-formyl compounds (infrared spectra) hydrolysed without purification (see above) to the appropriate *N*-monomethylamides. Clearly, the *N*-formyl derivative can be obtained except where there is a neighbouring carboxyl group.

Experimental

Melting points were taken on a Kofler block. Unless otherwise specified, optical rotations were measured in chloroform, ultraviolet spectra in ethanol, and infrared spectra in Nujol or, for liquids, as thin films. N.m.r. spectra were taken at 20° on ~10% w/v solutions in deuterochloroform (unless stated otherwise) with tetramethylsilane as internal standard. Gas chromatograms were run on a Pye Argon instrument at 150° using a polyethylene glycol adipate stationary phase.

Oxidation of Glauconic Acid Ketone.—The ketone (5 g.) was added, with cooling, to chromium trioxide (15 g.) in acetic acid (220 ml.) containing water (11 ml.), and left at room temperature for 24 hr. The solution was poured into excess of aqueous sodium pyrosulphite. Thorough ether extraction afforded a gum which was digested under reflux with ethyl acetate (5 × 100 ml.). Removal of the ethyl acetate *in vacuo*, dissolution of the residue in aqueous sodium hydrogen carbonate, extraction with ether, acidification with dilute sulphuric acid, and further ether extraction gave the acidic product. This was taken up in the minimum of acetonitrile and left overnight at 0°. Crystallisation of the precipitate from ethyl acetate–chloroform gave *meso*-diethylsuccinic acid (32 mg.) (m. p., mixed m. p., and infrared spectrum).

Chromatography of the material in the mother-liquors over silica gel (B.D.H.; 80 g.), eluting with benzene containing increasing proportions of ether, gave the *dicarboxylic acid* (II; R = OH) (39 mg.), m. p. 202—204° (from ethyl acetate–ether), $[\alpha]_D$ +61° (*c* 1·2), $\lambda_{max.}$ 224 mμ (ε 7500), $\nu_{max.}$ 1845, 1750, 1730, 1690 cm.$^{-1}$ (Found: C, 57·45; H, 7·1. $C_{15}H_{20}O_7$ requires C, 57·7; H, 6·45%). The derived (diazomethane) *dimethyl ester* (II; R = OMe) had m. p. 91—92° (from ethyl acetate–chloroform), $[\alpha]_D$ +55° (*c* 1·30), $\nu_{max.}$ 1830, 1770, 1730 cm.$^{-1}$ (Found: C, 60·25; H, 7·05. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1%).

Concentration of the mother-liquors from crystallisation of the dicarboxylic acid (II; R = OH) gave, on addition of chloroform and leaving at 0°, the isomer (III; R = OH), m. p. 203—205° (90 mg.) (from ethyl acetate–chloroform), $\lambda_{max.}$ 222 mμ (ε 8600), $\nu_{max.}$ 1840, 1775, 1705 cm.$^{-1}$. The derived (diazomethane) *dimethyl ester* (III; R = OMe) had m. p. 85—86° [from benzene–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +43° (*c* 0·93), $\nu_{max.}$ 1830, 1770, 1730 cm.$^{-1}$ (Found: C, 59·8; H, 7·2. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1%). The two dimethyl esters (II; R = OMe) and (III; R = OMe) gave a marked mixed m. p. depression and had different infrared spectra.

The isomeric dicarboxylic acid (III; R = OH) (36 mg.) in benzene (0·5 ml.) and oxalyl chloride (1 ml.) was heated under reflux for 2 hr. Removal of the excess reagent *in vacuo* gave the acid chloride (infrared spectrum). This was treated at room temperature for 15 min. with benzene (2 ml.) and anhydrous dimethylamine (0·5 ml.). Removal of the solvent *in vacuo* and separation into neutral and acidic fractions with aqueous sodium hydrogen carbonate gave, in the fomer, the bis-*NN-dimethylamide* (III; R = NMe_2), m. p. 213—214° (from ethyl acetate), $\lambda_{max.}$ 238 mμ (ε 7500), $\nu_{max.}$ 1835, 1770, 1643 cm.$^{-1}$ (Found: C, 61·8, 62·4; H, 8·1, 8·75. $C_{19}H_{30}N_2O_5$ requires C, 62·25; H, 8·25%).

