943. *Aliphatic Hydroxy-acids. Part I. Some Sapogenin Degradation Products.*

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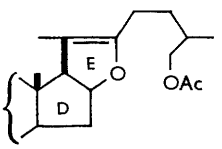
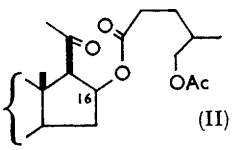
The racemic forms of two sapogenin degradation products (III and IV) related to a methyl-branched aliphatic hydroxy-acid have been synthesised. (±)-5-Acetoxy-4-methylpentanoic acid (III) was obtained by oxidation of 2-methylhex-5-en-1-yl acetate (V; R = Ac) and was converted into (±)-*N*-diphenylmethyl-5-hydroxy-4-methylpentanamide (IV), that was also obtained from the lactone resulting from demethylation of 5-methoxy-4-methylpentanoic acid.

Degradation of sarsasapogenin (25L-5β,22β-spirostan-3β-ol) by Callow and Massy-Beresford's procedure gave the (−)-form of the diphenylmethylamide (IV).

Two degradative procedures for sapogenins are known which lead to optically active derivatives of 5-hydroxy-4-methylpentanoic acid containing the 22—27-side-chain. In both, rings E and F are opened by conversion of the sapogenin into the corresponding pseudosapogenin acetate (I), which on controlled oxidation gives the related pregnan-20-one (II). In one procedure, based on the work of Marker,[1] the 16-acyloxy-substituent



(I)



(II)

(III) $AcO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H$ $HO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO{\cdot}NH{\cdot}CHPh_2$ (IV)

is eliminated by treatment with acids or bases and can be isolated as 5-acetoxy-4-methylpentanoic acid (III). Although this degradation has been performed on sapogenins of both the 25D- and the 25L-configuration, the acid (III) has only been isolated in experiments with 25D-sapogenins (hecogenin,[2] diosgenin [3]), the (+)-isomer being obtained. In the other procedure, due to Callow and Massy-Beresford,[4] acid-catalysed methanolysis of the 16-acyloxy-derivative (II) gives methyl 5-hydroxy-4-methylpentanoate, contaminated by lactonic impurities, from which the crystalline diphenylmethylamide (IV) is easily obtained. This procedure has hitherto only been applied to a 25D-sapogenin (tigogenin).

We now report direct syntheses of the racemic forms of the degradation products (III and IV) and the degradation of a 25L-sapogenin by the second procedure.

Our initial aim was the synthesis of the (±)-acetoxy-acid (III) by oxidation of the unsaturated acetate (V; R = Ac), which was prepared as follows. But-3-en-1-ol, ob-

(V) $RO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CH{=}CH_2$ $HO_2C{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CH{=}CH_2$ (VI)

tained by the Grignard synthesis from allyl chloride,[5] was converted into the toluene-*p*-sulphonate, which was condensed with ethyl methylsodiomalonate; the best yield was obtained by carrying out the condensation in a non-polar solvent. Hydrolysis and decarboxylation of the disubstituted malonic ester gave 2-methylhex-5-enoic acid (VI), which with lithium aluminium hydride afforded the alcohol (V; R = H). The terminal position of the double bond in the derived acetate (V; R = Ac) and its precursors was established by infrared spectroscopy.

[1] Marker, *J. Amer. Chem. Soc.*, 1940, **62**, 518, 3350; Wall, Kenney, and Rothman, *ibid.*, 1955, **77**, 5665; cf. Martín Panizo, *Anales real Soc. espaň. Fis. Quím.*, 1961, **57** *B*, 299.
[2] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[3] F. Giral and J. Giral B., *Chem. Ber.*, 1960, **93**, 2825.
[4] Callow and Massy-Beresford, *J.*, 1958, 2645.
[5] Ettlinger and Hodgkins, *J. Amer. Chem. Soc.*, 1955, **77**, 1831

Two examples of the permanganate oxidation of esters containing a terminal double bond to the ester-acid having one less carbon atom are known,[6] but oxidation of the unsaturated acetate (V; R = Ac) with potassium permanganate in acetone gave impure material. Accordingly we prepared the aldehyde (III; CHO in place of CO_2H) and oxidised this by air in aqueous manganous chloride [7] to the desired (±)-5-acetoxy-4-methylpentanoic acid (III), which was characterised as its *S*-benzylthiouronium salt. The corresponding crude methyl ester afforded the (±)-diphenylmethylamide (IV).

