Alkanediazoates. Part XIII.† Synthesis of Azoxyalkanes: L-Dihydroelaiomycin [4-Methoxy-3-(octyl-*ONN*-azoxy)butan-2-ol]

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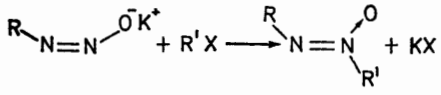
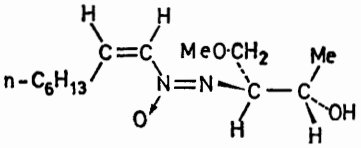
L-Threonine was converted in ten steps into potassium (2*R*,3*R*)-1-methoxy-3-tetrahydropyranyloxybutane-2-diazoate (10), which was then alkylated with *n*-octyl iodide. Removal of the tetrahydropyranyl group afforded L-dihydroelaiomycin in an overall yield of 8% for twelve steps. The synthetic product was compared with its D-enantiomer, prepared by reduction of natural elaiomycin over 5% rhodium–alumina.

We recently showed that the alkylation of alkanediazoates constituted a regiospecific synthesis of unsymmetrical azoxyalkanes.[1] Moreover, chirality could



readily be introduced at either R or R′; the synthesis was, in fact, stereospecific.[2] Our attention next turned to synthesis of the more complicated, naturally occurring azoxyalkanes, elaiomycin (1)[3] and LL-BH872α (2);[4] the former exhibits both antibiotic and carcinogenic properties.[5]



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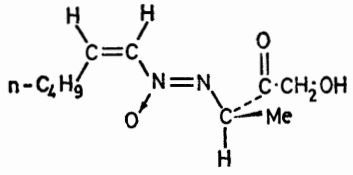
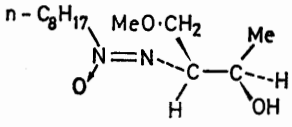


(2)

Our initial objective was L-dihydroelaiomycin (3); we now report a synthesis of this compound from L-threonine ‡ in twelve steps and in 8% overall yield, and comment briefly on the mechanism of the coupling reaction.

The key urethane (4) was obtained from the corresponding amine, itself derived from L-threonine by a modification of Stevens' method.[3d] L-Threonine was



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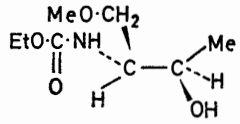
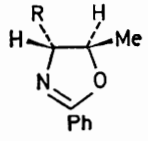


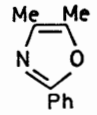
(4)

quantitatively converted into its ethyl ester hydrochloride,[6] and thence, by reaction with ethyl benzimidate,[7] into the oxazoline ester (5). Hydride reduction then gave the alcohol (6) § in 98% yield, which quantitatively yielded a syrupy tosylate (7); this could be purified by t.l.c. on silica gel.

Refluxing crude (7) with sodium methoxide in methanol[3d] gave, in addition to the desired ether (8), *ca.* 15% of 4,5-dimethyl-2-phenyloxazole (9), isolated by g.l.c. and identified by comparison of its i.r. spectrum with published data.[8] The extent of the elimination reaction leading to (9) was reduced to 5%, when a 0·23M-solution of (7) was treated with 0·4M-sodium



(5) R = CO_2Et
(6) R = CH_2OH
(7) R = CH_2OTs
(8) R = CH_2OMe



(9)

methoxide in methanol, at 50—52° for 96 h. Pure (8) could then be isolated by g.l.c., or by careful distillation; yield, 70%.

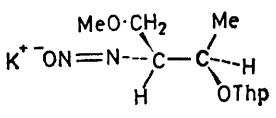
† Part XII, ref. 2.
‡ Natural elaiomycin is related to D-threonine.[3d]
§ This is a skin irritant; contact should be avoided.

