the degeneracy, and the result is a *two-peak* spectrum for H_2, H_4, H_6, and H_8. The ratio of the separation of these peaks (37 ± 1 Hz) to the total separation of the H_2, H_8 and H_4, H_6 signals in frozen barbaralone (669 ± 2Hz) provides the IIA ⇄ IIB equilibrium value of 44.5 (± 0.5) *vs.* 55.5 (±0.5)%, respectively.

Although our analysis of the effects of deuterium at C_2–C_4 positions (IV) is complicated by partial isotopic scrambling (only two-thirds of the sample is IV, the rest being II),[11] we were able to ascertain from normal- and low-temperature pmr spectra that a deuterium isotope effect did exist, favoring attachment of deuterium to the cyclopropanoid positions C_2 (IVA).[13]

Substitution of methyl for hydrogen in the barbaralyl system has, as expected, a more pronounced effect. Methyl at C_1 was found by pmr[14] to shift the equilibrium in the direction of substitution on cyclopropyl rather than aliphatic; quantitatively, 76.6 ± 0.8% of the mixture of isomers is represented by structure IIIA. Preference of methyl for a vinylic rather than cyclopropyl position is clearly demonstrated in the pmr spectrum of V, in which isomer B is preferred (>75%).

Although equilibrium deuterium isotope effects have been observed only recently, it has long been known that deuterium prefers attachment to C_{sp^3} over C_{sp^2}.[15] Our investigation extends such equilibrium studies to cyclopropyl C_{sp^2}, the ordering C_{sp^3}(aliphatic) > $C_{\sim sp^2}$(cyclopropyl) > C_{sp^2}(vinylic) being observed.[16]

Our data indicate an inverse ordering for methyl attachment: olefinic > cyclopropane > aliphatic. That methyl groups prefer double bonds is well known and is in accord with available thermodynamic data, *e.g.*, eq 1. Our results contrast with available enthalpy data on ethylcyclopropane, eq 2, which indicate ethyl attachment to prefer aliphatic to cyclopropane positions.[17]

$$\text{c-}C_3H_5\text{-H} + i\text{-}C_3H_7\text{-}CH_3 \longrightarrow \text{c-}C_3H_5\text{-}CH_3 + i\text{-}C_3H_7\text{-H} \quad (1)$$
exothermic, $\Delta H_{isom} = 1.59$ kcal/mol[17]

$$\text{c-}C_3H_5\text{-Et} + i\text{-}C_3H_7\text{-H} \longrightarrow \text{c-}C_3H_5\text{-H} + i\text{-}C_3H_7\text{-Et} \quad (2)$$
exothermic, $\Delta H_{isom} = 0.46$ kcal/mol[17]

A fuller discussion of these effects will be presented later, as well as an assessment of the influences of other substituents, especially of the π-donor and -acceptor types for which theoretical predictions are available.[1-3]

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(18) National Institutes of Health Postdoctoral Fellow, 1969–1970.

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Nucleic Acid Related Compounds. III. A Facile Synthesis of 5-Fluorouracil Bases and Nucleosides by Direct Fluorination[1]

Sir:

We wish to report the preparation of 5-fluorouracil (**2a**), 5-fluoro-1-methyluracil (**2b**), 5-fluorouridine (**2c**), and 5-fluoro-2′-deoxyuridine (**2d**) from the corresponding uracils (**1a–d**) as examples of the first direct synthesis of the biochemically and therapeutically important fluoropyrimidines and nucleosides.

Since the first publication[2] on the preparation of 5-fluorouracil (**2a**) by construction of the pyrimidine ring beginning with ethyl fluoroacetate, all syntheses of analogous bases and nucleosides[3] have employed this basic approach—construction of the appropriate 5-fluoropyrimidine from a fluoro-substituted aliphatic fragment followed by transformations on the base and/or sugar after standard nucleoside-coupling procedures.[4]

These *de novo* procedures[3] have been employed to give an assortment of 5-fluoropyrimidine compounds which have been studied in great detail in biological systems.[4,5] As well, 5-fluorouracil (**2a**) and 5-fluoro-2′-deoxyuridine (**2d**) are employed as standard clinical drugs for certain solid tumors and viral infections.[5]

