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

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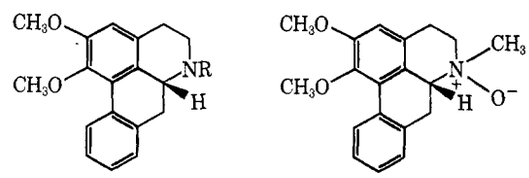
Received July 26, 1971

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.

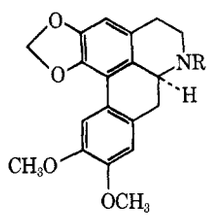
(1) For recent reviews of the aporphine alkaloids, see (a) M. Shamma in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) M. P. Cava and A. Venkateswarlu, *Annu. Rep. Med. Chem.*, 331 (1968). Earlier reviews are cited in these references.

A recent study of the mechanism of the reductive demethylation of trimethylamine *N*-oxide by sulfur dioxide[2] led us to investigate the applicability of this reaction to the aporphine series. Thus, (−)-nuciferine (**1**) was treated with hydrogen peroxide in aqueous methanol at room temperature to give the corresponding *N*-oxide **2**. Reductive demethylation of **2** to (−)-nornuciferine (**3**) was achieved in fair yield (34%) by

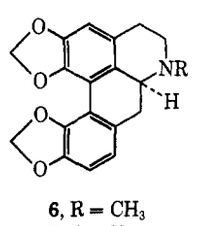


1, R = CH_3
3, R = H

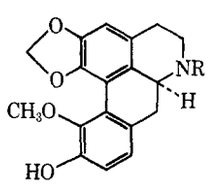
2



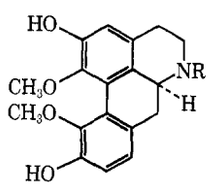
4, R = H
5, R = CH_3



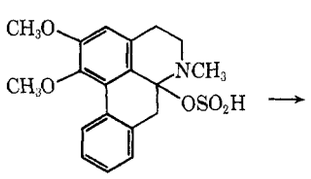
6, R = CH_3
7, R = H



8, R = CH_3
10, R = H



9, R = CH_3
11, R = H



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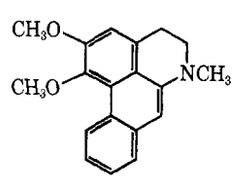

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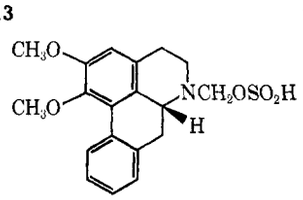

14

reaction with liquid sulfur dioxide, followed by hydrolysis with hydrochloric acid; under these conditions very little nuciferine was regenerated and the product was readily purified. Under similar conditions, the rare alkaloid (+)-nordicentrine (**4**) was obtained in 32% yield from the relatively common aporphine, (+)-dicentrine (**5**). Also, (+)-*N*-methylovigerine (**6**) was demethylated in 28% yield to (+)-ovigerine (**7**). Since racemic **6** has been synthesized,[3] this conversion completes the formal total synthesis of natural ovigerine except for the resolution of racemic **6**.

(2) J. C. Craig and K. K. Purushothaman, *Tetrahedron Lett.*, 5305 (1969). Earlier work is cited in this reference.

(3) M. P. Cava and M. Srinivasan, *Tetrahedron*, **26**, 4649 (1970).

The reaction conditions employed proved to be sufficiently mild to allow the N-demethylation of two representative phenolic aporphines to be carried out, although yields were not so good as with the nonphenolic examples. Thus, (+)-*N*-methylnandigerine (**8**) and (+)-*N*-methylhernovine (**9**) afforded (+)-nandigerine (**10**) and (+)-hernovine (**11**) in 22 and 18% yields, respectively.

Since the objective of this study was a simple preparative conversion of aporphines into *N*-noraporphines, we were interested in avoiding procedures which afforded mixtures of water-insoluble reaction products. It was found, indeed, that such mixtures were produced from (−)-nuciferine *N*-oxide (**2**) under a variety of conditions. For example, reaction of **2** with sulfur dioxide in methanol–benzene, followed by hydrolysis with dilute acid, gave a 5:2 mixture of (−)-nuciferine and (−)-nornuciferine. A similar reaction, followed by dilute base hydrolysis, gave a mixture of (−)-nuciferine, (−)-nornuciferine, and dehydronuciferine (**12**) in a ratio of about 8:2:5. The formation of dehydronuciferine in the alkaline hydrolysis reaction is rather interesting, since it probably arises by way of a base-catalyzed elimination of an intermediate of structure **13**; the isomeric structure **14** is the expected intermediate which gives rise to (−)-*N*-nornuciferine, on the basis of what is known concerning the mechanism of the corresponding demethylation of trimethylamine *N*-oxide.[2]

Experimental Section[4]

