Organic Reactions of Fluoro-oxy-compounds. Fluorination of Griseofulvin

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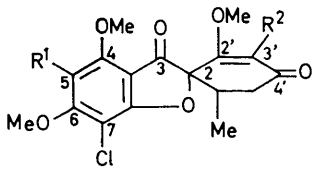
Fluorination of griseofulvin (I) with trifluorofluoro-oxymethane affords 5-fluorogriseofulvin (2) (major product), 3'-fluorogriseofulvin (3), and 3',5-difluorogriseofulvin (4). These results confirm the value of trifluorofluoro-oxymethane as a selective electrophilic reagent for fluorination, comparable in its reactions to conventional reagents for direct halogenation.

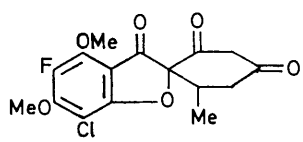
We have reported that fluoro-oxy-compounds such as trifluorofluoro-oxymethane are useful and remarkably general reagents for 'electrophilic' fluorination.[1] Fluorination with these reagents may occasionally involve different problems from those encountered in conventional halogenation; however these difficulties provide no greater impediment to the synthesis of fluoro-compounds than those encountered during conventional halogenation. We now present evidence in support of this contention.

Griseofulvin (1) is a useful[2,3] antifungal antibiotic produced by several *Penicillium* species. Inasmuch as it bears two functions susceptible to electrophilic attack (phluoroglucinol residue and enolised β-diketone methyl ether) and tends to undergo ready decomposition and/or rearrangement on treatment with either base or acid,[2] this substrate comprises a severe test of the selectivity and mildness of an electrophilic fluorination agent.

Addition of a solution of griseofulvin to a solution of trifluorofluoro-oxymethane (**1·1** equiv.) at −78° gave three new fluorinated products. The major product (*ca.* 67% of the total) was a monofluorinated substitution product which no longer exhibited the resonance at τ 3·85



(1) $R^1=R^2=H$
(2) $R^1=F, R^2=H$
(3) $R^1=H, R^2=F$
(4) $R^1=R^2=F$



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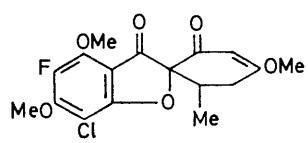


(6)

attributed to the 5-proton of griseofulvin. A resonance at τ 4·45 attributed to the 3-proton was present, and the

[1] D. H. R. Barton, L. S. Godhino, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804; D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, and M. M. Pechet, *ibid.*, 1968, 806; D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *ibid.*, 1969, 227.

[2] J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. Thorold Rogers, *J. Chem. Soc.*, 1952, 3944; A. W. Dawkins and T. P. C. Mulholland, *ibid.*, 1959, 1830 and intervening papers in this series.

[3] J. Arkley, J. Attenburrow, G. I. Gregory, and T. Walker, *J. Chem. Soc.*, 1962, 1260; J. E. Page and Susan E. Staniforth, *ibid.*, 1962, 1292 and other papers in this series; D. Taub and N. L. Wendler, *Angew. Chem.*, 1962, **74**, 586; M. Gerecke, E. Kyburz, C. V. Planta, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 2241.

4- and 6-methoxy-resonances were shifted to lower field and each exhibited a small splitting due to long-range coupling with the newly introduced fluorine (the ^{19}F n.m.r. spectrum comprised a multiplet at ϕ^* +154·8). These data, together with the i.r. and u.v. spectral data (Tables 1 and 2) characterise the major product as 5-

TABLE 1

I.r. spectra ($\nu_{max.}$/cm^{-1})

	C(3)=O	C(4')=O
(1)	1710	1665
(2)	1720	1665
(3)	1710	1700
(4)	1720	1700

TABLE 2

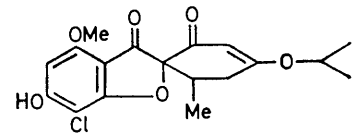
U.v. spectra [$\lambda_{max.}$ (MeOH)/nm (log ε)]