[1] R. A. Moss, M. J. Landon, K. M. Luchter, and A. Mamantov, *J. Amer. Chem. Soc.*, 1972, **94**, 4392.
[2] R. A. Moss and G. M. Love, *J. Amer. Chem. Soc.*, 1973, **95**, 3070.
[3] (*a*) T. H. Haskell, A. Ryder, and Q. R. Bartz, *Antibiot. Chemother.*, 1954, **4**, 141; (*b*) C. L. Stevens, B. T. Gillis, J. C. French, and T. H. Haskell, *J. Amer. Chem. Soc.*, 1956, **78**, 3229; (*c*) *ibid.*, 1958, **80**, 6088; (*d*) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *ibid.*, 1959, **81**, 1435; (*e*) K. G. Taylor and T. Riehl, *ibid.*, 1972, **94**, 250.
[4] (*a*) W. J. McGahren and M. P. Kunstmann, *J. Amer. Chem. Soc.*, 1969, **91**, 2808; (*b*) *ibid.*, 1970, **92**, 1587; (*c*) *J. Org. Chem.*, 1972, **37**, 902; (*d*) see also ref. 3*e*.
[5] R. Schoental, *Nature*, 1969, **221**, 765; A. G. Karlson, *Antibiot. Chemother.*, 1962, **12**, 446; J. Ehrlich, *et. al.*, *ibid.*, 1954, **4**, 338.
[6] D. F. Elliot, *J. Chem. Soc.*, 1949, 589.
[7] A. Pinner, *Ber.*, 1883, **16**, 1654; C. A. Mackenzie, G. A. Schmidt, and L. R. Webb, *J. Amer. Chem. Soc.*, 1951, **73**, 4990.
[8] Y. Yura, *Chem. and Pharm. Bull* (*Japan*), 1962, **10**, 1087.

The ether (8), containing 4% of (9), was hydrolysed in refluxing 6N-hydrochloric acid for 6 h. Benzoic acid was extracted with ether, and the aqueous amine hydrochloride was neutralized with sodium carbonate and converted *in situ* into the urethane (4) with ethereal ethyl chloroformate. The crude product contained 69% of (4) and 31% of the oxazole (9), which was identified in the mixture by its characteristic n.m.r. methyl singlets at δ ($CDCl_3$) 2·12 and 2·27. More oxazole had apparently formed during the hydrolysis of (8).

Treatment of the product mixture in ether with dry hydrogen chloride, followed by cooling and dilution with pentane, precipitated the hydrochloride of (9); the supernatant yielded the urethane (4) in 48% yield based on (8).

The tetrahydropyranyl (Thp) derivative of (4) was prepared in 98% yield by treatment with ethereal dihydropyran and a catalytic amount of toluene-*p*-sulphonic acid. Conversion into the *N*-nitroso-urethane with dinitrogen tetraoxide was followed by cleavage to the diazoate (10), with 2 equiv. of potassium t-butoxide in ether, according to established methods.[9,10] The



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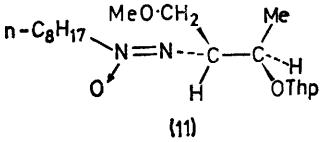


(11)

diazoate (10) in dry hexamethylphosphoric triamide reacted with 5 equiv. of 1-iodo-octane to give the octyl derivative (11), which on treatment with methanolic toluene-*p*-sulphonic acid, followed by repetitive thick-layer chromatography on silica gel, gave pure L-dihydroelaiomycin (3), in 36% yield based on the *N*-nitroso-tetrahydropyranyl derivative of (4).

The i.r. spectrum of the product (3) [$\nu_{max.}$ 3440m (OH), 2900s (CH), 1494s and 1305m (azoxy [1]), and 1116s cm^{-1} (ether)] was nearly identical with the published spectrum of elaiomycin (1),[3a] but lacked olefinic bands at 1654 and 790 cm^{-1}. The wavenumber of the azoxy-band of (3) (1494 cm^{-1}) was *ca.* 30 cm^{-1} more than that of (1). The n.m.r. spectrum ($CDCl_3$) showed δ 0·73—2·26 (15H, m, CH_3 and CH_2), 2·60br (1H, OH), 3·35 (3H, s, OCH_3), 3·64 (2H, m, OCH_2), and 4·23 [4H, t, *J* 7 Hz, CH_2·N(O)=N, superimposed on m's, CHN=N(O) and C*H*OH]. The δ 4·23 resonance is characteristic;[1,11] a similar triplet is shown by the dihydro-derivative of (2).[4a] The u.v. spectrum (cyclohexane) showed $\lambda_{max.}$ 226 (ε 9500) and 283sh nm (193).[12]

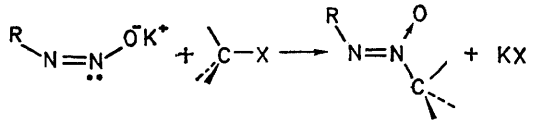
L-Dihydroelaiomycin (3) had $[\alpha]_D^{26}$ −20·8° (*c* 1·0 in EtOH), and showed c.d. maxima (cyclohexane) at 218 ([θ] $-3{\cdot}64 \times 10^3$) and 277 ([θ] $+2{\cdot}56 \times 10^2$), with an inversion point at 259 nm. The spectrum is similar to those of related chiral azoxyalkanes.[1,2,4b,c]

