ogeneous system of acetonitrile–water. Since glycine NCA cannot be transformed to the isocyanate through the NCA anion in the heterogeneous system, hydantoic acid is not formed in this system.

Experimental Section

Glycine NCA.[16]—Into a suspension of 10 g of finely powdered glycine in 400 ml of dry tetrahydrofuran, dry phosgene was bubbled at 45° with magnetical stirring. A clear solution was obtained after 2 hr. The solution was concentrated at reduced pressure at 30°, then glycine NCA crystallized out. To the residue was added 200 ml of *n*-hexane in order to crystallize out the NCA completely. The crystals of the product were filtered off and dried over P_2O_5 in a vacuum desiccator. The crude product was recrystallized twice from ethyl acetate to yield 9.8 g (73%) of the chlorine-free NCA,[17] mp 100° (lit.[18] 100°).

General Procedure for Synthesis of Glycyl Dipeptides.—To a solution of 0.01 mol of α-amino acid and 1 g of sodium carbonate in 10 ml of 1 *N* sodium hydroxide and 40 ml of water was added 40 ml of acetonitrile and the system was cooled to −10°. A solution of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile was added to the system and allowed to react for 3 hr at −10° with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile under cooling and neutralized with concentrated sulfuric acid. Sodium sulfate was removed by addition of 200 ml of ethanol followed by filtration and the alcoholic solution was concentrated *in vacuo* at 35°. Addition of 50 ml of ethanol and 100 ml of diethyl ether to the residue gave a crystalline product. The crude product was recrystallized from aqueous methanol to yield a crystalline dipeptide.

Glycyl-L-leucyl-L-alanine.—To a heterogeneous system of 50 ml of acetonitrile and 50 ml of 0.2 *N* sodium hydroxide containing 0.89 g (0.01 mol) of L-alanine and 1 g of sodium carbonate was added a solution of 1.73 g (0.011 mol) of L-leucine NCA in 17.3 ml of acetonitrile. The condensation reaction was allowed for 2 hr at −10° with stirring. After the reaction the acetonitrile layer of the system was separated off and the aqueous layer was washed with 100 ml of acetonitrile under cooling. The solution was warmed to 40° for 5 min. Then 50 ml of acetonitrile and 20 ml of 0.2 *N* sodium hydroxide were added to the solution and the system was cooled again to −10°. After the addition of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile, the system was kept at −10° for 3 hr with stirring. The aqueous layer of the system was treated by the same manner as above, washing, neutralization, and condensation. The crude product was recrystallized from aqueous ethanol.

Reaction of Glycine NCA with L-Tryptophan.—To a solution of 2.05 g (0.01 mol) of L-tryptophan and 1 g of sodium carbonate in 10 ml of 1 *N* sodium hydroxide and 40 ml of water, 40 ml of acetonitrile was added and the system was cooled to −10°. After the addition of 1.2 g of glycine NCA in 24 ml of acetonitrile the system was allowed to stand for 3 hr with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile and diluted with water to a volume of 50 ml. A 40-μl sample of the solution was analyzed by tlc on silica gel in pyridine–water (4:1). A strip showed three ninhydrin-positive spots, unreacted L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Three Ehrlich-positive spots were detected on another strip, L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Then the pertinent areas of the tlc developed anew were scraped off and extracted with 100 ml of water. The transmittancy of the extracts was measured at 280 mμ.[19] The residual sample was treated as above to isolate the dipeptide. The crude product was recrystallized from methanol to yield 2.33 g (89%) of a pure dipeptide: $[\alpha]_D$ 33.5° (*c* 2.5, 5 *N* HCl) [lit.[20] $[\alpha]_D$ 34.3° (*c* 2, 5 *N* HCl)]. *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.75; H, 5.80; N, 16.08. Found: C, 59.94; H, 6.06; N, 16.15.