We next investigated the action of acetic anhydride and toluene-*p*-sulphonic acid on (±)-5-methoxy-4-methylpentanoic acid, $MeO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H$, as this reagent converts certain methyl ethers into the corresponding acetates.[8] The toluene-*p*-sulphonate of (±)-3-methoxy-2-methylpropan-1-ol (readily available [9] from methyl methacrylate) with ethyl sodiomalonate gave the required methoxy-acid after the usual hydrolysis and decarboxylation. When this acid was treated with acetic anhydride–toluene-*p*-sulphonic acid for 1 hr. at 140° and the product was heated for 2 hr. with acetic acid (to decompose anhydrides) a complex mixture was obtained from which none of the desired acetoxy-acid (III) could be isolated. A small quantity of (±)-5-hydroxy-4-methylpentanoic acid lactone was, however, isolated and it was converted into the (±)-diphenylmethylamide (IV), identical with that prepared as described above.

In order to make spectroscopic comparisons we prepared the optically active counterparts of our synthetic products from (+)-5-acetoxy-4-methylpentanoic acid (III) derived from hecogenin [3] (a 25D-sapogenin) supplied by Glaxo Laboratories Ltd. Some amide derivatives of this acid have recently been prepared [3] through the acid chloride, but we find that the acid is most conveniently characterised as its *S*-benzylthiouronium salt. Acid-catalysed methanolysis of the (+)-acid (III) gave (+)-methyl 5-hydroxy-4-methylpentanoate, contaminated with lactone, from which the (+)-diphenylmethylamide [4] (IV) and the hydrazide were prepared. The infrared spectra of the racemic and the optically active forms of the acetoxy-acid (III) and of its *S*-benzylthiouronium salt and diphenylmethylamide (IV) were severally identical.

Finally, we degraded sarsasapogenin (25L-5β,22β-spirostan-3β-ol) by Callow and Massy-Beresford's method [4] (the most convenient on a small scale) to (−)-*N*-diphenylmethyl-5-hydroxy-4-methylpentanamide (IV) which, like the (+)-isomer, had m. p. 118—119°. A mixture of equal parts of the enantiomorphous amides (IV) had m. p. 101—102°; the m. p. was undepressed on admixture with the synthetic racemic amide (IV) of m. p. 101—102°.

Experimental

Solutions in organic solvents were dried over anhydrous sodium sulphate. Petrol refers to light petroleum of b. p. 60—80°. Rotations marked (E) were measured on an ATL–NPL automatic polarimeter, of type 143A, with a 0·2 dm. cell. Other rotations were measured in a 2 dm. tube.

2-Methylhex-5-enoic Acid.—But-3-en-1-ol was prepared [5] from formaldehyde and allylmagnesium chloride and was treated with pyridine and toluene-*p*-sulphonyl chloride. The crude toluene-*p*-sulphonate (99 g.) was condensed with ethyl methylsodiomalonate (from 70 g. of ethyl methylmalonate and 12·0 g. of sodium hydride in 1 l. of xylene under nitrogen), giving *ethyl but-3-enylmethylmalonate* (*hex-5-ene-2,2-dicarboxylate*) (63·0 g., 69%), b. p. 123—127°/17 mm., n_D^{22} 1·4344. In earlier experiments this ester, b. p. 113—115°/10 mm., n_D^{20} 1·4330, $\nu_{max.}$ 910, 995 (=C=CH_2) cm.$^{-1}$ (Found: C, 62·9; H, 8·9. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%), was prepared from 1-bromobut-3-ene [10] and ethyl methylsodiomalonate in ethanol. Ethyl butenylmethylmalonate (9·3 g.), potassium hydroxide (9·5 g.), and water (10 c.c.) were shaken at room temperature for 8 hr. *Butenylmethylmalonic acid* (5·0 g., 71%), isolated by acidification

[6] Ställberg, *Acta Chem. Scand.*, 1956, **10**, 1360; Grün and Wirth, *Ber.*, 1922, **55**, 2206.
[7] Cf. Diaper and Mitchell, *Canad. J. Chem.*, 1960, **38**, 1976.
[8] Huffmann and Lott, *J. Biol. Chem.*, 1948, **172**, 789; Morgan and Polgar, *J.*, 1957, 3779.
[9] Brettle and Polgar, *J.*, 1959, 664.
[10] Linstead and Rydon, *J.*, 1934, 1995; Newman and Rydon, *J.*, 1936, 261.