Impure elaiomycin * was reduced over 5% rhodium–alumina.† Preparative g.l.c. of the product on SE-30 gave 3 mg of D-(3), which was *ca.* 90% pure (g.l.c.). The u.v. maxima were identical with those of synthetic L-(3). The i.r. spectrum of D-(3) revealed extraneous bands at 1670br,w and 965m cm^{-1}, but was otherwise identical with that of L-(3). Neither 'extra' band appeared in the i.r. spectra of L-(3) or (1). The c.d. data of D-(3) were related in a 'mirror-image' manner to those of synthetic L-(3), with an inversion point at 259 nm.

The synthesis of azoxyalkanes by diazoate alkylation proceeds with complete retention at a chiral diazoate α-carbon atom,[2] and the conversion of L-threonine into the diazoate (10) should also be stereoconservative. Thus our synthetic L-(3) should be of high enantiomeric purity.

The present synthesis of L-dihydroelaiomycin establishes the potential of our new method [1] for the construction of complicated azoxyalkanes. Moreover, the comparison of synthetic and naturally derived (3) confirms the elegant structure elucidation of (1) by Stevens' group.[3b,d]

The simplest mechanism to explain the alkylation reaction involves direct displacement of halide from the substrate by the diazoate's central nitrogen atom.



This mechanism is consistent with the observation of complete inversion at substrate carbon in the formation of (−)-(*R*)-2-octyl-*ONN*-azoxyethane from ethanediazoate and (+)-(*S*)-2-chloro-octane.[2] It is further consistent with the finding that the *syn*-diazoates,[13] prepared from *N*-alkyl-*N*-nitrosourethanes and t-butoxide, react with alkyl halides directly, affording *trans*-azoxyalkanes. The stereochemistry at the azoxy-groups follows from the u.v. maxima, which are uniformly below 230 nm; *cis*-azoxyalkanes have $\lambda_{max.}$ >230 nm.[3e] We infer the direct nature of *trans*-azoxyalkane formation from isolation of the *trans*-azoxyalkanes *via* ambient temperature t.l.c. of the crude product mixtures,[14] an isolation procedure which should not induce *cis* → *trans* isomerization.[3e] The azoxyalkane synthesis thus preserves configuration at the N=N(O) linkage, and inverts configuration at the newly created α-carbon centre. Analogies to the present synthesis include Jones' apparent intramolecular diazoate alkylation, which leads

* We thank Dr. T. H. Haskell (Parke Davis Co.) for this sample, which contained *ca.* 25% of (1) by g.l.c.

† We thank Dr. McGahren for details of his reduction method.[4a]

[9] R. A. Moss, *Tetrahedron Letters*, 1966, 711.

[10] R. A. Moss, *J. Org. Chem.*, 1966, **31**, 1082.

[11] J. P. Freeman, *J. Org. Chem.*, 1963, **28**, 2508.

[12] B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 1952, 4191.

[13] E. H. White, T. J. Ryan, and K. W. Field, *J. Amer. Chem. Soc.*, 1970, **92**, 1360.

[14] R. A. Moss and M. J. Landon, *Tetrahedron Letters*, 1970, 3897.

to a cyclic azoxyalkane,[15] and the formation of nitrones by the alkylation of oximate ions.[16]

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 137 spectrometer. N.m.r. spectra were determined on either a Varian T-60 or a JEOLCO JNH-MH-100 instrument, with an internal tetramethylsilane standard. U.v. spectra were measured on a Cary 14 spectrometer. For c.d. determinations we employed a Cary 60 instrument. Optical rotations were obtained with a Perkin-Elmer 141 spectropolarimeter. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMU-7 spectrometer. Elemental analyses were done by Micro-Tech Laboratories, Skokie, Illinois, and by Robertson Laboratory, Florham Park, New Jersey. G.l.c. was carried out on a Varian Aerograph A-90-P3 instrument. Preparative thick-layer chromatography (p.l.c.) was done on Brinkmann silica gel F-254 precoated plates (20 × 20 cm, 2 mm thick).