(1)	325 (3·6)	292 (4·23)	234 (4·24)	
(2)	345 (3·64)	284 (4·22)	236 (4·28)	
(3)	326 (3·75)	292 (4·39)	257 (4·18)	236 (4·29)
(4)	345 (3·70)	276 (4·30)	257 (4·25)	

fluorogriseofulvin (2). The second monofluorinated substitution product lacked the resonance at τ 4·49 attributed to the 3'-proton but exhibited a resonance at τ 3·82 (due to the 5-proton). The 2'-methoxy-resonance was shifted to lower field and was split by long-range coupling with the newly introduced fluorine (ϕ^* 156·2). These data and other spectral data lead to the formulation of this compound as 3'-fluorogriseofulvin (3). The third product was a difluorinated substitution product which lacked the resonances of both the 3'- and 5-protons; each of the three methoxy-resonances was shifted to lower field and split by long-range coupling. The ^{19}F n.m.r. spectrum exhibited two sets of resonances (ϕ^* 154·9 and 156·4) and the other spectral data (Tables 1 and 2) were essentially a combination of those observed for compounds (2) and (3), leading to structure (4) (3',5-difluorogriseofulvin) for this compound.

3',5-Difluorogriseofulvin (4) must result from the fluorination of compound (2) or (3); however, attempts to achieve complete difluorination gave intractable by-products. Indeed, neither compound (2) nor (3) when exposed to the reagent was fluorinated cleanly (spectroscopic examination of such reaction mixtures indicated the formation of *gem*-difluoro-compounds). The formation of compound (4) could, however, be minimised by decreasing the molar ratio of reagent to substrate. The starting material could easily be recovered and the yield of compound (2) based on recovered starting material was *ca.* 60%. 5-Fluorogriseofulvin (2), as expected, reacted with hydrochloric acid to afford 5-fluorogriseofulvic acid (5), and on incubation with methanolic acid isomerised to 5-fluoroisogriseofulvin (6). The latter transformation was also observed when the crude fluorinated product was subjected to methanolic work-up.

The direct chlorination of griseofulvin has been reported to afford both 5-chlorogriseofulvin and 3',5-dichlorogriseofulvin.[4] Although the direct bromination of griseofulvin apparently led to 3'-bromogriseofulvic acid,[5] bromination of the mercuric acetate adduct is reported to afford both the analogous 5-bromo- and 3',5-dibromo-derivatives of griseofulvin. While direct fluorination of griseofulvin has not hitherto been described, the fluorination of the analogue (7) with perchloryl fluoride ($FClO_3$) has been reported to afford (among other products) the dienone (8), which was then



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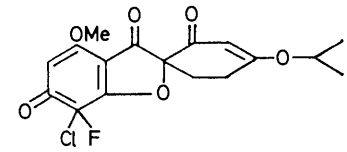

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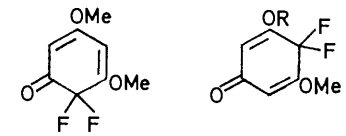

(9a) (9b)

converted by reduction and methylation to 7-dechloro-7-fluorogriseofulvin.[6] In parallel studies phluoroglucinol derivatives were found to react with perchloryl fluoride to afford difluoro-dienones of structure (9) rather than substitution products.[7,8] Thus direct fluorination of the sensitive substrate, griseofulvin, with trifluorofluoroxymethane compares favourably both with respect to selectivity, and with respect to the preservation of sensitive functional groups, with direct halogenation by conventional reagents.

EXPERIMENTAL

U.v. spectra were measured for solutions in methanol with a Cary model 11 instrument. I.r. spectra were measured for solutions in chloroform with a Perkin-Elmer model 137 instrument. N.m.r. spectra were recorded with a Varian T-60 instrument, ^1H at 60 MHz for solutions in [^2H]-chloroform with tetramethylsilane as internal standards, and ^{19}F at 56·4 MHz for solutions in chloroform with tri-

[4] D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 2752.