and ether-extraction and crystallised from benzene–petrol (19 : 1), had m. p. 93° (Found: C, 55·9; H, 7·0. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%). This acid was decarboxylated at 160°; distillation then gave *2-methylhex-5-enoic acid*, b. p. 107—108°/12 mm., n_D^{22} 1·4354, $\nu_{max.}$ 915, 990 (=C=CH_2) cm.$^{-1}$ (Found: C, 66·0; H, 9·4. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%).

2-Methylhex-5-en-1-yl Acetate.—2-Methylhex-5-enoic acid (15·4 g.) in ether (50 c.c.) was added to a stirred suspension of lithium aluminium hydride (5 g.) in ether (150 c.c.) at such a rate that the ether boiled gently. The excess of hydride was decomposed in the usual way, 3·6N-sulphuric acid (550 c.c.) added, and the aqueous layer extracted three times with ether. The combined ethereal solutions were washed with saturated aqueous sodium hydrogen carbonate and water, ied, and distilled, affording *2-methylhex-5-en-1-ol* (10·5 g., 77%), b. p. 166—168°/736 mm., n_D^{22} 1·4382, $\nu_{max.}$ 910, 995 (=C=CH_2) cm.$^{-1}$ (Found: C, 73·4; H, 12·4. $C_7H_{14}O$ requires C, 73·6; H, 12·4%). The alcohol (9·5 g.) with acetic anhydride (8·5 g.) and a trace of sulphuric acid at 140° (2 hr.) gave the *acetate* (9·5 g., 73%), b. p. 182—184°/747 mm., n_D^{22} 1·4253, $\nu_{max.}$ 910, 995 (=C=CH_2) cm.$^{-1}$ (Found: C, 69·1; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

Ozonolysis of 2-Methylhex-5-en-1-yl Acetate.—A stream of ozone and oxygen was passed through a solution of the acetate (10 g.) in acetic acid (100 c.c.) at room temperature for 20 hr. The solution was diluted with ether (200 c.c.) and treated with zinc dust (2 g.) and water (0·5 c.c.), then more water (5 c.c.) was slowly added; the mixture was stirred and refluxed until all the ozonide had been reduced (6 hr.). Solids were removed and washed with ether, and the combined ethereal solutions washed with water (2 × 100 c.c.), saturated aqueous sodium hydrogen carbonate (2 × 100 c.c.), and water (2 × 100 c.c.). Organic material was recovered from the washings by continuous ether-extraction and was added to the bulk of the ethereal solution. Distillation of the dried ethereal solution gave fractions (7 g.) of b. p. 100—160°/14 mm., which were oxidised as described below. In a similar experiment ozonolysis of the acetate (3·9 g.) gave a crude aldehyde fraction (1 g., 25%), b. p. 100—105°/10 mm., from which the (±)-*5-acetoxy-4-methylpentanal 2,4-dinitrophenylhydrazone* was prepared as orange needles, m. p. 86° (Found: C, 49·9; H, 5·5; N, 16·3. $C_{14}H_{18}N_4O_6$ requires C, 49·7; H, 5·4; N, 16·6%).

(±)-*5-Acetoxy-4-methylpentanoic Acid.*—The above ozonolysis product of 2-methylhex-5-en-1-yl acetate (7 g.) was added to 2% aqueous manganous chloride (120 c.c.), and air was drawn through the mixture for 72 hr. Continuous ether-extraction then gave (±)-*5-acetoxy-4-methylpentanoic acid*, b. p. 149—151°/8 mm., n_D^{19} 1·4412 (Found: C, 54·8; H, 8·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%). The S-*benzylthiouronium* salt, after recrystallisation from water, had m. p. 127° (Found: C, 56·7; H, 7·0; N, 8·2; S, 9·65. $C_{16}H_{24}N_2O_4S$ requires C, 56·5; H, 7·1; N, 8·2; S, 9·4%). The infrared spectra of the (±)-acid and its derivative were identical with those of the corresponding optically active compounds (see below).