(With Dr. J. E. Baldwin) Oxidation of the acid (II; R = OH) with chromic acid, under the conditions specified above, gave *meso*-diethylsuccinic acid, detected by paper chromatography.

Ozonolysis of Glaucanic Acid.—Glaucanic acid (500 mg.) in glacial acetic acid (redistilled; 100 ml.) was ozonised at room temperature until only weak ultraviolet absorption remained (24 hr.). The excess of ozone was removed by a rapid stream of nitrogen, and the acetic acid evaporated *in vacuo*, to furnish a colourless oil (637 mg.). Methylation (diazomethane; small portion) and gas chromatography showed that αβ-diethylglutaric acid and propane-1,2,2-tricarboxylic acid were the major products.

The combined ozonolysis product (1·27 g.) from two identical ozonolyses as above was chromatographed in chloroform over silica gel (B.D.H.; 600 g.) using 0·5N-hydrochloric acid

as the stationary phase.[9] Elution with chloroform containing n-butanol in increasing concentration gave αβ-diethylglutaric acid (215 mg.) (Equiv. 95. Calc. for $C_9H_{16}O_4$: 94·0). Methylation (diazomethane) and gas chromatography confirmed its identity. The acid gave a crystalline cyclohexylamine salt. After several crystallisations from dioxan the acid was recovered and sublimed in a high vacuum at 105°. It remained a viscous oil, $[\alpha]_D$ +24° (*c* 1·16), $\nu_{max.}$ ($CHCl_3$) 3500—2500, 1710 cm.$^{-1}$, although methylation (diazomethane) and gas chromatography confirmed its identity and homogeneity. A crystalline derivative was prepared as follows. The acid (47·5 mg.) in methanol (2 ml.) was adjusted to pH 6 and *p*-phenylphenacyl bromide (128 mg.) in methanol (2 ml.) added. After heating under reflux for 2 hr., slow cooling gave the *bis*-p-*phenylphenacyl ester* of (+)-αβ-*erythro*-diethylglutaric acid, m. p. 102—103° (76 mg.) (from methanol), $[\alpha]_D$ +65° (*c* 1·04), $\nu_{max.}$ 1738, 1695, 1605 cm.$^{-1}$ (Found: C, 76·65; H, 6·0. $C_{37}H_{36}O_6$ requires C, 77·05; H, 6·3%). The infrared spectrum of this ester in chloroform was identical with that of the corresponding bis-esters of (−)- and of (±)-αβ-*erythro*-diethylglutaric acid. The bis-ester from the glaucanic acid degradation gave the (±)-bis-ester on admixture with synthetic (see below) (−)-bis-ester.

More extensive ozonolysis of glaucanic acid (3—8 days) gave decreased yields of the αβ-diethylglutaric acid. Treatment of the acidic product with chloroform gave propane-1,2,2-tricarboxylic acid.[10] Pyrolysis *in vacuo* furnished methylsuccinic acid (m. p., mixed m. p., and infrared spectrum). Methylation (diazomethane) of the tricarboxylic acid gave the trimethyl ester (gas chromatography).