Registry No.—Glycine NCA, 2185-00-4; Gly-Gly, 556-50-3; Gly-L-Ala, 3695-73-6; Gly-L-Val, 1963-21-9; Gly-L-Leu, 869-19-2; Gly-L-Phe, 3321-03-7; Gly-L-Leu-L-Ala, 32557-24-7; Gly-L-tryptophan, 2390-74-1.

(16) Y. Iwakura K. Uno, and S. Kang, *J. Org. Chem.*, **30**, 1158 (1965). We synthesized glycine NCA by the reaction of glycine with phosgene in tetrahydrofuran. The reaction time needed in phosgenation of the amino acid was shorter in this solvent than in any other solvents. High yield and high purity of the product were obtained in this solvent.

(17) M. Oya, K. Uno, and Y. Iwakura, *Kogyo Kagaku Zasshi*, **69**, 741 (1966).

(18) H. Leuchs, *Ber.*, **39**, 857 (1906).

(19) Uv spectra of peptides were measured with Shimazu MPS-50 L and Hitachi Perkin-Elmer 139 spectrophotometers.

(20) K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952).

A Convenient Synthesis of 5-Fluorouracil

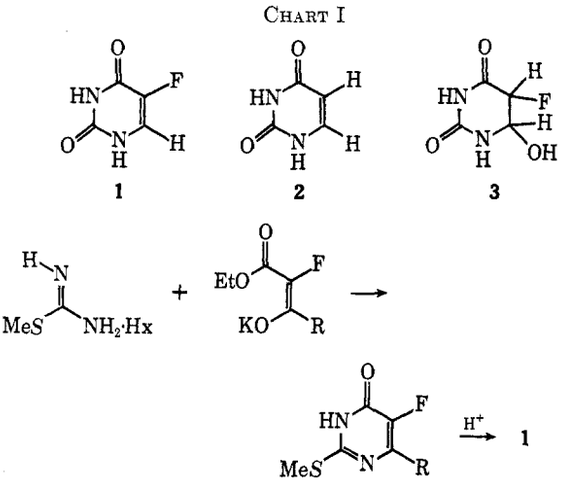
D. H. R. BARTON, R. H. HESSE,* H. T. TOH, AND M. M. PECHET

Communication No. 54[1] from the Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02142

Received August 13, 1971

5-Fluorouracil (**1**) is a cytotoxic analog of uracil of use in biochemical research and also of a certain value in medicine.[2] This derivative of uracil is typically prepared by a total synthesis as expressed in Chart I[3]

CHART I



which requires the use of a persistent and insidious toxin, fluoroacetic acid. The discovery that fluoroxytrifluoromethane (CF_3OF) is a useful reagent for the heretofore difficult direct electrophilic fluorination of aromatic compounds[4] led us to consider that the reaction of CF_3OF with uracil (**2**) (or an appropriate derivative thereof) might lead directly to 5-fluorouracil (or a derivative thereof) and thus constitute a convenient synthesis of such compounds. We now report that the direct conversion of uracil to 5-fluorouracil may be accomplished in high yield by electrophilic fluorination.

Electrophilic substitution at the 5 position of the pyrimidine ring is well known.[5] Uracil itself undergoes nitration at position 5 without complication,[6] and

(1) For no. 53, see D. H. R. Barton, T. J. Bentley, R. H. Hesse, F. Mutterer, and M. M. Pechet, *Chem. Commun.*, 912 (1971).

(2) G. Ramirez, *et al.*, *Amer. J. Surg.*, **120**, 400 (1970); J. Dule, *Bull. Soc. Fr. Dermatol. Syphiligr.*, **77**, 218 (1970); L. Y. Deemarsky, *et al.*, *Cancer*, **26**, 771 (1970); M. S. Mitchell, *et al.*, *ibid.*, **26**, 884 (1970); M. Hursthouse, *Brit. J. Dermatol.*, **82**, 218 (1970).

(3) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957).

(4) D. H. R. Barton, *et al.*, *Chem. Commun.*, 806 (1968).