[5] (*a*) J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. Thorold Rogers, *J. Chem. Soc.*, 1952, 3949; (*b*) T. Walker, W. K. Warburton, and G. B. Webb, *ibid.*, 1962, 1277.

[6] D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 2752.

[7] D. Taub, *Chem. and Ind.*, 1962, 558.

[8] B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Amer. Chem. Soc.*, 1963, **85**, 627.

chlorofluoromethane as internal standard. Optical rotations were measured for solutions in chloroform unless stated otherwise. M.p.s were measured with Kofler hot-stage apparatus. G.l.c. analyses were performed on a 3% SE-30 column. The neutral alumina used throughout was deactivated to activity III.

Fluorination of Griseofulvin (1).—To a stirred suspension of calcium oxide (5 g) in trichlorofluoromethane (400 ml) containing trifluorofluoro-oxymethane (15·5 mmol) at −78° was added a cold (−78°) solution of griseofulvin (1) (5·03 g, 14·3 mmol) in dichloromethane (100 ml) in one portion. One min after addition, a sample (1 ml) of the mixture was added to a solution of potassium iodide without liberation of iodine (consumption of the fluoro-oxycompound). The mixture was filtered into sodium hydrogen carbonate solution, and the organic layer was washed with fresh sodium hydrogen carbonate solution, water, saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to give a gummy solid. Chromatography on alumina (500 g) and elution with dichloromethane (1650 ml) gave a fraction (A) (3·18 g) containing three fluorinated products and griseofulvin. Further elution, with chloroform (250 ml) and ethyl acetate (300 ml), gave unchanged griseofulvin (1·56 g).

Isolation of 5-Fluorogriseofulvin (2) *and 3′-Fluorogriseofulvin* (3).—Rechromatography of fraction (A) on alumina (300 g) and elution with benzene (1400 ml) gave fraction (B) (1·15 g) as a mixture of two products. Continued elution with benzene (1000 ml) gave *5-fluorogriseofulvin* (2) (1·26 g), m.p. 140—141° (from ether–hexane); $\nu_{max.}$ 1720 and 1665 (C=O) cm^{-1}; $\lambda_{max.}$ (log ε) 345 (3·64), 284 (4·22), and 236 nm (4·28); τ 4·45 (3′-H), 5·74 (d, *J* 1·2 Hz, 6-OMe), 5·79 (d, *J* 2·0 Hz, 4-OMe), and 6·36 (2′′-OMe); ϕ^* 154·8 (m, 5-F); $[\alpha]_D^{25}$ +308° (*c* 0·981) (Found: C, 55·2; H, 4·30; Cl, 10·2; F, 5·45. $C_{17}H_{10}ClFO_6$ requires C, 55·05; H, 4·35; Cl, 9·55; F, 5·1%).

Continued elution, with benzene (200 ml) and dichloromethane (300 ml), gave *3′-fluorogriseofulvin* (3) (0·56 g), m.p. 213—214° (from ether–hexane); $\nu_{max.}$ 1710 and 1700 (C=O) cm^{-1}; $\lambda_{max.}$ (log ε) 326 (3·75), 292 (4·39), 257 (4·18), and 236 nm (4·29); τ 3·82 (5-H), 5·96 (6-OMe), 6·01 (4-OMe), and 5·99 (d, *J* 6 Hz, 2′-OMe); ϕ^* 156·2 (3′-F); $[\alpha]_D^{25}$ +287° (*c* 0·730) (Found: C, 54·6; H, 4·4; Cl, 9·75. $C_{17}H_{16}ClFO_6$ requires C, 55·05; H, 4·35; Cl, 9·55%).

Elution with chloroform (350 ml) gave unchanged griseofulvin (1) (0·15 g).

