Synthesis of 5-Fluoropyrimidines

By **Derek H. R. Barton, William A. Bubb, Robert H. Hesse,*** and **Maurice M. Pechet,** Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02132, U.S.A.

Fluorination with trifluorofluoro-oxymethane is a convenient general procedure for the synthesis of 5-fluoropyrimidines, including 5-fluorobarbituric acids.

DIRECT fluorination of biologically important pyrimidines and pyrimidine nucleosides has heretofore [1] been confined to the preparation of 5-fluorinated derivatives of uracil, cytosine, and the corresponding nucleosides. In view of the facility of our synthesis [1a] of 5-fluorouracil, we considered that direct fluorination with trifluorofluoro-oxymethane (CF_3OF) should be generally feasible for pyrimidines activated towards electrophilic attack, so that a variety of 5-fluorinated pyrimidines would, in principle, be accessible. This expectation has been experimentally verified and we now report the ready electrophilic fluorination of thymine (1), 5-hydroxymethyluracil (2), 5-fluorouracil (3), orotic acid (4), barbituric acid (5), and 5-phenylbarbituric acid (6).

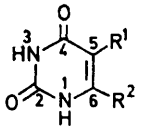
Fluorination was effected with CF_3OF in a mixture of 50% aqueous trifluoroacetic acid and trichlorofluoromethane at ambient temperature or in methanol–trichlorofluoromethane at −78°. Although several of the substrates were not appreciably soluble in the former solvent system, no difficulty was encountered in carrying the reactions to completion (see Experimental section).

Fluorination proceeded almost exclusively at C-5 and in each case the n.m.r. spectrum of the material obtained from the initial crystallisation indicated the presence of one pure product. Nevertheless, in some instances the m.p. of this material was lower than that of the analytically pure product, which might be attributable to contamination by small amounts of *N*-fluorinated compounds analogous to the *N*-chlorinated products obtained [2] on chlorination of uracil and several of its derivatives.

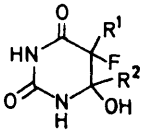
[1] (*a*) D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, 1972, **37**, 329; (*b*) M. J. Robins and S. R. Naik, *J. Amer. Chem. Soc.*, 1971, **93**, 5277; (*c*) D. Cech, H. Meinert, G. Etzold, and P. Langen, *J. prakt. Chem.*, 1973, **315**, 149; (*d*) H. Meinert and D. Cech, *Z. Chem.*, 1972, **12**, 292; (*e*) H. Meinert and D. Cech, *ibid.*, p. 335; (*f*) J. S. Fowler, R. D. Finn, R. M. Lambrecht, and A. P. Wolf, *J. Nuclear Medicine*, 1973, **14**, 63; (*g*) A. Lazdins, D. Snikeris, A. Veinberga, S. Hillers, I. L. Knunyants, L. S. German and N. B. Kaz'mina, U.S.S.R. P., 322,053 (*Chem. Abs.*, 1973, **79**, 78,834a); (*h*) M. J. Robins and S. R. Naik, *J.C.S. Chem. Comm.*, 1972, 18.

[2] Y. Hoyano, V. Bacon, R. E. Summons, W. E. Pereira, B. Halpern, and A. M. Duffield, *Biochem. Biophys. Res. Comm.*, 1973, **53**, 1195.

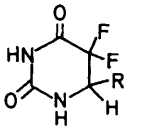
Treatment of compounds (1) and (2) with a slight excess of CF_3OF in aqueous trifluoroacetic acid–trichlorofluoromethane at ambient temperature gave the adducts (7) and (8), respectively. The gross structures



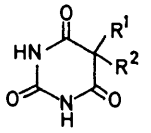
(1) R^1 = Me, R^2 = H
(2) R^1 = CH_2OH, R^2 = H
(3) R^1 = F, R^2 = H
(4) R^1 = H, R^2 = CO_2H
(5) R^1 = H, R^2 = OH
(6) R^1 = Ph, R^2 = OH
(12) R^1 = F, R^2 = CO_2H



(7) R^1 = Me, R^2 = H
(8) R^1 = CH_2OH, R^2 = H
(11) R^1 = H, R^2 = CO_2H



(9) R = OH
(10) R = OMe



(13) R^1 = R^2 = F
(14) R^1 = Ph, R^2 = F

of these adducts follow readily from their spectroscopic properties (see Experimental section), but the stereochemistry about the 5,6-bond cannot be readily inferred as the only precedents [3] on which to base stereochemical assignments in hydrouracil derivatives have been formulated on very tenuous evidence.

