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 trifluoromethylhypofluorite (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.

(6) L. Szabo, T. I. Kalman, and T. J. Bardos, *J. Org. Chem.*, **35**, 1434 (1970).

(7) (a) C. C. Cheng and L. R. Lewis, *J. Heterocycl. Chem.*, **1**, 260 (1964); (b) T. T. Sakai, A. L. Pogolotti, Jr., and D. V. Santi, *ibid.*, **5**, 849 (1968).

(8) K. B. Kellogg and G. H. Cady, *J. Amer. Chem. Soc.*, **70**, 3986 (1948); J. A. C. Allison and G. H. Cady, *ibid.*, **81**, 1089 (1959); D. H. R. Barton, *Pure Appl. Chem.*, **21**, 285 (1970).

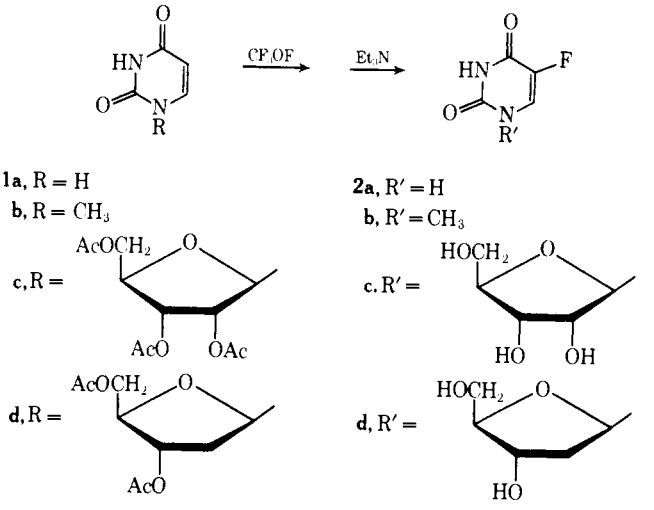
(9) These compounds were found to have microanalytical values for C, H, F, and N within ±0.3% of theory.

(10) J. Žemlička, J. Smrt, and F. Šorm, *Collect. Czech. Chem. Commun.*, **29**, 635 (1964).

(11) R. J. Cushley, J. F. Codington, and J. J. Fox, *Can. J. Chem.*, **46**, 1131 (1968).

(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.

Morris J. Robins,* S. R. Naik
Department of Chemistry, The University of Alberta
Edmonton, Alberta, Canada
Received July 6, 1971

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

(1) Issued as N.R.C.C. No. 12080.

(2) M. Gomberg, *J. Amer. Chem. Soc.*, **22**, 757 (1900).

(3) S. Goldschmidt and K. Renn, *Ber. Deut. Chem. Ges.*, **55**, 628 (1922).

(4) A. K. Hoffmann and A. T. Henderson, *J. Amer. Chem. Soc.*, **83**, 4671 (1961).

(5) C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953);

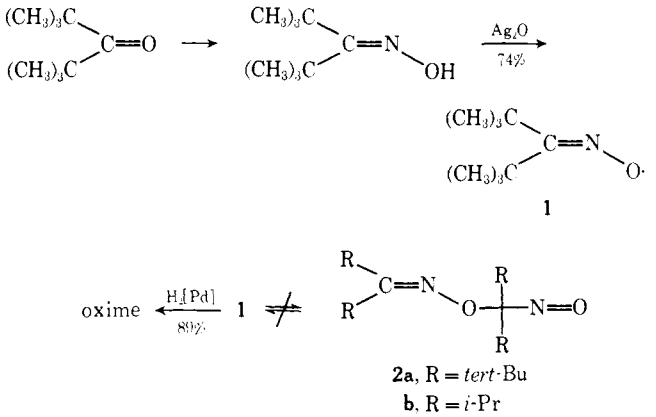
(6) E. Muller and K. Ley, *Z. Naturforsch. B*, **8**, 694 (1953).

(7) K. Adamic, D. F. Bowman, T. Gillan, and K. U. Ingold, *J. Amer. Chem. Soc.*, **93**, 902 (1971).

(8) J. L. Brokenshire, J. R. Roberts, and K. U. Ingold, unpublished results.

(9) W. H. Jones and E. W. Tristram, U. S. Patent 3,256,331 (1966).

camphor. Two distillations at 25° by the bulb-to-bulb technique gave material that analyzed correctly (C, H, N) and which gave a value of 160 for the molecular weight (vapor pressure thermistor). Other properties were fp −21°, $n^{21}D$ 1.4452, and $d^{22°}$ 0.824; strong absorption at 1610 cm^{-1} (C=N and/or N=O); mass spectrum superimposable on that of parent oxime (parent ion *m/e* 157).[10]



2a, R = *tert*-Bu
b, R = *i*-Pr

The esr spectrum of **1** in benzene showed a triplet with a_N = 32.2 G. Each of the three peaks was further resolved into at least 24 lines with a_H = 0.4 G at 24–42°, decreasing to 16 lines at 60° and 14 lines at 75°. Syn–anti isomerization was described in the first report of iminoxy radicals,[11] but we feel the complexity of this splitting must be explained in part in terms of proton nonequivalence due to hindered rotation of the *tert*-butyl groups.

We could find no compelling evidence for dimerization of **1**. A plot of esr signal intensity *vs.* concentration is linear up to 0.3 *M* in cyclohexane at 25°.[12] An isopentane solution 0.21 *M* in **1** was cooled from 25 to −150°. The doubly integrated esr signal showed only an *increase* by a factor of 2.70. This is the same within error as the increase shown by a dilute DPPH solution under these conditions (2.84).[13] The color of pure **1** is not visibly changed at −196°.