(−)-Nornuciferine (3) from (−)-Nuciferine (1).—A solution of (−)-nuciferine (**1**, 0.100 g) in methanol (10 ml) and 30% hydrogen peroxide (2 ml) was stirred at room temperature overnight, after which time tlc showed the complete disappearance of **1**. A suspension of 5% Pd on charcoal (0.020 g) was added and the mixture was stirred for 2 hr in order to decompose excess hydrogen peroxide. The filtered solution was saturated with sodium chloride and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract gave an oil, which was further dried by repeated addition of 2:5 methanol–benzene and evaporation *in vacuo* to give a foam of *N*-oxide **2** (0.100 g). To this foam was added liquid sulfur dioxide (10 ml), followed by *N*,*N*-dimethylacetamide (1 ml). After 48 hr at about −70°, excess liquid SO_2 was removed, concentrated hydrochloric acid (1 ml) was added, and the mixture was heated (steam bath) until SO_2 was no longer evolved. Basification with aqueous ammonia, followed by chloroform extraction, yielded a crude product (0.043 g) which was purified by chromatography on silica. Elution with chloroform gave a few milligrams of recovered **1**, after which chloroform–methanol (99:1) eluted the major product, which was converted to the hydrochloride. After several crystallizations from methanol–ethyl acetate there was obtained 0.039 g (34%) of pure (−)-nornuciferine hydrochloride, mp 268–270° dec (lit.[5] mp 264–266°), $[\alpha]^{25}D$ (EtOH) −122°.

(+)-Nordicentrine (4) from (+)-Dicentrine (5).—The N-oxidation and subsequent demethylation of **5** were carried out as in the nuciferine case to give **4** in 32% yield. The product was crystallized from methanol as its hydrobromide, mp 262–265° dec (lit.[6] mp 278° dec), $[\alpha]^{25}D$ (EtOH) +34°.

(+)-Ovigerine (7) from (+)-*N*-Methylovigerine (6).—The usual conditions afforded **7** (28% from **6**), isolated as the crys-

(4) Melting points are uncorrected and were determined using a Thomas–Hoover apparatus. Infrared spectra were determined in KBr using a Perkin-Elmer Model 137 instrument. Tlc analyses were carried out using 9:1 chloroform–methanol with silica plates. The identity of all products was confirmed by ir and tlc comparison with authentic alkaloids from natural sources.

(5) S. M. Kupchan, B. Dasgupta, E. Fujita, and M. L. King, *Tetrahedron*, **19**, 227 (1963).

(6) A. Venkateswarlu, Ph.D. Dissertation, Wayne State University, 1969.

talline hydrochloride, mp 298–300° dec (lit.[7] mp 300° dec), $[\alpha]^{25}D$ (EtOH) +207°.

(+)-**Nandigerine (10) from (+)-*N*-Methylnandigerine (8).**—The usual conditions afforded **10** (22% from **8**), isolated as the crystalline hydrochloride, mp 242–245° dec (lit.[7] mp 245–247° dec), $[\alpha]^{25}D$ (EtOH) +240°.

(+)-**Hernovine (11) from (+)-*N*-Methylhernovine (9).**—The usual conditions afforded **11** (18% from **9**) as crystals, mp 235–237° dec (lit.[7] mp 236–240° dec), $[\alpha]^{25}D$ (EtOH) +253°.

Reaction of *N*-Oxide 2 with Sulfur Dioxide in Methanol–Benzene.—Dried *N*-oxide **2** (50 mg) was dissolved in 1:1 methanol–benzene (20 ml) and SO_2 was passed into the mixture for 0.5 hr. Aqueous hydrochloric acid (2 *N*, 10 ml) was added and the solution was refluxed for 3 hr. Basification with ammonia, followed by chloroform extraction, gave a crude product (40 mg), shown by tlc to contain only nuciferine (**1**) and nornuciferine (**3**). Chromatography on neutral alumina gave **1** (25 mg) and **3** (10 mg).

The above experiment was repeated, with the modification that the *N*-oxide SO_2 complex was refluxed not with acid, but with 5% aqueous sodium hydroxide. Preparative tlc (2% MeOH in $CHCl_3$, Al_2O_3) gave **1** (38 mg), **3** (18 mg), and dehydronuciferine (**12**, 25 mg).

Registry No.—**3**, 32557-14-5; **4**, 25394-59-6; **7**, 6410-87-3; **10**, 5544-70-7; **11**, 5544-69-4.

Acknowledgment.—We thank the National Institutes of Health for a grant (CA 11445) in support of this work.

(7) M. P. Cava, K. Bessho, B. Douglas, S. Markey, R. F. Raffauf, and J. A. Weisbach, *Tetrahedron Lett.*, 1577 (1966).

Inductive Effects on Molecular Ionization Potentials. IV. Hydrogen Sulfide and Mercaptans

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Received June 17, 1971

The ionization potentials of alkyl free radicals, R·, have been correlated[1] with the polar substituent constants, σ^*, and we have shown recently that the ionization energies of alcohols,[2] ethers,[3] and amines[4] are linear functions of both σ^* and the inductive substituent constants, σ_I.

