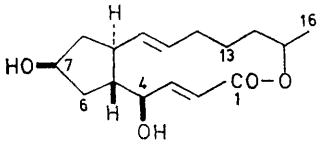
Preparation of Some Fluoropalmitic Acids and Fluorination of Brefeldin A

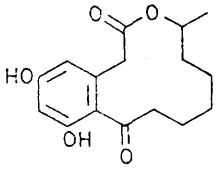
By **Brian E. Cross** * and **Paul Hendley**, Department of Organic Chemistry, The University, Leeds LS2 9JT

Syntheses of 6-, 7-, 13-, and 16-fluoropalmitic acid are described. Treatment of brefeldin A (1) with 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine afforded the difluorodideoxybrefeldin A (3).

In continuation of our studies [1,2] on the preparation of fluorinated natural products we have synthesised 6-, 7-, 13-, and 16-fluoropalmitic acid by the routes described below. At the time when this work was carried out, intact palmitic acid units were believed to act as precursors of brefeldin A (1) and curvularin (2).[3,4] However addition of these fluoropalmitic acids to cultures of *Penicillium lilacinum* and *Cochliobolus intermedius*,



(1)



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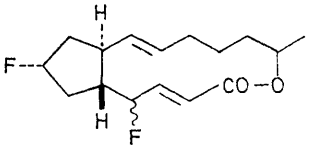

(3)

respectively, which produce the metabolites (1) and (2), yielded no detectable amounts of their fluoro-analogues (*cf.* ref. 1). We therefore re-examined the biosynthesis of brefeldin A and found no evidence that palmitate units were incorporated.[5]

The failure to produce fluorinated analogues of brefeldin A by fermentation prompted an examination of the reaction of brefeldin A with 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine (fluoro-amine), a reagent known to convert alcohols into fluorides under mild conditions.[6] Treatment of brefeldin A with an excess of the fluoro-amine gave the expected difluoro-derivative (3) as the major product and a small amount of an isomer. Since the conversion of saturated alcohols into fluorides with the fluoro-amine reagent normally takes place with inversion of configuration,[7] the 7-fluorine atom in difluorodideoxybrefeldin A (3) was assigned the α-orientation. However, the reaction of the fluoro-amine with allylic alcohols may proceed by a mechanism involving an allylic carbocation,[2] so that the configuration of the 4-fluorine atom is unknown. If such an ion is formed in brefeldin A at C-4, molecular rearrangement could easily follow [6] and lead to the isomeric difluoride whose structure has not yet been determined. The biological activity of the difluoro-brefeldin A (3) is under investigation.

The fluoropalmitic acids were conveniently prepared from the corresponding hydroxy-acids or esters by reaction with the fluoro-amine (*cf.* ref. 8); 6- and 7-hydroxypalmitic acids and methyl 13-hydroxypalmitate were obtained by reduction of the corresponding oxo-compounds, prepared as described below, with sodium borohydride.

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[3] J. D. Bu'Lock and P. T. Clay, *Chem. Comm.*, 1969, 237.
[4] W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971, p. 72.
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[6] J. Fried and J. A. Edwards, 'Organic Reactions in Steroid Chemistry,' vol. I, Van Nostrand–Reinhold, New York, 1972, p. 436.
[7] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, 1964, **29**, 2187.
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Thus, reaction of n-decylmagnesium bromide with cyclohexanone afforded 1-decylcyclohexanol, which on oxidation by Fieser's method [9] gave 6-oxopalmitic acid.[10] 7-Oxopalmitic acid [11] was derived from the alkaline hydrolysis of 2-decanoylcyclohexanone, which was prepared by the condensation of decanoic anhydride and cyclohexanone in the presence of boron trifluoride gas (*cf.* ref. 12).

Methyl 13-oxopalmitate, synthesised by condensation of the acid chloride of methyl hydrogen decanedioate [13] with n-propylcadmium,[14] afforded methyl 13-fluoropalmitate *via* the 13-hydroxy-ester. Hydrolysis of the fluoro-ester with ethanolic potassium hydroxide yielded the 13-fluoro-acid.

16-Fluoropalmitic acid, previously isolated from *Dichapetalum toxicarium*,[15] was prepared from dihydroambrettolide, *via* the 16-hydroxy-acid.[16]

EXPERIMENTAL

Details of chromatographic materials and conditions used for the determination of physical data, *etc.*, have been reported.[1]