Derivatives of (+)-*5-Acetoxy-4-methylpentanoic Acid.*—Pure (+)-5-acetoxy-4-methylpentanoic acid had b. p. 158—160°/10 mm., n_D^{26} 1·4388, $[\alpha]_D^{19}$ +7·2° (*c* 20·7 in $CHCl_3$) (Found: C, 55·3; H, 8·3%; equiv., 176. Calc. for $C_8H_{14}O_4$: equiv., 174). Brettle, Polgar, and Smith record [11] b. p. 160°/10 mm., n_D^{18} 1·4400. Giral and Giral [3] give $[\alpha]_D^{20}$ +7·5°. The S-*benzylthiouronium salt*, crystallised from water, had m. p. 135° (Found: C, 56·3; H, 7·1; N, 8·2; S, 9·1). The *p*-bromoanilide had m. p. 66° (lit.,[3] 63—66°) (Found: C, 50·9; H, 5·6; Br, 24·6; N, 4·4. Calc. for $C_{14}H_{18}BrNO_3$: C, 51·2; H, 5·5; Br, 24·3; N, 4·3%).

(+)-*5-Hydroxy-4-methylpentanoic Acid Lactone.*—(+)-5-Hydroxy-4-methylpentanoic acid lactone, prepared from the corresponding acetoxy-acid, had b. p. 101—102°/7 mm., n_D^{22} 1·4520, $[\alpha]_D^{20}$ + 12·75° (homogeneous), +16·8° (*c* 10·5 in $CHCl_3$) (Found: C, 63·3; H, 8·9. Calc. for $C_6H_{10}O_2$: C, 63·1; H, 8·8%). Giral and Giral [3] record b. p. 100—105°/4 mm. The lactone remained liquid at room temperature for 10 days, but when heated for 18 hr. at 100° was converted into the linear polyester, m. p. 66—69°, $[\alpha]_D^{21}$ +8·1° (*c* 9·6 in $CHCl_3$). Giral and Giral [3] record $[\alpha]_D^{20}$ +5·3° (*c* 0·6 in $CHCl_3$).

(+)-*N-Diphenylmethyl-5-hydroxy-4-methylpentanamide.*—Crude (+)-methyl 5-hydroxy-4-methylpentanoate, b. p. 112—114°/13 mm., was prepared by acid-catalysed methanolysis of the (+)-acetoxy-acid and was converted into derivatives in the usual way. The *hydrazide* had m. p. 54° (from ethyl acetate–petrol) (Found: C, 49·4; H, 9·3; N, 19·65. $C_6H_{14}N_2O_2$ requires C, 49·3; H, 9·6; N, 19·2%). The (+)-*N*-diphenylamide, crystallised from benzene, had m. p. 118—119°, $[\alpha]_D^{23}$ +8·0° (*E*; *c* 10·0 in $CHCl_3$). Callow and Massy-Beresford [4] record m. p. 118—119°, $[\alpha]_D$ +8°.

[11] Brettle, Polgar, and Smith, *J.*, 1960, 2802.

(−)-N-*Diphenylmethyl-5-hydroxy-4-methylpentanamide*.—Sarsasapogenin, m. p. 198—200°, $[\alpha]_D^{20}$ −65° (lit.,[12] m. p. 200°, $[\alpha]_D$ −75°), was converted into pseudosarsasapogenin, m. p. and mixed m. p. 167—169°, in 55% yield by the method of Wall and Serota.[13] Pseudosarsasapogenin (6·5 g.) was heated in 1 : 1 pyridine–acetic anhydride on a steam-bath for 1 hr. The solvents were evaporated under reduced pressure, and the residue was dissolved in carbon tetrachloride and evaporated to dryness six times. Chromic oxide (6·5 g.) in 80% aqueous acetic acid (65 c.c.) was added to the resultant diacetate in acetic acid (65 c.c.). The temperature rose to 60°, and the mixture was stirred at room temperature for 2 hr. Ethanol (5 c.c.) was added, and the solution poured into water (500 c.c.). This solution was saturated with sodium chloride and extracted with ether (5 × 200 c.c.), and the extracts were washed with aqueous sodium hydrogen carbonate and water, and dried. The oxidation product (6·4 g.), obtained on distillation of the ether, was refluxed for 3 hr. with N-methanolic hydrogen chloride (65 c.c.) and then left overnight at room temperature. The pH was adjusted to 6 with methanolic potassium hydroxide, and the solution was evaporated. The residue was dissolved in ether, which was then dried, filtered, and distilled, giving crude (−)-methyl 5-hydroxy-4-methylpentanoate (700 mg.), b. p. 90—95°/7 mm., which was converted into the *N*-diphenylmethylamide in the known manner. (−)-N-*Diphenylmethyl-5-hydroxy-4-methylpentanamide* had m. p. 118—119°, $[\alpha]_D^{23}$ −8·2° (E; *c* 16·8 in $CHCl_3$) (Found: C, 76·8; H, 7·55; N, 5·0. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8; N, 4·7%). The infrared spectrum was identical with that of the (+)-isomer.