Synthesis of (±)-αβ-erythro-*Diethylglutaric Acid from* meso-*Diethylsuccinic Acid.*—*meso*-Diethylsuccinic acid (527 mg.) in acetic anhydride (redistilled, 25 ml.) was heated on a steam-bath for 2 hr., and the excess reagent then removed *in vacuo* to furnish *meso*-diethylsuccinic anhydride (474 mg.) (infrared spectrum). Dissolution of a small portion in aqueous sodium hydroxide (2N), and acidification, gave back *meso*-diethylsuccinic acid free from the (±)-diastereoisomer. *meso*-Diethylsuccinic anhydride (450 mg.) in methanol (5 ml.) was treated at 0° with the calculated volume of methanolic sodium methoxide (0·715N). Removal of the solvent *in vacuo* afforded monomethyl *erythro*-diethylsuccinate sodium salt (604 mg.) (infrared spectrum). This salt, suspended with stirring in methylene dichloride (15 ml.) at 0°, was treated with oxalyl chloride (5 ml.) for 14 hr. (exclusion of moisture). Filtration and evaporation *in vacuo* gave the crude acid chloride (570 mg.) (infrared spectrum). This, in anhydrous ether (10 ml.), was added dropwise with stirring to excess of ethereal diaomethane at 0° and left for 14 hr. at this temperature. The solvent was removed *in vacuo* and the resultant oily diazo-ketone (infrared spectrum) in tetrahydrofuran (75 ml.) and water (25 ml.) was irradiated at room temperature in a Pyrex flask with a high-pressure mercury-arc lamp under nitrogen for 14 hr. (infrared control with respect to the diazo-ketone band at 2130 cm.$^{-1}$). The bulk of the tetrahydrofuran was removed *in vacuo* and the product separated into acidic and neutral fractions. The former (325 mg.), having $\nu_{max.}$ 1728, 1712 cm.$^{-1}$, in methanolic potassium hydroxide (10%; 25 ml.) was heated under reflux for 16 hr. Working up in the usual way gave an acidic oil (263 mg.). Purified by distillation in a high vacuum at 105°, this crystallised on contact with light petroleum (b. p. 60—80°). Further purification by sublimation afforded (±)-αβ-*erythro*-diethylglutaric acid, m. p. 75—80°, $\nu_{max.}$ ($CHCl_3$) 3500—2500, 1710 cm.$^{-1}$. Treatment with *p*-phenylphenacyl bromide [as for the (+)-isomer; see above] gave the *bis*-p-*phenylphenacyl ester*, m. p. 104—105° (from methanol), $\nu_{max.}$ 1738, 1695, 1605 cm.$^{-1}$ (Found: C, 77·1; H, 6·3. $C_{37}H_{36}O_6$ requires C, 77·05; H, 6·3%).

Synthesis of (−)-αβ-erythro-*diethylglutaric Acid.*—*meso*-Diethylsuccinic anhydride (see above) (12·4 g.) in anhydrous ether (250 ml.) at 0° was treated with stirring with anhydrous dimethylamine (redistilled over potassium hydroxide; 25 ml.) and then left for 48 hr. at room temperature. The amine salt of the dimethylamide crystallised as large prisms. The ether and excess of dimethylamine were removed *in vacuo*. The product in ether (250 ml.) was stirred with water (50 ml.) containing Methyl Orange indicator while hydrochloric acid (6N) was added dropwise until neutral. Separation into acidic and neutral fractions gave, in the former, (±)-NN-*dimethyl*-erythro-*diethylsuccinamic acid* (13·25 g.), m. p. 102—103° [from ether–light petroleum (b. p. 60—80°)], $\nu_{max.}$ 1720, 1605 cm.$^{-1}$ (Found: C, 59·9; H, 9·6; N, 7·0. $C_{10}H_{19}NO_3$ requires C, 59·65; H, 9·5; N, 6·95%).

[9] C. S. Marvel and R. D. Rands, *J. Amer. Chem. Soc.*, 1950, **72**, 2642.
[10] E. E. Blaise and H. Gault, *Bull. Soc. chim. France*, 1911, **9**, 460.