Ethyl (4S,5R)-5-*Methyl*-2-*phenyl*-Δ^2-*oxazoline*-4-*carboxylate* (5).—L-Threonine ethyl ester hydrochloride [6] (229 g, 1 mol) dissolved in water (100 ml) was stirred in a Morton flask, while a solution of ethyl benzimidate [7] (257 g, 1·72 mol) [b.p. 75—76° at 4 mmHg (lit.,[7] 107·5—109° at 16·5 mmHg)] in ether (650 ml) was added. After stirring for 10 h at 25°, water (150 ml) was added; the ethereal layer was separated, combined with ethereal extracts of the aqueous layer, washed with brine, and dried ($MgSO_4$). Removal of the ether left an orange oil (373 g), which was distilled to give unchanged ethyl benzimidate (99 g) and the oxazoline ester (5) (164 g, 70%), b.p. 130—131° at 0·1 mmHg (lit.,[3d] 132—138° at 1 mmHg), $\nu_{max.}$ (neat) 1735, 1645, 1243, 1190, 1082, 1060, and 1038 cm^{-1}, δ ($CDCl_3$) 1·28 (3H, t, *J* 7 Hz, ester CH_3), 1·40 (3H, d, *J* 7 Hz, 5-CH_3), 4·19 (2H, q, *J* 7 Hz, CH_2), 4·30 (1H, d, *J* 7 Hz, 4-H), 4·94 (1H, m, 5-H), and 7·42 and 7·98 (3H, and 2H, m, aromatic).

(4R,5R)-5-*Methyl*-2-*phenyl*-Δ^2-*oxazoline*-4-*methanol* (6).—Reduction of the ester (5) with ethereal lithium aluminium hydride [3d] gave the alcohol (6) (98%), m.p. 99—100° (from ether) (lit.,[3d] 99·5—100°), $\nu_{max.}$ (CCl_4) 3200, 1640, 1089, 1058, and 1028 cm^{-1}, δ ($CDCl_3$) 1·44 (3H, d, *J* 6 Hz, CH_3), 3·19br (1H, s, exchangeable with D_2O, OH), 3·52—4·06 (3H, m, CH_2, 4-H), 4·70 (1H, quintet, *J* 6 Hz, 5-H), and 7·38 and 7·90 (3H and 2H, m, aromatic).

(4R,5R)-4-*Methoxymethyl*-5-*methyl*-2-*phenyl*-Δ^2-*oxazoline* (8).—The tosylate (7) was prepared by adding, with stirring, during 1 h, a solution of (6) (25 g, 0·13 mol) in anhydrous pyridine (100 ml) to recrystallized (benzene–pentane) toluene-*p*-sulphonyl chloride (38 g, 0·2 mol) in pyridine (20 ml) at 0°. The mixture was then stirred for 3 h at 0°, and kept at 4° for an additional 10 h. Pyridine was removed *in vacuo* at 0—5°, ether (400 ml) and pentane (50 ml) were added, and the precipitate of pyridinium hydrochloride was filtered off. The filtrate was dried ($MgSO_4$) and evaporated to give crude (7) as an orange syrup (46·4 g) containing some pyridine. The tosylate could be purified by t.l.c. on silica gel (65% ether–pentane); $\nu_{max.}$ (neat) 1640, 1355, 1188, 1180, 1097, 1058, and 1028 cm^{-1}, δ (CCl_4) 1·39 (3H, d, *J* 6 Hz, 5-CH_3), 2·40 (3H, s, *p*-CH_3), 3·97 (2H, m, CH_2), 4·28 (1H, m, 4-H), 4·62 (1H, quintet, *J* 6 Hz, 5-H), and 7·44 and 7·93 (9H, m, aryl).

To a solution of crude (7) (46 g, *ca.* 0·13 mol) in dry methanol (320 ml) was added sodium methoxide (14·7 g, 0·23 mol) in dry methanol (260 ml). The solution was maintained at 50—52° for 96 h. Methanol was removed, and ether (600 ml) and water (120 ml) were added. The ethereal layer, combined with ethereal extracts (200 ml) of the aqueous layer, was dried (Na_2SO_4) and evaporated; distillation of the residue gave two fractions, b.p. 75—90° at 0·1 mmHg (4·2 g), and 94—96·5° at 0·1 mmHg (16·4 g). G.l.c. analysis (10 ft × 0·25 in 10% SE-30 on Chromosorb R column; 180°; helium flow 100 ml min^{-1}) showed the same two components in each fraction. That of shorter retention time, 4,5-dimethyl-2-phenyloxazole (9), constituted 22 and 4%, respectively, of the distillate fractions. Its i.r. spectrum was identical with that reported.[8] Its n.m.r. spectrum showed δ ($CDCl_3$) 2·12 and 2·27 (each 3H, s, Me) and 7·32 and 7·92 (3H and 2H, m, aromatic) (Found: C, 76·0; H, 6·4; N, 7·8%; M^+, 173. $C_{11}H_{11}NO$ requires C, 76·3; H, 6·4; N, 8·1%; *M*, 173).