(±)-5-*Methoxy-4-methylpentanoic Acid*.—(±)-3-Methoxy-2-methylpropan-1-ol, b. p. 154—158°, n_D^{20} 1·4175, was prepared by reduction of methyl 3-methoxy-2-methylpropionate (from methanol and methyl methacrylate) as described previously,[9] and was treated with pyridine and toluene-*p*-sulphonyl chloride. Condensation of the toluene-*p*-sulphonate with ethanolic ethyl sodiomalonate in the usual manner, followed by hydrolysis and decarboxylation, yielded (±)-5-*methoxy-4-methylpentanoic acid*, b. p. 132—133°/10 mm., n_D^{21} 1·4328 (Found: C, 57·2; H, 9·5%; equiv., 149. $C_7H_{14}O_5$ requires C, 57·5; H, 9·65%; equiv., 146). The S-*benzylthiouronium salt*, after crystallisation from water, had m. p. 146—147° (Found: C, 57·4; H, 7·4; N, 8·8; S, 10·4. $C_{15}H_{24}N_2O_3S$ requires C, 57·7; H, 7·7; N, 9·0; S, 10·3%). The overall yield of the acid, calculated on (±)-3-methoxy-2-methylpropan-1-ol, was 53%.

(±)-N-*Diphenylmethyl-5-hydroxy-4-methylpentanamide*.—(*a*) (±)-5-Methoxy-4-methylpentanoic acid (14·6 g., 1 mol.), toluene-*p*-sulphonic acid (19·1 g., 1 mol.), and acetic anhydride (150 g., 15 mol.) were heated under reflux for 1 hr. The solution was then cooled, diluted with water (500 c.c.), and stirred. The product was extracted with ether, the extracts were washed with water and dried, and the ether was removed. The residue was refluxed with acetic acid (150 g.) for 2 hr. Distillation then gave two fractions, b. p. 105—107°/8 mm., n_D^{20} 1·4431, and b. p. 150—152°/8 mm., n_D^{19} 1·5148. (±)-5-Acetoxy-4-methylpentanoic acid has b. p. 149—151°/8 mm., but n_D^{19} 1·4412. Fractionation of the lower-boiling fraction gave (±)-5-*hydroxy-4-methylpentanoic acid lactone*, b. p. 110—112°/18 mm., n_D^{18} 1·4574 (Found: C, 62·6; H, 8·4. $C_6H_{10}O_2$ requires C, 63·1; H, 8·2%). The (+)-lactone has b. p. 101—102°/7 mm., n_D^{22} 1·4520, and an almost identical infrared spectrum. Reaction of the (±)-lactone with diphenylmethylamine gave (±)-N-*diphenylmethyl-5-hydroxy-4-methylpentanamide*, m. p. 101—102° (from benzene) (Found: C, 76·8; H, 7·7; N, 4·9. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·8; N, 4·7%).

(*b*) (±)-*N*-Diphenylmethyl-5-hydroxy-4-methylpentanamide was prepared from a specimen of (±)-acid containing some of the (±)-lactone by the method used for the (+)-amide, and, after recrystallisation from benzene, had m. p. and mixed m. p. 100—101°.

(*c*) A mixture of equal weights of the (−)- and the (+)-form of the amide had m. p. 101—102°, undepressed on admixture with the synthetic (±)-amide. The infrared spectra of (+)-, (−)-, and (±)-amides were identical.

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[12] Fieser and Fieser, "Steroids," Reinhold Publ. Corpn., New York, 1959, p. 831.
[13] Wall and Serota, *J. Amer. Chem. Soc.*, 1957, **79**, 6481.