This acid was resolved as follows. The acid (10·0 g.) in ethanol (150 ml.) was titrated to pH 9—10 with quinine methohydroxide.[11] The solvent was removed *in vacuo* (rotatory evaporator) and the residue dried by azeotropic distillation *in vacuo* with absolute ethanol and then ethyl acetate. The resultant product in ethyl acetate (100 ml.), left at 0° overnight, gave white crystals (15·36 g.), m. p. 205—210°. Fractional crystallisation from ethyl acetate–ethanol gave the salt (5·11 g.), m. p. 216—217°, of constant rotation, $[\alpha]_D$ −104° (*c* 1·07 in ethanol). The salt (4·7 g.) in water (150 ml.) was acidified at 0° with aqueous sulphuric acid (3N) to pH 4 in the presence of ether (150 ml.). The ether layer was separated, and the aqueous layer further extracted with ether. The product (1·63 g.) crystallised slowly. Recrystallisation from ether gave (+)-*NN*-dimethyl-*erythro*-diethylsuccinamic acid, m. p. 85—86°, $[\alpha]_D$ +31° (*c* 2·50 in ethanol), $\nu_{max.}$ 1720, 1605 cm.$^{-1}$. The infrared spectrum in chloroform was identical with that of the (±) isomer (see above).

The acid (1·0 g.) in ether (10 ml.) was treated with excess of ethereal diazomethane (redistilled). Removal of the solvent *in vacuo* and short-path distillation at 10^{-4} mm. gave (+)-*methyl* NN-*dimethyl*-erythro-*diethylsuccinamate*, n_D^{25} 1·452, $[\alpha]_D$ +29° (*c* 1·92), $\nu_{max.}$ 1730, 1645 cm.$^{-1}$ (Found: C, 61·15; H, 9·75; N, 6·4. $C_{11}H_{21}NO_3$ requires C, 61·35; H, 9·85; N, 6·5%).

This amide-ester (537 mg.) in acetic acid (redistilled; 55 ml.) was ozonised for 9 hr. at room temperature with infrared control (disappearance of band at 1645 and appearance of a new band at 1675 cm.$^{-1}$). Excess of ozone was removed with a vigorous stream of nitrogen, water (55 ml.) added, and the solution heated on a steam-bath for 1·5 hr. Removal of the solvent *in vacuo* and crystallisation of the product from benzene–light petroleum (b. p. 40—60°) gave (+)-*methyl* N-*methyl*-erythro-*diethylsuccinamate*, m. p. 120—121° (404 mg.). Further purified by sublimation *in vacuo*, this had m. p. 121—122°, $[\alpha]_D$ +28° (*c* 1·39), $\nu_{max.}$ 3495, 1725, 1670, 1550 cm.$^{-1}$ (Found: C, 59·75; H, 9·4; N, 6·65. $C_{10}H_{19}NO_3$ requires C, 59·65; H, 9·5; N, 6·95%).

This ester (345 mg.) in glacial acetic acid (14 ml.) and acetic anhydride (redistilled; 6 ml.) was treated at 5° for 4 hr. with nitrous fumes generated from the dropwise addition of aqueous sulphuric acid (6N) to sodium nitrite (60 g.). Removal of the solvents *in vacuo* at room temperature gave the *N*-nitroso-amide as a yellow oil (411 mg.), $\nu_{max.}$ ($CHCl_3$) 1725, 1010, 955 cm.$^{-1}$, which, in aqueous sodium hydrogen carbonate [15 ml. of saturated solution diluted with water (10 ml.)] was heated on a steam-bath for 30 min. (disappearance of yellow colour). After shaking with chloroform (50 ml.) the solution was acidified with aqueous sulphuric acid (2N), saturated with sodium chloride, and again extracted with chloroform. Removal of the solvent *in vacuo* gave a yellow oil which, in methanol, was treated with charcoal and filtered through Celite. Removal of the solvent *in vacuo* gave crystalline (−)-*methyl hydrogen* meso-*diethylsuccinate*. Further purified by sublimation *in vacuo* this had m. p. 63—64°, $[\alpha]_D$ −4° (*c* 1·56), $\nu_{max.}$ 3500—2500, 1723, 1710 cm.$^{-1}$ (Found: C, 57·45; H, 8·3. $C_9H_{16}O_4$ requires C, 57·45; H, 8·55%). The neutral chloroform extract (see above) was rehydrolysed, to furnish a further crop of the (−)-monomethyl ester (total yield, 92%). Treatment of the (−)-monomethyl ester with diazomethane gave homogeneous (gas chromatography) dimethyl *meso*-diethylsuccinate. (−)-Methyl hydrogen *meso*-diethylsuccinate was removed unchanged (and unracemised) after heating at 70° with excess of anhydrous dimethylamine in ethylene dichloride for 24 hr. in a sealed tube.