In order to explore the biochemical and therapeutic properties of selected fluoronucleosides with modified carbohydrate moieties without the necessity of recourse to relatively inaccessible and expensive 5-fluorouracil nucleosides or bases as starting materials,[3] we sought a direct method for introduction of fluorine into preformed nucleosides. Treatment of *dl*-1-methyl-5-bromo-6-methoxy-5,6-dihydrouracil[6] with silver fluoride and with various other fluoride nucleophiles gave only 1-methyluracil, unlike an analogous approach to 5-mercaptouracils using the same heterocycle and hydrosulfide.[6]

(1) This work was generously supported by the National Cancer Institute of Canada.

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Reaction of 0.336 g (0.003 mol) of uracil (**1a**) or 0.378 g (0.003 mol) of 1-methyluracil[7] (**1b**) with a twofold excess of trifluoromethyl hypofluorite[8] in methanol–fluorotrichloromethane at −78° resulted in complete loss of the uracil chromophore at 260 nm. Solvent and excess reagent were removed at 20° and the resulting somewhat unstable adduct mixture (presumably 5-fluoro-6-trifluoromethoxy-5,6-dihydrouracil or the corresponding 1-methyl derivative) was dissolved in a 10% solution of triethylamine in 50% aqueous methanol and allowed to stand at room temperature for 24 hr. Evaporation of this solution to dryness and recrystallization of the resulting solid from water gave 0.33 g (84%) of 5-fluorouracil[2,9] (**2a**): mp 284–286° dec; uv_{max} (0.1 *N* HCl) 266 nm (ε 7000), (0.1 *N* NaOH) 280 nm (ε 5100); nmr (^1H, DMSO-d_6) δ 7.74 (d, 1, J_{6-5} = 6.0 Hz, H_6), (^{19}F, DMSO-d_6, ppm from CCl_3F external standard) δ 171 (d, 1, J_{5-6} = 6.0 Hz, F_5); mass spectrum calcd for M^+ ($C_4H_3FN_2O_2$) 130.0178; *m/e* 130.0169. Corresponding treatment gave 0.36 g (84%) of 5-fluoro-1-methyluracil[3f,7b,9] (**2b**): mp 257–260°; uv_{max} (0.1 *N* HCl) 273 nm (ε 8240), (0.1 *N* NaOH) 271 nm (ε 6100); nmr (^1H, DMSO-d_6) δ 3.30 (s, 3, 1-CH_3), 8.16 (d, 1, J_{6-5} = 7.0 Hz, H_6), (^{19}F, DMSO-d_6, CCl_3F ext) δ 170 (d, 1, J_{5-6} = 7.0 Hz, F_5); mass spectrum calcd for M^+ ($C_5H_5FN_2O_2$) 144.0335; *m/e* 144.0343.