Fluorination of compound (3) under similar conditions or in methanol–trichlorofluoromethane at −78° gave the adducts (9) and (10), respectively, which are entirely analogous to the hydrouracil derivatives obtained on chlorination,[4] bromination,[4] or nitration [5] of 5-fluorouracil.

The total synthesis of 5-fluoro-orotic acid has been described by several groups.[6] We have found that orotic acid reacts readily with a slight excess of CF_3OF at ambient temperature to give an adduct which, although not isolated, was identified as (11) by the ^{19}F n.m.r. spectrum (δ +208 p.p.m. from Cl_3CF, J 46 Hz), and by analogy with our adducts (7)—(10). A similar adduct has been reported [7] as the initial product obtained on bromination of orotic acid under mild conditions. Dehydration, without decarboxylation, of the adduct (11) was effected by careful heating under reduced pressure and yielded 5-fluoro-orotic acid (12) as the sublimed product.

We considered that the formation [8] of 5,5-dibromo- and 5,5-dichloro-barbituric acid on treatment of 6-aminouracil with the appropriate halogen probably proceeded *via* the monohalogenobarbituric acid, so that preparation of fluorinated barbituric acid derivatives by direct fluorination seemed feasible. Indeed, treatment of the parent compound (5) with 2·5 equiv. of CF_3OF at ambient temperature gave the expected 5,5-difluorobarbituric acid (13). With approximately equimolar quantities of substrate and fluorinating agent we also obtained (13), but found no evidence for the presence of 5-fluorobarbituric acid, the latter apparently being more susceptible to fluorination than (5) itself. Treatment of compound (6) with CF_3OF at −78° in methanol–trichlorofluoromethane containing a small volume of trifluoroacetic acid to promote enolisation proceeded cleanly to give the anticipated fluoro-compound (14).

Thus direct fluorination with CF_3OF provides a convenient route to various 5-fluorinated pyrimidines and hydropyrimidines.

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. N.m.r. data were recorded on a Varian T-60 instrument, at 60 MHz for ^1H spectra (with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard for solutions in deuterium oxide and tetramethylsilane for all other solutions), and at 56·4 MHz for ^{19}F spectra (with trichlorofluoromethane as internal standard unless otherwise indicated). Chemical shifts are in p.p.m. from the standards indicated. I.r. spectra are quoted for Nujol mulls.

Compounds (1)—(6) were obtained from commercial sources and purified, when necessary, by recrystallisation.

Fluorinations at Ambient Temperature.—A suspension of the substrate (1—5 mmol) in equal volumes of fluorotrichloromethane (25—50 ml) and 50% aqueous trifluoroacetic acid (25—50 ml) contained in a glass autoclave (Fischer–Porter aerosol compatibility bottle) was cooled in liquid nitrogen. Trifluorofluoro-oxymethane [1·25—2·5 equiv. in the case of (5)] was added from a pre-calibrated vacuum line. The mixture was allowed to warm to ambient temperature and vigorously stirred. In each case [except for (8)] the product was soluble in the solvent system and the end of the reaction (time taken from the addition of CF_3OF) was indicated by the complete dissolution of the substrate. The reaction mixture was purged with nitrogen and concentrated under reduced pressure to give the crude product.

5-Fluoro-5,6-dihydro-5-methyl-6-hydroxyuracil (7).—Thymine (1) (0·50 g) was treated with CF_3OF for 2·5 h. The

[3] (*a*) H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry*, 1964, **3**, 1844; (*b*) M. Fikus, K. L. Wierzchowski, and D. Shugar, *Biochem. Biophys. Res. Comm.*, 1964, **16**, 478; (*c*) M. Chabre, D. Gagnaire, and C. Nofre, *Bull. Soc. chim. France*, 1966, 108.