The major component of both fractions was the ether (8), $\nu_{max.}$ (neat) 1640, 1133, 1086, 1056, and 1028 cm^{-1}, δ ($CDCl_3$) 1·43 (3H, d, *J* 6 Hz, 5-CH_3), 3·40 (3H, s, OCH_3), 3·50 (2H, m, CH_2), 3·95 (1H, m, 4-H), 4·63 (1H, quintet, *J* 6 Hz, 5-H), and 7·46 and 8·00 (3H and 2H, m, aromatic), $[\alpha]_D^{25}$ +72·8° (*c* 1·81 in $CHCl_3$) (lit.,[3d] $[\alpha]_D^{25}$ +56·4°, same conditions). Careful distillation over a 25 cm Vigreux column gave a sample of b.p. 115—116° at 0·1 mmHg (lit.,[3d] 87—89° at 4 mmHg) (Found: C, 70·2; H, 7·3; N, 6·7. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%). The overall yield of (8) was *ca.* 70%, and the second distillate fraction (see above) was used for the subsequent hydrolysis.

Ethyl (1R,2R)-2-*Hydroxy*-1-*methoxymethylpropylcarbamate* (4).—The oxazoline (8) (16·0 g, 0·076 mol) was refluxed for 6 h in 6N-hydrochloric acid (220 ml). Extraction of the cooled solution with ether (2 × 150 ml) removed benzoic acid (7 g, *ca.* 75%). The aqueous phase was treated with sodium carbonate (82 g, 0·77 mol), and a solution of ethyl chloroformate (6·2 ml, 0·078 mol) in ether (200 ml) was added, with stirring, at 0°. The mixture was then stirred for 2 h at 25°, the ethereal layer was removed, and the aqueous layer was extracted with ether (2 × 100 ml). The combined ethereal layers were dried (Na_2SO_4), filtered, and evaporated to give a 31 : 69 mixture (13·6 g) of the oxazole (9) and the urethane (4), as determined by n.m.r.

The crude product, in ether (200 ml), was treated with anhydrous hydrogen chloride and kept at 4° for 2 days. Pentane (50 ml) was added and the hydrochloride of (9) was filtered off. The filtrate was evaporated and distilled to afford the pure *urethane* (4) [6·9 g, 48% based on (8)], b.p. 91—92° at 0·2 mmHg, $\nu_{max.}$ 3460, 1708, 1521, 1247, and 1084 cm^{-1}, δ ($CDCl_3$) 1·23 and 1·17 (6H, t and d, *J* 7 Hz, $OCH_2{\cdot}CH_3$ and $CH{\cdot}CH_3$), 2·80br (1H, OH), 3·37 (3H, s, OCH_3), 3·57 (3H, m, $OCH_2{\cdot}CH{\cdot}N$), 4·16 (5H, q, *J* 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$ superimposed on m, $CH{\cdot}OH$), and 6·34br (1H, NH) (NH and OH protons were exchangeable in D_2O); polarimetry gave $[\alpha]_D^{25}$ −23·9° (*c* 1·10 in $CHCl_3$) (Found: C, 50·3; H, 9·0; N, 6·9. $C_8H_{17}NO_4$ requires C, 50·2; H, 9·0; N, 7·3%).

Ethyl (1R,2R)-1-*Methoxymethyl*-2-(*tetrahydropyran*-2-*yloxy*)*propylcarbamate*.—The urethane (4) (3 g, 0·0157 mol), dihydropyran (2·15 ml, 0·0235 mol), and toluene-*p*-sulphonic acid (1·63 mg) in dry ether (35 ml), kept at 25° for 2 h, gave (after washing with 10% $NaHCO_3$, drying over $MgSO_4$, and removal of drying agent, solvent, and the excess of dihydropyran) the crude *tetrahydropyranyl ether* (4·2 g, 98%).

[15] D. J. Northington and W. M. Jones, *J. Org. Chem.*, 1972, **37**, 693.

[16] E. Buehler, *J. Org. Chem.*, 1967, **32**, 261; J. Hamer and A. Maculuso, *Chem. Rev.*, 1964, **64**, 473.