(5) C. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 235 ff.

(6) T. B. Johnson, *J. Amer. Chem. Soc.*, **30**, 19 (1908); *Chem. Abstr.*, **2**, 2792 (1909).

reacts with halogens to afford at least initially 5-substituted products.[7] Although the latter reactions are often further complicated by addition of halogen to the initial substitution product,[7a] successful monohalogenation can be achieved.[7b] We find that uracil dissolved in water, trifluoroacetic acid, or preferably a mixture thereof, reacts slowly but cleanly with CF_3OF to afford a mixture of 5-fluorouracil and a second substance in variable proportions. The companion product, which is quite unstable, may be smoothly converted to 5-fluorouracil by heating. Indeed, heating *in vacuo* of the total crude reaction product leads to isolation by sublimation of 5-fluorouracil in approximately 85% yield.

The precursor of I shows no high-intensity absorbtion in the uv, no $-OCF_3$ or CF_3CO-absorption in the infrared or ^{19}F nmr spectra, and exhibits a complex series of resonances at δ 5–6 ppm in the ^1H nmr spectrum. These characteristics, together with the thermal conversion to 5-fluorouracil, suggest that this material is an addition product of uracil. The ^{19}F nmr spectrum, which consists of a doublet (J = 45 Hz) at ϕ^* 207.6, and the composition, $C_4H_5N_2O_3F$, lead to expression **3** for this product.[8] The formation of adduct **3** at the expense of 5-fluorouracil is promoted as expected by the presence of water in the reaction medium. This is fortunate, as, while **1** undergoes some reaction with CF_3OF to afford overfluorinated by-products, adduct **3** is essentially inert to CF_3OF and an aqueous medium thus ensures a very clean reaction product.

While we have found uracil inert to exposure to perchloryl fluoride ($FClO_3$) under conditions considerably more forceful than required to ensure reaction with CF_3OF, this substrate does react avidly with elemental fluorine. Although little 5-fluorouracil is formed in the reaction of uracil with F_2, heating the reaction mixture *in vacuo* leads to the sublimation and isolation of 5-fluorouracil in approximately 60% yield. The spectral and chromatographic properties of the progenitor of 5-fluorouracil formed in this reaction suggest that it is analogous with or identical with **3**. Therefore, while it is possible that the direct fluorination of uracil with elemental fluorine may afford yields of 5-fluorouracil comparable to those achieved by fluorination with CF_3OF, the reaction with the latter reagent is more easily controlled and the reagent itself is more amenable to utilization with usual laboratory techniques.

It is appropriate to point out that, as methods are extant for the conversion of 5-fluorouracil to other 5-fluoropyrimidine derivatives,[9] the method described in this paper provides a synthesis of such derivatives, particularly the important 5-fluorocytosine.

Experimental Section

All melting points were taken on the Kofler hot stage and are reported uncorrected. ^1H nmr spectra were obtained at 60 MHz using a Varian T-60 spectrometer and are reported as shifts downfield from internal tetramethylsilane (δ). ^{19}F nmr spectra were obtained at 56.4 MHz on the above instrument and are reported as shifts from internal $CFCl_3$ (ϕ^*). Ir spectra were obtained with a Perkin-Elmer Model 137 spectrometer. Solutions of CF_3OF were prepared by passing the gaseous reagent into $CFCl_3$ at $-78°$; aliquots were treated with an excess of aqueous KI and the concentration of CF_3OF was estimated by titration of the I_2 liberated ($CF_3OF + 2KI + H_2O \rightarrow I_2 + 2KF + 2HF + CO_2$).