Analogous reaction of 3.7 g (0.01 mol) of 2′,3′,5′-tri-*O*-acetyluridine[10] (**1c**) or 0.62 g (0.002 mol) of 3′,5′-di-*O*-acetyl-2′-deoxyuridine[11,12] (**1d**) with trifluoromethyl hypofluorite (twofold excess in chloroform–fluorotrichloromethane solution) followed by aqueous methanolic triethylamine gave 2.10 g (80%) of 5-fluorouridine[3b,9] (**2c**): mp 181–182°; $[\alpha]^{26}D$ 16.5° (*c* 1.1, H_2O); uv_{max} (0.1 *N* HCl) 268 nm (ε 10,000), (0.1 *N* NaOH) 268 nm (ε 7280); nmr (^1H, D_2O) δ 4.13 (m, 2, $H_{5',5''}$), 4.26–4.64 (m, 3, $H_{4',3',2'}$), 6.17 (d of d, 1, $J_{1'-2'}$ = 4.2 Hz, $J_{1'-5F}$ = 1.6 Hz, $H_{1'}$), 8.37 (d, 1, J_{6-5} = 6.5 Hz, H_6), (^{19}F, D_2O, CCl_3F ext) δ 165.8 (d of d, 1, J_{5-6} = 6.5 Hz, $J_{5F-1'}$ = 1.6 Hz, F_5); mass spectrum calcd for M^+ ($C_9H_{11}FN_2O_6$) 262.0601; *m/e* 262.0617. Corresponding treatment gave 0.27 g (55%) of 5-fluoro-2′-deoxyuridine[3a,9] (**2d**): mp 149–150°; $[\alpha]^{26}D$ 36° (*c* 1.1, H_2O); uv_{max} (0.1 *N* HCl) 268 nm (ε 8400), (0.1 *N* NaOH) 268 nm (ε 6600); nmr (^1H, D_2O) δ 2.66 (m, 2, $H_{2',2''}$), 4.08 (m, 2, $H_{5',5''}$), 4.31 (m, 1, $H_{4'}$), 4.72 (m, 1, $H_{3'}$), 6.52 (t of d, 1, $J_{1'-2',2''}$ = 6.5 Hz, $J_{1'-5F}$ = 1.6 Hz, $H_{1'}$), 8.31 (d, 1, J_{6-5} = 6.5 Hz, H_6), (^{19}F, D_2O, CCl_3F ext) δ 165.8 (d of d, 1, J_{5-6} = 6.6 Hz, $J_{5F-1'}$ = 1.6 Hz, F_5); mass spectrum calcd for M^+ ($C_9H_{11}FN_2O_5$) 246.0652; *m/e* 246.0662. These data agree well with corresponding physical constants, where published, and, in addition, mixture melting points of **2c** and **2d** with authentic samples were undepressed.

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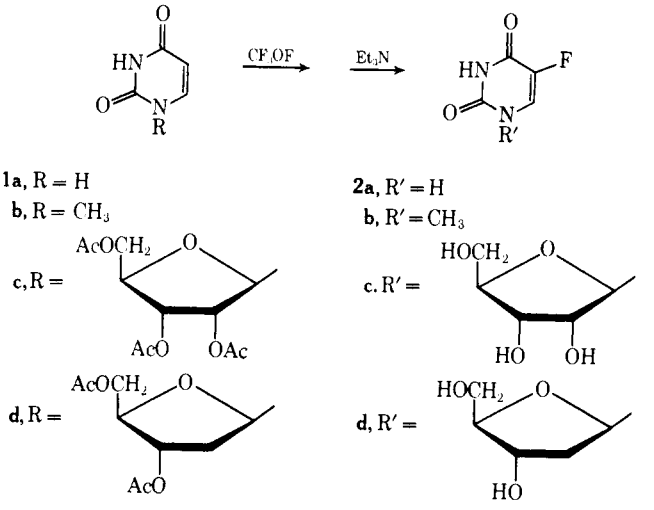
(12) An improved procedure has been devised which gives this pure product in 90% yield without chromatography.

Thus, a facile direct route to 5-fluorouracil nucleosides is now available. The application of this procedure to provide new potential antitumor and antiviral agents containing fluorinated bases[13] and the investigation of the adduct structures will be reported in detail.



(13) The addition of CF_3OF followed by elimination of CF_3OH to give the "aromatic" fluoro heterocycle is also successful with cytosine and other bases.

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Di-*tert*-butyliminoxy, a Free Radical of Moderate Stability[1]

Sir:

The importance of steric effects in stabilizing radicals of the triarylmethyl class was early recognized.[2] In many other organic radicals, including well-known examples such as diphenylpicrylhydrazyl (DPPH),[3] di-*tert*-butyl nitroxide,[4] and 2,4,6-tri-*tert*-butylphenoxy,[5,6] dimerization is hindered by bulky groups around the radical center. For di-*tert*-butyl nitroxide and the title radical, the lack of α protons confers stability in a different way by preventing their disproportionation, one decomposition pathway which renders less-substituted homologs of both types much more labile.[7,8]

We wish to report the preparation of an iminoxy radical sufficiently stable to be isolated and characterized. Di-*tert*-butyl ketone was converted to its oxime by means of the high-pressure method of Jones and Tristram.[9] A solution of 0.306 g of oxime in 30 ml of benzene was shaken for 1.5 hr with 0.7 g of silver oxide (Fisher). Work-up at 25° afforded a sky-blue liquid (0.224 g) with an odor resembling

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