Distillation at 118—121° and 0·1 mmHg, afforded a sample with $\nu_{max.}$ 3380 (NH), 1715 (C=O), 1515, 1227, 1200, 1109, 1071, 1031, and 1018 cm^{-1} (Found: C, 56·5; H, 9·2; N, 5·2. $C_{13}H_{25}NO_5$ requires C, 56·7; H, 9·2; N, 5·1%).

Ethyl (1R,2R)-1-*Methoxymethyl*-2-(*tetrahydropyran*-2-*yloxy*)*propyl*-N-*nitrosocarbamate*.—Following our standard nitrosation method,[10] we obtained 4·2 g (97%) of the yellow nitroso-urethane from the foregoing ether (4·0 g, 0·0145 mol), dinitrogen tetraoxide (2·55 g, 0·026 mol), and sodium hydrogen carbonate (4·37 g, 0·052 mol) in anhydrous ether, kept at −30° for 2 h. The crude product showed $\nu_{max.}$ 1740 cm^{-1}, δ (CCl_4) 4·48 (2H, q, *J* 7 Hz, $OCH_2{\cdot}CH_3$) [the deshielding relative to the parent ether (δ 4·11) is characteristic [9]].

(2R,3R)-4-*Methoxy*-3-(*octyl*-ONN-*azoxy*)*butan*-2-*ol* (L-*Dihydroelaiomycin*) (3).—To a well stirred suspension of potassium t-butoxide (2·58 g, 0·023 mol) in dry ether (18 ml) at −25 to −35°, was added a solution of the foregoing nitroso-urethane (3·5 g, 0·0115 mol) in a little ether. After stirring for 2 h, ether was removed *in vacuo* at 0°, and the diazoate (10) was dissolved in hexamethylphosphoric triamide (12 ml) (Aldrich; distilled from CaH_2) at 25°. The red solution thus obtained was slowly added to 1-iodo-octane (13·85 g, 0·0575 mol), with vigorous stirring. The temperature was unmoderated, and rose to *ca.* 40° during the addition. After 15 h, ether was removed to leave a red oil (14·5 g). Distillation gave 1-iodo-octane (8·8 g) and a small fraction (b.p. range 55—108° at 0·1 mmHg) containing mostly carbonates from the nitrosourethane cleavage. The residue (2·6 g) contained the protected azoxy-compound (11), $\nu_{max.}$ 1495 cm^{-1}, δ (CCl_4) 4·25 [t, $CH_2{\cdot}N(O)=N$].[11]

Without purification, the residue (1·0 g) was treated with toluene-*p*-sulphonic acid (340 mg) in methanol (30 ml) at 25° for 2 h. Methanol was removed; the residue, dissolved in ether (30 ml), was washed ($NaHCO_3$ solution and water) and dried (Na_2SO_4). Filtration and evaporation gave the crude *product* (3) (850 mg), 220 mg of which was purified by successive p.l.c. with 1 : 1, followed by 3 : 2 ethyl acetate–pentane. Thus pure L-dihydroelaiomycin (102 mg, 36%, based on the *N*-nitroso-tetrahydropyranyl ether) was obtained. The crude (3) could also be purified by dry-column chromatography on neutral alumina (Woelm, activity III), with 1 : 1 ethyl acetate–pentane as eluant. Dihydroelaiomycin had a g.l.c. retention time of 9·0 min on a 12 ft × 0·25 in 2% SE-30 on Anakrom 60—70-ABS column (injector at 230°; column, 178°; helium, 120 ml min^{-1}). Some g.l.c. fragmentation (*ca.* 5%) to two components with longer retention times was observed. The spectra of (3) are described in the Discussion section (Found: C, 60·2; H, 10·9; N, 10·6. $C_{13}H_{28}N_2O_3$ requires C, 59·9; H, 10·8; N, 10·8%).

Reduction of Natural Elaiomycin (1).—A sample of (1) (100 mg; *ca.* 25% pure by g.l.c.) [under the g.l.c. conditions described for synthetic (3), there was a 25% component with a retention time of 9 min] was dissolved in absolute ethanol (4 ml); 5% rhodium–alumina (5 mg) (Pfaltz and Bauer) was added, and the mixture was hydrogenated at 25° and 1 atm for 45 min (uptake 30 ml). Ether was added (*ca.* 3 ml), the catalyst was removed by centrifugation, and solvents were evaporated off in a stream of nitrogen. Preparative g.l.c. of the residue, under the conditions described for synthetic (3), afforded 90% pure (g.l.c.) D-(3) (3 mg) (see Discussion section).

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