We now demonstrate that the ionization energies of thiols, RSH, are also linear functions[5] of both σ^* and σ_I. The gas-phase expulsion of an electron from the nonbonding lone pair on the sulfur atom of a mercaptan molecule is in accord with the equation

$$R{-}\ddot{S}{-}H \xrightarrow{E_I} R{-}\overset{+}{\ddot{S}}{-}H + e^-$$

and the ionization potential, E_I, of course, corresponds approximately to the energy of the highest occupied molecular orbital.[6–8] The entire chemistry of thiols, in fact, is dependent upon the behavior of the 3p sulfur lone pair electrons. Electron-releasing alkyl groups bonded to the S atom of a thiol molecule should obviously facilitate the electron removal, and thereby lower the E_I; and the presence of electron-withdrawing groups should likewise cause an increase in the requisite ionization energy.[9] It is interesting that we are able to include hydrogen sulfide as the simplest thiol in the series.

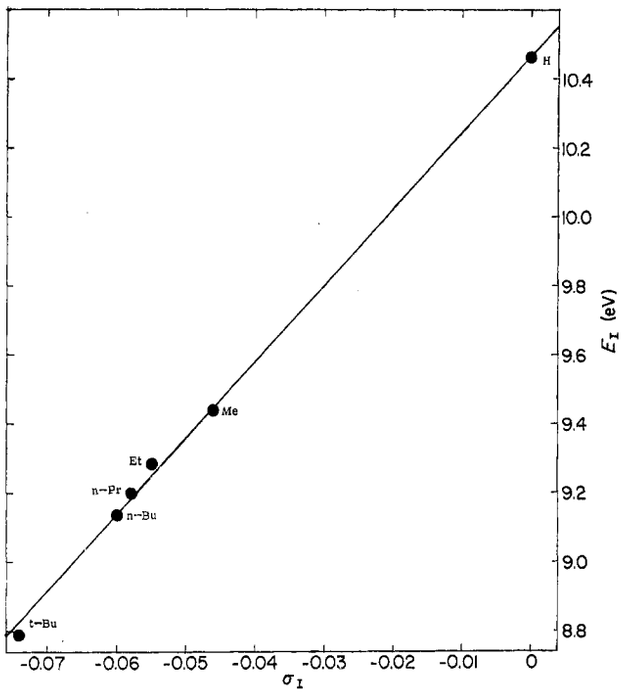

Figure 1.—A plot of ionization potentials, E_I, of the thiols *vs.* the inductive substituent constants, σ_I, of the corresponding R groups.

Table I presents the σ^* and the σ_I[10] values together with the photoionization potentials[11] (eV) for various aliphatic mercaptans and hydrogen sulfide.

TABLE I

Thiol	σ^*	σ_I	E_I, eV (exptl)[a]	E_I, eV (eq 1a)	E_I, eV (eq 2)
H_2S	+0.49	0	10.46	10.46	10.46
MeSH	0	−0.046	9.44	9.45	9.44
EtSH	−0.10	−0.055	9.29	9.25	9.24
n-PrSH	−0.12	−0.058	9.20	9.18	9.17
n-BuSH	−0.13	−0.060[b]	9.14	9.14	9.13
i-PrSH	−0.19	−0.064	[c]	9.05	9.04
tert-BuSH	−0.30	−0.074	8.79	8.77	8.81

[a] Reference 11. [b] Value suggested in ref 3. [c] Experimental value not available.

An excellent correlation is shown in Figure 1 where the E_I values are plotted *vs.* σ_I. The equation for the correlation line is given by

$$E_{RSH} = E_{H_2S} + a_I\sigma_I \quad (1)$$

The slope, a_I, is found to be 22.2 and therefore we have

$$E_{RSH} = 10.46 + 22.2\sigma_I \quad (1a)$$

(1) A. Streitwieser, Jr., *Progr. Phys. Org. Chem.*, **1**, 1 (1963).
(2) L. S. Levitt and B. W. Levitt, *Chem. Ind. (London)*, 990 (1970).
(3) B. W. Levitt and L. S. Levitt, *Experientia*, **26**, 1183 (1970).
(4) B. W. Levitt and L. S. Levitt, *Israel J. Chem.*, **9**, 71 (1971).
(5) The ionization potentials of X–SH have been correlated with the three-parameter extended Hammett equation: $E_I = 3.22\sigma_I + 9.06\sigma_R + 10.37$ [M. Charton and B. I. Charton, *J. Org. Chem.*, **34**, 1882 (1969)].
(6) R. S. Mulliken, *J. Chem. Phys.*, **3**, 564 (1935).
(7) T. Koopmans, *Physica*, **1**, 104 (1933).
(8) J. C. Lorquet, *Rev. Mod. Phys.*, **32**, 312 (1960).
(9) The same effect manifests itself in a greater basicity, the greater is the electron density at the S atom of the mercaptan molecule, similar to that recently demonstrated for alcohols: L. S. Levitt and B. W. Levitt, *J. Phys. Chem.*, **74**, 1812 (1970); also *Tetrahedron*, **27**, 3777 (1971).
(10) R. W. Taft, Jr., and I. C. Lewis, *ibid.*, **5**, 210 (1959).
(11) K. Watanabe, T. Nakayama, and J. Mottl, *J. Quant. Spectrosc. Radiat. Transfer*, **2**, 369 (1962).