Fluorination of Brefeldin A.—Brefeldin A (1 g, 0.36 mmol) suspended in dichloromethane (150 ml) at 0 °C was treated dropwise with the fluoro-amine (1.58 ml, 1 mmol) over 15 min. The brefeldin A dissolved, and the solution was stirred for 30 min at 0 °C and was then allowed to reach room temperature and stirred for a further 30 min. Evaporation *in vacuo* followed by chromatography on silica gel (150 g) and elution with ethyl acetate–light petroleum (2 : 98), afforded the 4ξ, 7α-*difluoro*-4,7-*dideoxybrefeldin A* (3), which crystallised from ether–light petroleum (b.p. 40—60°) in rods (118 mg), m.p. 86.5—88°, $[\alpha]_D^{23}$ +90.3° (*c* 2.2 in MeOH) (Found: C, 68.15; H, 7.55; F, 13.6%; *m/e*, 284.1581. $C_{16}H_{22}F_2O_2$ requires C, 67.8; H, 7.75; F, 13.35%; *M*, 284.1588), $\nu_{max.}$ 1 728, 1 718, 1 648, and 980 cm^{-1}; τ (90 MHz) 8.73 (3 H, d, *J* 6.5 Hz, 16-H_3), 5.4—4.1 (5 H, multiplets), 4.08 (1 H, dd, *J* 15.5 and 1.5 Hz, 2-H), and 2.75 (1 H, 8 lines, *J* 28.5, 15.5, and 2.5 Hz, 3-H); ϕ^* 181.6 (m) and 171.6 (m).

Elution with ethyl acetate–light petroleum (4 : 96) gave a fraction which, after repeated cystallisation from ether–light petroleum (b.p. 40—60°), afforded microprisms of a difluoro-compound (12 mg), m.p. 127.5—129°, $[\alpha]_D^{23}$ +46.3° (*c* 1.1 in MeOH) (Found: C, 67.7; H, 7.5; F, 13.3%; *m/e*, 284.1589. Calc. for $C_{16}H_{22}F_2O_2$: C, 67.8; H, 7.75; F, 13.35%; *M*, 284.1588), τ (90 MHz) 8.71 (3 H, d, *J* 6.5 Hz, 16-H_3), 7.02 (1 H, d, *J* 10 Hz), 6.0 (1 H, dt, *J* 48 and 9.5 Hz), 5.18 (2 H, m), 4.57 (1 H, m), and 4.11br (2 H, s); ϕ^* 164.4 and 163.3.

6-*Hydroxypalmitic Acid.*—6-Oxopalmitic acid [10] (2.2 g) in methanol (20 ml) was treated at 0 °C with sodium borohydride (2.2 g) and left overnight at room temperature. The solution was acidified with dilute hydrochloric acid and evaporated *in vacuo*. Recovery in ether gave 6-hydroxypalmitic acid, which crystallised from light petroleum as microcrystals, m.p. 105—111°, $\nu_{max.}$ ($CHCl_3$) 3 300 and 1 710 cm^{-1}; τ 9.11 (3 H, virtually coupled Me), 7.68 (2 H, m, 2-H_2), and 6.38br (1 H, m, 6-H).

6-*Fluoropalmitic Acid.*—6-Hydroxypalmitic acid (1.75 g) was suspended in dry dichloromethane (170 ml) with stirring at 0 °C and 2-chloro-*NN*-diethyl-1,1,2-trifluorothylamine (2.5 ml) was added over 6 min. The homogeneous solution was allowed to reach room temperature and was then evaporated *in vacuo*. The residual fluoro-acid fluoride was heated under reflux with N-hydrochloric acid (50 ml) for 2 h. Recovery in ether gave 6-*fluoropalmitic acid*, which crystallised from light petroleum as prisms (1.1 g), m.p. 69—70.5° (Found: C, 70.05; H, 11.1; F, 6.95. $C_{16}H_{31}FO_2$ requires C, 70.0; H, 11.4; F, 6.9%), τ 9.13 (3 H, virtually coupled Me), 7.68 (2 H, t, *J* 7 Hz, 2-H_2), and 5.47 (1 H, dm, *J* 48 Hz, 6-H); ϕ^* 180.7 (m, 6-F).

7-*Oxopalmitic Acid.*—Decanoic anhydride (25 g) and cyclohexanone (3.5 g) were dissolved in 1,2-dichloroethane and kept at 0—10 °C while boron trifluoride gas was passed onto the surface of the solution [12] until 15 min after dissolution of the gas ceased. The orange-red solution was poured into sodium acetate solution (12.5%; 100 ml) and the mixture was distilled until the vapour temperature reached 95 °C; it was then refluxed for 2 h. Recovery in ether and evaporation *in vacuo* gave 2-decanoylcyclohexanone as oil (6.25 g), $\nu_{max.}$ (film) 3 350, 1 705, and 1 630 cm^{-1}.

The diketone (35 g) was hydrolysed for 3 h under reflux with a 10% excess of a 5% solution of sodium hydroxide in ethanol–water (2 : 1). The ethanol was evaporated off *in vacuo*, the solution was extracted with ether and acidified, and the product was recovered in ether. It crystallised from light petroleum (b.p. 40—60°) as prisms of 7-oxopalmitic acid (14.5 g), m.p. 75—75.5° (lit.,[11] 78°) (Found: C, 71.3; H, 11.0. Calc. for $C_{16}H_{30}O_3$: C, 71.0; H, 11.2%).