Isolation of 3′,5-Difluorogriseofulvin (4).—Fraction (B) was chromatographed on alumina (250 g). Elution with benzene (750 ml) gave *3′,5-difluorogriseofulvin* (4) (0·54 g), m.p. 97—99° (from ether–hexane); $\nu_{max.}$ 1720 and 1700 (C=O) cm^{-1}; $\lambda_{max.}$ (log ε) 345 (3·70), 276 (4·30), and 257 nm (4·25); τ 5·74 (d, *J* 1·2 Hz, 6-OMe), 5·79 (d, *J* 2·0 Hz, 4-OMe), and 5·99 (d, *J* 6 Hz, 2′-OMe); ϕ^* 154·91 (m, 5-F) and 156·4 (m, 3′-F); $[\alpha]_D^{25}$ +258° (*c* 0·970) (Found: C, 52·55; H, 4·05; Cl, 8·8; F, 9·75. $C_{17}H_{15}ClF_2O_6$ requires C, 52·5; H, 3·9; Cl, 9·1; F, 9·7%).

Further elution with benzene (750 ml) gave 5-fluorogriseofulvin (2) (0·47 g), identical with that isolated before.

Fluorination of the Fluorogriseofulvin (3) *or* (4).—To a stirred suspension of calcium oxide (50 mg) in trichlorofluoromethane (50 ml) containing trifluorofluoro-oxymethane (0·2 mmol) at −78°, a cold (−78°) solution of the fluorogriseofulvin (3) or (4) (50 mg) in dichloromethane (2 ml) was added in one portion. Work-up and evaporation gave a yellow gum. T.l.c. on silica gel in two solvents (3% MeOH–CH_2Cl_2 and 30% EtOAc–PhH) and g.l.c. on 3% SE-30 at 165° indicated the formation of 3′,5-difluorogriseofulvin in low yield.

Conversion of 5-Fluorogriseofulvin (2) *into 5-Fluoroisogriseofulvin* (6) *and 5-Fluorogriseofulvic Acid* (5).—5-Fluorogriseofulvin (2) (200 mg) in methanol (10 ml) saturated with hydrogen chloride was heated under reflux for 2 h. The methanol was then removed *in vacuo* and the crude product partitioned between dichloromethane and aqueous 5% sodium carbonate. The organic layer was then washed successively with aqueous 5% sodium carbonate, water, and brine, then dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography of the residue on alumina afforded *5-fluoroisogriseofulvin* (6) (eluted with benzene), m.p. 103—105° (from ether–hexane), $\nu_{max.}$ (KBr) 1710 and 1660 cm^{-1}, $\lambda_{max.}$ (log ε) 345 (3·65), 285 (4·17), and 266 nm (43·4); τ 8·97 (d, *J* 6 Hz, 6′-Me), 6·2 (4′-OMe), and 5·87 and 5·83 (d, *J* 3 Hz, 4-OMe and 6-OMe); $[\alpha]_D^{26\cdot2}$ +157° (*c* 1·40 in Me_2CO) (Found: C, 54·9; H, 4·45; Cl, 9·4; F, 5·35. $C_{17}H_{16}ClFO_6$ requires C, 55·1; H, 4·4; Cl, 9·6; F, 5·1%).

Identical material was isolated when the crude product from the fluorination of griseofulvin (1) was subjected to an unbuffered methanolic work-up.

The aqueous sodium carbonate extracts were combined, acidified, and extracted with dichloromethane. This extract was washed with water and brine, dried (Na_2SO_4), and concentrated to afford *5-fluorogriseofulvic acid* (5) (53 mg), m.p. (from ethyl acetate) 230—235°; $\nu_{max.}$ (KBr) 1730, 1630, and 1605 cm^{-1}; $\lambda_{max.}$ (log ε) 342 (3·39) and 283 nm (4·29); τ (C_5H_5N–$CDCl_3$) 8·98 (d, *J* 6 Hz, 6′-Me), 5·90 and 5·85 (d, 4-OMe and 6-OMe), and 4·57 (3′-H, exchangeable with D_2O); ϕ^* C_5D_5N +155·58; $[\alpha]_D^{25}$ +101·3° (*c* 0·39) (Found: C, 53·7; H, 4·15; Cl, 9·8; F, 4·95. $C_{16}H_{14}ClFO_6$ requires C, 53·85; H, 3·95; F, 5·35%).

[2/1515 *Received*, 28*th June*, 1972]