The visible spectrum of **1** (0.02 *M* in cyclohexane) showed a weak maximum at 720 nm (ε 4.5). At high concentration this shifted to shorter wavelengths (λ_{max} 701 nm at 0.39 *M*). The solutions obey Beer's law only if the absorbance at λ_{max} is plotted against concentration. This shift is either a solvent effect or the result of dimerization (*cf.*[8] **2b**: λ_{max} 703 nm (ε 11)). The first explanation is more consistent with the esr results and is the preferred one.

Finally, the ir spectrum of **1** as a neat liquid shows only a weak shoulder at 1560 cm^{-1}, whereas a strong peak assigned to the N=O group appears at this frequency in **2b**.[8]

Di-*tert*-butyliminoxy is stable to air, diffuse light, concentrated HCl, and aqueous NaOH at 25°. The radical liberates iodine from acidified starch–iodide paper. Catalytic reduction affords the parent oxime in high yield. In the neat state at 25° the radical decomposes within a week,[14] and a new absorption at 1555 cm^{-1} appears after 4 days even at −20°. The stability increases with dilution, however. A *ca.* 0.02 *M* solution of **1** in benzene shows a 15% decrease in the esr signal after 5 hr at 50°, and 50% after 9 days at 25°, but is stable indefinitely when frozen at −20°.

Di-*tert*-butyliminoxy is the first isolated example of a large number of iminoxy radicals hitherto observed only in solution.[10,15–18] The behavior of this compound can be determined leisurely and in the absence of the reagents of formation. We hope that further study of this radical will shed light on the properties of less stable members of its class.

(10) We have observed analogous behavior with some hydroxylamines, which give mass spectra identical with those of the corresponding nitroxides.
(11) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964).
(12) From the maximum error in the plot we calculate that K_{eq} must be greater than 10 *M*.
(13) Both values are somewhat larger than that predicted (2.42) from the Boltzmann equation over this temperature range.
(14) The nmr of a decomposed sample displayed eight singlets of different intensities between δ 1.1 and 1.6. The major product (~45%) is di-*tert*-butyl ketone.
(15) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 981 (1967), and preceding papers.
(16) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 1985 (1964).
(17) W. M. Fox and M. C. R. Symons, *J. Chem. Soc. A*, 1503 (1966), and preceding papers.
(18) L. Burlamacchi and E. Tiezzi, *Gazz. Chim. Ital.*, **99**, 1313 (1969).
(19) NRC Postdoctoral Fellow, 1969–1971.
(20) NRC Postdoctoral Fellow, 1971–1972.

J. L. Brokenshire,[19] G. D. Mendenhall,[20] K. U. Ingold*
National Research Council of Canada
Ottawa, Canada K1A 0R9
Received July 6, 1971

Formation of A/B *cis*- and *trans*-19-Norlanosterols by Enzymic Cyclization of 6′-Norsqualene 2,3-Oxide

Sir:

Replacement of an individual methyl by hydrogen at position 15,[1a] 10,[1b] or 6[2] in squalene 2,3-oxide does not preclude cyclization to a norlanosterol by lanosterol squalene 2,3-oxide cyclase. While such transformations are no longer novel, the enzymic formation of skeletal or stereoisomeric lanosterol analogs from squalene 2,3-oxide variants is noteworthy. We now report that 6′-norsqualene (I) cyclizes enzymically not only to the A/B *trans*-19-norlanosterol II, but also to the A/B cis isomer III.[3]

Radiolabeled *all-trans*-oxide I was obtained by overall reductive coupling of *trans,trans*-farnesyl bromide with stereoselectively prepared allylic bromide IV.[4]

(1) (a) E. E. van Tamelen, R. P. Hanzlik, K. B. Sharpless, R. B. Clayton, W. J. Richter, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **90**, 3284 (1968); (b) E. E. van Tamelen, R. P. Hanzlik, R. B. Clayton, and A. L. Burlingame, *ibid.*, **92**, 2137 (1970).
(2) That an individual methyl at C-6 is not essential for enzymic cyclization was mentioned, in a broader context, by E. E. van Tamelen and J. H. Freed, *ibid.*, **92**, 7206 (1970). Recently, E. J. Corey, A. Krief, and H. Yamamoto (*ibid.*, **93**, 1493 (1971)) reported the hog sterol cyclase catalyzed conversion of 6′-norsqualene 2,3-oxide to a single product, considered to be 19-norlanosterol on the strength of mass spectral analysis of the sterol, dihydrosterol, and its ene-7,11-dione. However, no stereochemical assignment or identification of product as either of the sterols II or III was possible on the basis of their published data.
(3) These epimers are believed to possess the lanosterol stereochemistry at centers other than C-10, since (1) the nmr spectral properties are very similar to those of lanosterol and its stereochemical analogs, and (2) various other squalene oxide modifications are enzymically converted to products proved to be in the lanosterol stereochemical class. See E. E. van Tamelen and J. H. Freed[2] and preceding papers in this series.
(4) Alkylation of the dianion of 3-butyn-1-ol[5a] with β-bromopropionaldehyde ethylene acetal afforded the heptynol i,[6] reduction of which with sodium–liquid ammonia provided the *trans*-heptenol ii (X = OH).[6] Treatment of the corresponding *p*-toluenesulfonate with anhydrous lithium bromide in acetone gave the *trans*-heptenyl bromide