[4] (*a*) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenall and J. J. Fox, *J. Medicin. Chem.*, 1967, **10**, 47; (*b*) F. Hoffmann-La Roche and Co., Neth. Appl. 6,404,756 (*Chem. Abs.*, 1965, **62**, 14,693d).

[5] R. Duschinsky and U. Eppenberger, *Tetrahedron Letters*, 1967, 5103.

[6] (*a*) F. Hoffmann-La Roche and Co., B.P. 806,584/1958 (*Chem. Abs.*, 1959, **53**, 16,171a); (*b*) R. Duschinsky and C. Heidelberger, U.S.P. 2,948,725 (*Chem. Abs.*, 1961, **55**, 17,663f); (*c*) B. A. Ivin and V. G. Nemets, *Zhur. obshchei Khim.*, 1964, **34**, 4120 (*Chem. Abs.*, 1965, **62**, 9127b); (*d*) R. Riemschneider and H. Pehlmann, *Z. Naturforsch.*, 1965, **20b**, 540.

[7] J. Moravek and L. Leseticky, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1352.

[8] J. Wojciechowski, A. Rudnicki, T. Mleczko, and L. Gedziorowska, Pol. P. 64,708 (*Chem. Abs.*, 1972, **77**, 164,749s).

crude products from four such reactions were combined and recrystallised from water to give the *adduct* (7) (2·09 g). A second recrystallisation afforded needles, m.p. 169—172°, which on further crystallisation gave granules, m.p. 150—152°, ^{1}H δ (D_2O) 1·67 (3H, d, *J* 22·5 Hz, Me) and 5·04 (1H, d, *J* 1·6 Hz, 6-H), ^{19}F δ (MeOH) +171 (q, *J* 22·5 Hz), $\nu_{max.}$ 3600 and 1730 cm^{-1} (Found: C, 35·3; H, 4·8; F, 11·6; N, 16·2. $C_5H_7FN_2O_3,0{\cdot}5H_2O$ requires C, 35·1; H, 4·7; F, 11·1; N, 16·4%), *m/e* 162 (M^+).

5-Fluoro-5,6-dihydro-5-hydroxymethyl-6-hydroxyuracil (8).—5-Hydroxymethyluracil (2) hemihydrate (0·60 g) was treated with CF_3OF for 19 h. Recrystallisation of the crude product from water afforded the *adduct* (8) (0·53 g), m.p. 206—209° (decomp.), ^{1}H δ (D_2O) 4·02 (2H, d, *J* 23·0 Hz, CH_2) and 5·20 (1H, d, *J* 1·4 Hz, 6-H), ^{19}F δ (Me_2SO) +183 (t, *J* 23·0 Hz), $\nu_{max.}$ 3250 and 1700 cm^{-1} (Found: C, 33·6; H, 4·3; F, 10·4; N, 15·6. $C_5H_7FN_2O_4$ requires C, 33·7; H, 4·0; F, 10·7; N, 15·7%), *m/e* 160 ($M^+ - H_2O$).

5,5-Difluoro-5,6-dihydro-6-hydroxyuracil (9).—5-Fluorouracil (3) (0·52 g) was treated with CF_3OF for 4 h to give the *adduct* (9) (0·50 g), m.p. 186—188° (from ethyl acetate–hexane). Sublimation (170—180°; 0·2 mmHg) gave a sample of m.p. 191—192°, ^{1}H δ (Polysol; Stohler Isotope Chemicals) 4·90 [1H, m (dd when sample treated with D_2O, *J* 5·6 and 2·5 Hz), 6-H], 6·10br (2H, m, 1- and 3-H), and 8·25br (1H, s, OH), ^{19}F δ (MeOH) +112 (dd, *J* 278 and 5·6 Hz) and +130 (d, *J* 278 Hz), $\nu_{max.}$ 3500, 3300, and 1720 cm^{-1} (Found: C, 28·7; H, 2·5; F, 22·7; N, 16·9. $C_4H_4F_2N_2O_3$ requires C, 28·9; H, 2·4; F, 22·9; N, 16·9%), *m/e* 166 (M^+).