The (−)-monomethyl ester (218 mg.) was homologised as for the (±)-monomethyl ester (see above), to give, after hydrolysis, (−)-αβ-*erythro*-diethylglutaric acid (35 mg.), $[\alpha]_D$ −24° (*c* 0·75), $\nu_{max.}$ ($CHCl_3$) 3500—2500, 1710 cm.$^{-1}$. This acid could not be crystallised. Its infrared spectrum in chloroform was identical with that of the (+)- and (±)-isomers (see above). The dimethyl esters (diazomethane) of all three isomers showed the same behaviour on gas chromatography. The (−)-acid was converted into its *bis*-p-*phenylphenacyl ester* in the usual way (see above), m. p. 102—103° (from methanol), $[\alpha]_D$ −65° (*c* 1·03), $\nu_{max.}$ 1738, 1695, 1605 cm.$^{-1}$ (Found: C, 76·55; H, 6·35. $C_{37}H_{36}O_6$ requires C, 77·05; H, 6·3%).

NN-*Dimethyl*-α-*ethylvaleramide and Derivatives*.—α-Ethylvaleric acid [12] (3·8 g.) in thionyl chloride (redistilled; 5 ml.) was heated under reflux for 2 hr. The resultant acid chloride, b. p. 156—158°/750 mm., $\nu_{max.}$ 1798 cm.$^{-1}$, in anhydrous ether (50 ml.) was added dropwise with vigorous stirring at 0° to aqueous dimethylamine (26% w/v; 30 ml.) and left for 15 min. at ambient temperature. Distillation of the product gave *NN*-dimethyl-α-ethylvaleramide

[11] R. T. Major and J. Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.
[12] P. Rasetti, *Bull. Soc. chim. France*, 1905, **33**, 685.

(3·4 g.), b. p. 59—60°/1 mm., n_D^{24} 1·444, $\nu_{max.}$ 1645 cm.$^{-1}$. The amide gave a single peak on gas chromatography.

NN-Dimethyl-α-ethylvaleramide (677 mg.) in anhydrous ether (10 ml.) was heated under reflux for 2 hr. with lithium aluminium hydride (1·0 g.) in the same solvent (100 ml.). Working up in the usual way gave *NN*-dimethyl-2-ethylpentylamine (405 mg.), b. p. 146—148°/760 mm., $\nu_{max.}$ ($CHCl_3$) 3300, 2810, 1780 cm.$^{-1}$. The derived *picrate* crystallised from benzene–light petroleum (b. p. 60—80°) as yellow plates, m. p. 84—85°, $\nu_{max.}$ 2730, 1635, 1615 cm.$^{-1}$ (Found: C, 48·4; H, 6·8; N, 15·45. $C_{15}H_{24}N_4O_7$ requires C, 48·45; H, 6·5; N, 15·05%).