7-*Fluoropalmitic Acid.*—The above 7-oxo-acid (4.5 g) was reduced with sodium borohydride (1.45 g), as in the preparation of the 6-hydroxy-acid (see above), and gave 7-hydroxypalmitic acid (3.2 g), which crystallised from light petroleum in microcrystals, m.p. 86—89°, $\nu_{max.}$ 3 400, 3 200, and 1 707 cm^{-1}.

Treatment of hydroxy-acid (3.2 g) with the fluoro-amine (4.4 ml) in dry dichlomethane (250 ml) and work-up as for 6-fluoropalmitic acid gave 7-*fluoropalmitic acid*, which crystallised from light petroleum in plates (1.22 g), m.p. 71.5—72.5° (Found: C, 69.9; H, 11.2; F, 6.95. $C_{16}H_{31}FO_2$ requires C, 70.0; H, 11.4; F, 6.9%), $\nu_{max.}$ 3 450br and 1 710 cm^{-1}; τ 9.1 (3 H, virtually coupled Me), 7.62 (2 H, t, *J* 7 Hz, 2-H_2), and 5.54 (1 H, dm, *J* 48 Hz, 7-H); ϕ^* 180.8 (m, 7-F).

Methyl 13-*Oxopalmitate.*—Methyl hydrogen tridecanedioate [13] (5.75 g) in dry benzene was refluxed with thionyl chloride (8.7 g) for 3 h and then the solvent was evaporated off to give the crude acid chloride as a gum (6.4 g), $\nu_{max.}$ 1 805 and 1 738 cm^{-1}.

n-Propylcadmium, prepared [14] from n-propyl bromide (4.25 g), was treated with the above acid chloride and the product was isolated [14] and chromatographed on Kieselgel G (300 g). Elution with chloroform containing a trace of formic acid (4 drops per l) and collection of 10 ml fractions, gave, in fractions 51—106, *methyl* 13-*oxopalmitate*, which crystallised from ether–light petroleum in prisms (5.3 g),

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m.p. 41.5—42.5° (Found: C, 71.6; H, 11.1%; *m/e* 284. $C_{17}H_{32}O_3$ requires C, 71.8; H, 11.3%; *M*, 284), $\nu_{max.}$ 1 732, 1 710, and 1 438 cm^{-1}.

Methyl 13-*Hydroxypalmitate*.—Reduction of the above oxo-ester (500 mg) with sodium borohydride (700 mg) gave *methyl* 13-*hydroxypalmitate*, which crystallised from light petroleum as a microcrystalline powder, m.p. 42.5—45.5° (Found: *m/e* 286.2505. $C_{17}H_{34}O_3$ requires *M*, 286.2508), $\nu_{max.}$ (film) 3 450 and 1 740 cm^{-1}.

13-*Fluoropalmitic Acid*.—The crude 13-hydroxy-ester (5.15 g) was treated with the fluoro-amine (9 ml) in the usual way and the product was chromatographed on Kieselgel G (275 g). Elution with benzene gave an oil (920 mg) shown by g.l.c. to contain *ca.* 82% of the fluoro-ester and *ca.* 18% of the olefin esters. Chromatography of the oil (200 mg) on alumina (100 g) impregnated with silver nitrate (25 g) and elution with ethyl acetate–light petroleum (1 : 99) gave two fractions. Hydrolysis of the first fraction with potassium hydroxide (400 mg) in ethanol (10 ml) under reflux for 2 h afforded 13-*fluoropalmitic acid* (120 mg), which crystallised from ether–light petroleum as plates, m.p. 67—68° (Found: C, 70.0; H, 11.15; F, 7.1. $C_{16}H_{31}FO_2$ requires C, 70.0; H, 11.4; F, 6.9%), $\nu_{max.}$ ($CHCl_3$) 2 500—2 800 and 1 710 cm^{-1}. Its methyl ester showed only one peak on g.l.c.

16-*Fluoropalmitic Acid*.—The hydroxy-acid (2.0 g) was treated with the fluoro-amine (2.8 ml) and the product worked-up as in the preparation of the 6-fluoro-acid (see above). The resulting material was chromatographed on silica gel (25 × 6 cm); elution with ethyl acetate–light petroleum (1 : 19) afforded 16-fluoropalmitic acid (516 mg), which crystallised from light petroleum as microcrystals, m.p. 74.5—75.5° (lit.,[15] 71—73°) (Found: C, 70.0; H, 11.4; F, 7.0. Calc. for $C_{16}H_{31}FO_2$: C, 70.0; H, 11.4; F, 6.9%); ϕ^* 218.6 (7 lines, 16-F).

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