5-Fluoro-orotic Acid (12).—Orotic acid (4) monohydrate (0·17 g) was treated with CF_3OF for 4 h to yield a crystalline solid which, on slow sublimation (220—240°; 0·3 mmHg), gave 5-fluoro-orotic acid (12) (0·16 g), m.p. 256—259° (lit.,[6a,b] 255°; lit.,[6c] 252°; lit.,[6d] 245—250°) [decarboxylating to give 5-fluorouracil, m.p. 278—279° (lit.,[1a] 282—283°)], ^{19}F δ (Me_3SO) +158 (d, *J* 3·8 Hz) (coupling removed by exchange with D_2O), $\nu_{max.}$ 3700—2200 and 1680 cm^{-1}. Recrystallisation from water gave *5-fluoro-orotic acid monohydrate*, m.p. 258—259° (Found: C, 31·4; H, 2·7; F, 9·9; N, 14·7. $C_5H_3FN_2O_4,H_2O$ requires C, 31·3; H, 2·6; F, 9·9; N, 14·6%).

5,5-Difluorobarbituric Acid (13).—Barbituric acid (5) dihydrate (0·38 g) was treated with CF_3OF for 1 h to give a white solid (0·50 g), which was dissolved in the minimum volume of water at ambient temperature. The solution was cooled to precipitate *5,5-difluorobarbituric acid* (13) (0·27 g), m.p. 210—213° (decomp.), ^{19}F δ (H_2O with $NaO_2C{\cdot}CF_3$ standard) +36·4 (s), $\nu_{max.}$ 3300 and 1730 cm^{-1} (Found: C, 28·9; H, 1·5; F, 23·2; N, 17·2. $C_4H_2F_2N_2O_3$ requires C, 29·3; H, 1·2; F, 23·2; N, 17·1%), *m/e* 164 (M^+).

Fluorinations at −78°.—*5,5-Difluoro-5,6-dihydro-6-methoxyuracil* (10). 5-Fluorouracil (3) (0·13 g) in methanol (50 ml) was added to a solution of CF_3OF (1·2 mmol) in trichlorofluoromethane (25 ml) at −78° and the mixture was stirred vigorously at −78° for 5 min, purged with nitrogen, and concentrated to give the *adduct* (10) (0·18 g), m.p. 179—184°. Two recrystallisations from water gave prisms, m.p. 201—202°, ^{1}H δ [$(CD_3)_2SO$] 3·38 (3H, s, OMe), 3·52br (2H, m, 1- and 3-H), and 4·92 [1H, m (dd when sample treated with D_2O, *J* 6·2 and 2·6 Hz), 6-H], ^{19}F δ (MeOH) +111 (dd, *J* 278 and 6·2 Hz) and +130 (d, *J* 278 Hz), $\nu_{max.}$ 3300, 3100, 1760, and 1720 cm^{-1} (Found: C, 33·6; H, 3·5; F, 21·0; N, 15·7. $C_5H_6F_2N_2O_3$ requires C, 33·3; H, 3·4; F, 21·1; N, 15·6%).

5-Fluoro-5-phenylbarbituric acid (14). Phenylbarbituric acid (6) (0·20 g) in methanol (50 ml) was added to a mixture of CF_3OF (1·1 mmol), trichlorofluoromethane (20 ml), and trifluoroacetic acid (2 ml) at −78° and the mixture was stirred vigorously for 5 min at −78°, purged with nitrogen, and concentrated to give *5-fluoro-5-phenylbarbituric acid* (14) (0·18 g), m.p. 251—253° (from water), ^{1}H δ (CD_3CN) 6·00—7·20br (2H, s, 1- and 3-H) and 7·52 (5H, m, Ph), ^{19}F δ (CD_3CN) +163 (s), $\nu_{max.}$ 3100, 1780, and 1725 cm^{-1}, $\lambda_{max.}$ (MeOH) 270 (ε 740) and 264 nm (890) (Found: C, 54·1; H, 3·4; F, 8·4; N, 12·8. $C_{10}H_7FN_2O_3$ requires C, 54·1; H, 3·2; F, 8·6; N, 12·6%), *m/e* 222 (M^+).

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