CF_3OF is a powerful oxidant and while we have experienced no difficulty with its use certain precautions are indicated: all reactions should be conducted with adequate shielding, accumulation of the reagent in the presence of oxidizable substances should be avoided, material for handling of the reagent should consist of glass, Teflon, Kel-F, or passivated metals. *On no account should PVC, rubber, polyethylene or similar substances be used.*

Fluorination of Uracil with CF_3OF.—Uracil (0.336 g, 3 mmol) in a mixture of trifluoroacetic acid (6 cc) and water (20 cc) was added to a solution of CF_3OF (4.5 mmol) in $CFCl_3$ (50 cc) at $-78°$ in a pressure bottle. The precipitated uracil redissolved in the aqueous layer when the mixture was warmed up to room temperature. The mixture was vigorously stirred for 15 hr. The excess CF_3OF was removed with nitrogen and solvent was removed under reduced pressure. The solid residue was sublimed at 210–230° under reduced pressure (0.5 mm) to give crude 5-fluorouracil (0.365 g, 94%), mp 260–270°. Recrystallization from methanol–ether gave pure 5-fluorouracil (0.33 g, 85%), mp 282–283°, mmp (with authentic 5-fluorouracil) 282–283°. ^1H nmr, ^{19}F nmr, ir, and uv spectra were identical with those of authentic 5-fluorouracil.

In a companion fluorination as above, the crude products were not subjected to heat, but instead separated by preparative tlc (silica gel GF 254; methanol–chloroform 20:80) into a fraction having R_f 0.5 (5-fluorouracil) and a fraction having R_f 0.3 (adduct **3** which on heating was quantitatively converted to 5-fluorouracil): ν (KBr) 3300 (s), 1720 (s), 1475 (m), 1250 (m), 1140 (m), 1080 (m), 880 (m), 800 cm^{-1} (m). The proton nmr showed a complex pattern of resonances at δ 5–6 ppm (AB pattern of an ABX system). The ^{19}F nmr had ϕ^* = 207.6 ppm (broad doublet, J = 45 Hz). The mass spectrum had a molecular ion at m/e 148$^+$; accurate mass, m/e 148.0291 (calcd for $C_4H_5FN_2O_3$, m/e 148.0284). *Anal.* Calcd for $C_4H_5FN_2O_3$: C, 32.45; H, 3.40; N, 18.92; F, 12.83. Found: C, 32.26; H, 3.5; N, 18.90; F, 13.84.

Fluorination of Uracil with Fluorine.—Fluorine gas diluted liberally with nitrogen was passed at room temperature into a vigorously stirred solution of uracil (150 mg, 1.34 mmol) in water (50 cc). After the disappearance of starting material (nmr control; *ca.* 2.5 mmol F_2) the solvent was removed under reduced pressure and the residue was sublimed to give 5-fluorouracil (95 mg, 0.74 mmol, 55% yield) identified by comparison with authentic 5-fluorouracil.

Registry No.—**1**, 51-21-8; CF_3OF, 373-91-1.

(7) (a) T. B. Johnson, *J. Amer. Chem. Soc.*, **65**, 1218 (1943). (b) T. Nishiwaki, *Tetrahedron*, **22**, 2401 (1966).

(8) Microanalysis suggest that 3 may be accompanied by 5–10% of the analogous 5,6-difluoro-5,6-dihydrouracil adduct.

(9) K. Undheim and M. Gacek, *Acta Chem. Scand.*, **23**, 294 (1969).

Conversion of Aporphines into *N*-Noraporphine Alkaloids

M. P. CAVA* AND M. SRINIVASAN

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received July 26, 1971

The *N*-noraporphines constitute an important subgroup of alkaloids corresponding to the more widely found N-methylated bases, the aporphines.[1] The aporphines may be obtained not only by total synthesis but, when practical, also by the N-methylation of *N*-noraporphines. On the other hand, *N*-noraporphines have been available only by isolation and by total synthesis *via* their *N*-benzyl derivatives. We now report the first procedure for the conversion of aporphines into the corresponding *N*-noraporphine bases.

(1) For recent reviews of the aporphine alkaloids, see (a) M. Shamma in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) M. P. Cava and A. Venkateswarlu, *Annu. Rep. Med. Chem.*, 331 (1968). Earlier reviews are cited in these references.