(±)-*NN*-Dimethyl-α-ethylvaleramide was ozonised as for (+)-methyl *NN*-dimethyl-*erythro*-diethylsuccinamate (see above) to furnish (±)-N-*methyl-α-ethylvaleramide*. After chromatography over alumina (neutral, Grade III; 30 g.), eluting with chloroform–benzene (1 : 9), and crystallisation from n-hexane, this had m. p. 71—72°, $\nu_{max.}$ 3340, 1645, 1575 cm.$^{-1}$. This amide was also prepared from α-ethylvaleryl chloride and methylamine (cf. above preparation with dimethylamine) and identity established (m. p., mixed m. p., and infrared spectrum).

Decarboxylation of (+)-NN-*Dimethyl*-erythro-*diethylsuccinamic Acid*.—The dimethylamide (1·39 g.) in dry carbon tetrachloride (350 ml.) containing lead tetra-acetate (4·7 g.) was stirred with a stream of dry oxygen-free nitrogen and irradiated with a tungsten lamp during the dropwise addition of iodine (2·5 g.) in the same solvent (100 ml.) until the violet colour persisted (83 ml. uptake). The precipitated lead diacetate (3·23 g.) was filtered off and the filtrate washed with excess of aqueous sodium pyrosulphite. Removal of the solvent *in vacuo* gave an iodine-containing oil (1·86 g.), which was taken up in glacial acetic acid (100 ml.) and shaken with zinc dust (activated; 10 g.) at room temperature for 48 hr. Working up of the neutral product in the usual way gave an oil (1·24 g.) having ε (221 mμ) 2700. Chromatography over neutral alumina (Grade III; 70 g.), eluting with ether–light petroleum (b. p. 60—80°) (1 : 4), afforded (+)-NN-*dimethyl-α-ethylvaleramide*. Purified by short-path distillation at 45°/0·1 mm., this had n_D^{23} 1·446, $[\alpha]_D$ +1·25° (neat; 1 dm.), $\nu_{max.}$ 1645 cm.$^{-1}$ (Found: C, 69·05; H, 11·9; N, 9·0. $C_9H_{19}NO$ requires C, 68·75; H, 12·2; N, 8·9%). The optical rotatory dispersion curve in n-hexane (*c* 1·44) showed [*M*]: (400 mμ) +8·4°; (300) +30; (250) +140. The infrared spectrum in chloroform was identical with that of the (±)-amide. The identity was further confirmed by a mixed gas chromatogram.

Reduction of (+)-*NN*-dimethyl-α-ethylvaleramide with lithium aluminium hydride as for the (±)-isomer (see above) gave the corresponding *NN*-dimethyl-2-ethylpentylamine characterised as the *picrate*, m. p. 77—78°, $\nu_{max.}$ 2730, 1635, 1615 cm.$^{-1}$ (Found: C, 48·45; H, 6·55. $C_{15}H_{24}N_4O_7$ requires C, 48·45; H, 6·5%). A satisfactory optical rotatory dispersion curve could not be obtained with this picrate.

(+)-*NN*-dimethyl-α-ethylvaleramide (198 mg.) was oxidatively demethylated with ozone (see above) to give (+)-N-*methyl-α-ethylvaleramide* (164 mg.), m. p. 94—95° (from n-hexane), $\nu_{max.}$ 3340, 1645, 1575 cm.$^{-1}$ (Found: C, 66·8; H, 11·65; N, 9·75. $C_8H_{17}NO$ requires C, 67·1; H, 11·95; N, 9·8%). The infrared spectrum in chloroform was identical with that of the (±)-isomer (see above), and the mixed gas chromatogram showed only one peak. The optical rotatory dispersion curve in methanol (*c* 0·66) showed [*M*]: (400 mμ) +9·15°; (345) +12·2; (291) +20·6; (286) +21·4; (278) +23·1; (256) +25·7; (250) +25·1; (233) +13·5.

NN-*Dimethyl*-threo-*diethylsuccinamic Acid and Derivatives*.—(+)-Diethylsuccinic acid [11] (3·0 g.) in thionyl chloride (redistilled; 5 ml.) was heated under reflux for 15 min., and the excess reagent removed *in vacuo*. Distillation of the residue gave the anhydride (2·7 g.),[11] b. p. 80°/0·1 mm., n_D^{25} 1·445, $[\alpha]_D^{25}$ +81° (*c* 8·10 in benzene), $\nu_{max.}$ 1859, 1786 cm.$^{-1}$. This compound (2·5 g.) in anhydrous ether (60 ml.) was treated with anhydrous dimethylamine (6 ml.) at 0° for 2 hr. and then left at ambient temperature for 24 hr. Removal of the solvent and excess of amine *in vacuo* gave, on short-path distillation at 70—90°/10^{-4} mm., *NN*-dimethyl-*threo*-diethylsuccinamic acid (3·16 g.), $[\alpha]_D$ +42° (*c* 2·40 in ethanol), $\nu_{max.}$ ($CHCl_3$) 3500—2500, 1723, 1595 cm.$^{-1}$. The derived p-*phenylphenacyl ester*, prepared in the usual way and purified by chromatography over neutral alumina (Grade III; 10 g.) eluting with 15% chloroform in benzene, had m. p. 101—102° (from benzene–cyclohexane), $[\alpha]_D$ +25° (*c* 1·00), $\nu_{max.}$ 1740, 1700, 1640, 1605 cm.$^{-1}$ (Found: C, 72·9; H, 7·85; N, 3·5. $C_{24}H_{29}NO_4$ requires C, 72·9; H, 7·35; N, 3·55%).

(+)-*NN*-Dimethyl-*threo*-diethylsuccinamic acid (2·39 g.) was decarboxylated with lead tetra-acetate–iodine as for the *erythro*-isomer (see above), and further processed to give (−)-NN-*dimethyl-α-ethylvaleramide*, b. p. 120—125°/10 mm., n_D^{24} 1·445, $[\alpha]_D$ −1·09° neat; 1 dm.), $\nu_{max.}$ 1645 cm.$^{-1}$ (Found: C, 68·9; H, 12·3; N, 9·3. $C_9H_{19}NO$ requires C, 68·75; H, 12·2; N,

8·9%). The infrared spectrum in chloroform was identical with those for the (+)- and (±)-isomers, and mixed gas chromatograms gave single peaks only. The optical rotatory dispersion curve in n-hexane (*c* 1·09) showed [*M*]: (400 mμ) −7°; (300) −22; (250) −94·5.

(−)-*NN*-dimethyl-α-ethylvaleramide (792 mg.) was oxidatively demethylated with ozone, as in the previous examples, to furnish (−)-N-*methyl-α-ethylvaleramide*, m. p. 92—93° (471 mg.) (from n-hexane), $\nu_{max.}$ 3340, 1645, 1575 cm.$^{-1}$ (Found: N, 9·8. $C_8H_{17}NO$ requires N, 9·8%). The optical rotatory dispersion curve in methanol (*c* 0·64) showed [*M*]: (400 mμ) −16°; (298) −30; (250) −20; (238) ±0, (230) +24. The infrared spectrum in chloroform was identical with those for the (+)- and (±)-isomers, and mixed gas chromatograms gave single peaks only. Admixture of equal amounts of (+)- and (−)-*N*-methyl-α-ethylvaleramides gave the (±)-isomer.

(−)-*N*-methyl-α-ethylvaleramide (348 mg.) was nitrosated and further processed as in the prior example, to furnish (−)-α-ethylvaleric acid (147 mg.), b. p. 120°/10 mm., n_D^{28} 1·416, $[\alpha]_D$ −4·2° (neat; 1 dm.), $\nu_{max.}$ 1705 cm.$^{-1}$. Methylation (diazomethane) gave the methyl ester which ran as a single peak on mixed gas chromatography with the racemic ester. The infrared spectra of the (−)- and (±)-acids were identical.

Further Examples of Oxidative De-N-*methylation.*—(a) *Chromic acid oxidations.* The oxidant solution was prepared and used as follows. Chromium trioxide (2·27 g.) in water (1·6 ml.) was diluted with glacial acetic acid (32 ml.). The reaction solutions were kept at room temperature for 24 hr. and then poured into excess of aqueous sodium pyrosulphite solution and the resultant solution extracted thoroughly with ether. After drying (Na_2SO_4) the ether was removed *in vacuo*.

NN-Dimethylstearamide (3·69 g.) with the oxidant (185 ml.) gave N-*methyl*-N-*formylstearamide*, m. p. 78—79° (660 mg.) (from methanol), $\nu_{max.}$ 1723, 1670 cm.$^{-1}$ (Found: C, 74·2; H, 11·85; N, 4·3%; *M*, 326. $C_{20}H_{39}NO_2$ requires C, 73·8; N, 12·1; N, 4·3%; *M*, 331). This compound (154 mg.) in acetic acid (12 ml.) and aqueous hydrochloric acid (6N; 6 ml.) was heated under reflux for 24 hr., to furnish stearic acid (136 mg.) (m. p., mixed m. p., and infrared spectrum). The amide (112 mg.) in acetic acid (8 ml.) and water (5 ml.) was heated on a steam-bath for 3 hr., to give *N*-methylstearamide (m. p., mixed m. p., and infrared spectrum) in essentially quantitative yield.

(±)-*NN*-Dimethyl-*erythro*-diethylsuccinamic acid (484 mg.) with the oxidant (24 ml.) gave (±)-N-*methyl*-erythro-*diethylsuccinamic acid* (138 mg.), m. p. 184—185° (from ethyl acetate), $\nu_{max.}$ 3340, 1705, 1650, 1570 cm.$^{-1}$ (Found: C, 57·25; H, 9·1; N, 7·55. $C_9H_{17}NO_3$ requires C, 57·75; H, 9·15; N, 7·5%), identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen prepared from *meso*-diethylsuccinic anhydride and methylamine as for the reaction of diethylamine (see above). The methylamide gave, with diazomethane, (±)-*methyl* N-*methyl*-erythro-*diethylsuccinamate*, m. p. 102—103° [from benzene–light petroleum (b. p. 60—80°)], $\nu_{max.}$ ($CHCl_3$) 3495, 1725, 1670, 1550 cm.$^{-1}$ (Found: C, 60·0; H, 9·45; N, 7·15. $C_{10}H_{19}NO_3$ requires C, 59·65; H, 9·5; N, 6·95%), identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen.

N-Methyl-*erythro*-diethylsuccinamic acid (22 mg.) with the oxidant (1·1 ml.) gave a crude product, m. p. 150—155°. Methylation (diazomethane) and gas chromatography showed the presence of 60% starting material and of 40% of *erythro*-diethylsuccinamic acid.

(b) *Ozonolysis.* The general procedure has already been given above for the ozonolysis of (+)-methyl *NN*-dimethyl-*erythro*-diethylsuccinamate. In a further example, (±)-*NN*-dimethyl-*erythro*-diethylsuccinamic acid (35 mg.) in glacial acetic acid (redistilled; 5 ml.) was ozonised at room temperature for 6 hr. The excess of ozone was removed with a vigorous stream of nitrogen for 30 min. The solvent was removed *in vacuo* and the product crystallised from ethyl acetate to give (±)-*N*-methyl-*erythro*-diethylsuccinamic acid (m. p., mixed m. p., and infrared spectrum). Further ozonolysis of this amido-acid under the same conditions gave back quantitatively unchanged starting material.

We thank Professor H. Schmid (Zürich) for a specimen of (+)-diethylsuccinic acid, Professor W. Klyne and Mr. J. P. Jennings (Westfield College) for the optical rotatory dispersion measurements, and Dr. J. E. Baldwin for the experiment indicated.

IMPERIAL COLLEGE, LONDON S.W.7. [*Received, August 10th,* 1964.]