carbamoyl)-cAMP (2), N^6,2′-O-bis(N-methylcarbamoyl)-8-bromo-cAMP (9), N^6,2′-O-bis(N-phenylcarbamoyl)-cAMP (4), and N^6-ethoxycarbonyl-cAMP (8) had I_{50} values within the same range as those of theophylline and showed little difference in inhibitory activity between the lung and heart enzymes. N^6,2′-O-Bis(N-methylcarbamoyl)-8-thio-cAMP (14), N^6-(N-n-propylcarbamoyl)-cAMP (5), and N^6,2′-O-bis(N-n-propylcarbamoyl)-cAMP sodium salt (3) were significantly more active against the lung enzyme, while N^6-(N-phenylcarbamoyl)-cAMP (7) was appreciably more active against the heart enzyme. 8-Benzylthio-N^6,2′-O-bis(N-phenylcarbamoyl)-cAMP (10) and 8-benzylthio-N^6-(N-phenylcarbamoyl)-cAMP (13) were the most active of all the compounds tested in this group, being 5 to 20 times more potent than theophylline. The low K_m cAMP phosphodiesterase was most strongly inhibited by those cAMP derivatives which contained a phenyl substitution. This structural specificity was similar to that observed for activation of the protein kinase.

The effects of the present series of compounds on tumor cell growth in tissue culture have been examined. No unusual cytotoxicity was seen, with the single possible exception of N^6,2′-O-bis(N-phenylcarbamoyl)-cAMP (4), which was cytotoxic to KB cells between 1 and 3.2 μg/ml. All of the other derivatives were nontoxic to the cells at doses nearly ten times greater (10–32 μg/ml).

Future studies are aimed at determining the pharmacological properties and biological effects in whole cell systems of these interesting derivatives.

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Hydrolysis of Hydroxybenzotrifluorides and Fluorinated Uracil Derivatives. A General Mechanism for Carbon–Fluorine Bond Labilization

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The kinetics of hydrolysis of o- and p-hydroxybenzotrifluoride (1 and 2) and 1-trifluoromethyl-2-(4-hydroxyphenyl)-ethylene (3) and the uracil derivatives 5-difluoromethyluracil (5) and 1-methyl-5-difluoromethyluracil (6) are described. Compounds 1 and 2 hydrolyze to the corresponding hydroxybenzoic acids and 3 gives p-coumaric acid upon hydrolysis. Reduction of the ethylenic double bond of 3 gives the hydrolytically stable 1-trifluoromethyl-2-(4-hydroxyphenyl)ethane (4). Compounds 5 and 6 hydrolyze to the corresponding 5-formyluracil derivatives. The data obtained from these reactions implicate the anchimeric assistance of the phenolate or uracil anion in the hydrolysis mechanisms. A general mechanism for carbon–fluorine bond labilization is presented which is predictively useful for the study of enzyme mechanisms and perhaps in the design of effective chemotherapeutic drugs.

Our previous studies on the mechanisms of hydrolysis of various 5-trifluoromethyluracil derivatives[1] led us to begin studies on 5-difluoromethyluracils to determine if there was any relation between the chemistry of these two groups of compounds. The data from these studies suggested we consider the generality and utility of such reactions; that is, are such carbon–fluorine bond labilization reactions general enough that they may be utilized in the design of potential medicinal agents and/or can they be used in the determination of enzyme mechanisms?

Organic fluorine compounds have been utilized to a great extent in the study of biological systems. The replacement of hydrogen by fluorine in biologically active materials confers upon these molecules properties which may be used to gain insight into the means by which normal substrates react. Frequently, such altered compounds are enzyme inhibitors and use has been made of their pharmacological activities. The more notable of these are 5-fluorouracil and 5-trifluoromethyluracil and their derivatives,[1,2] which have been used in cancer chemotherapy, and fluorinated analogs of compounds involved in the tricarboxylic acid cycle[3] used to study that system.

In most cases studied, the carbon–fluorine bond appears unreactive to displacement or elimination reactions; however, there are systems in which it is substantially more labile than would be expected from the nature of "normal" carbon–fluorine bonds. The general properties of organofluorine compounds and carbon–fluorine bonds are well documented[4] and will be described only briefly. The

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Table I. Examples of Labile Carbon–Fluorine Bonds

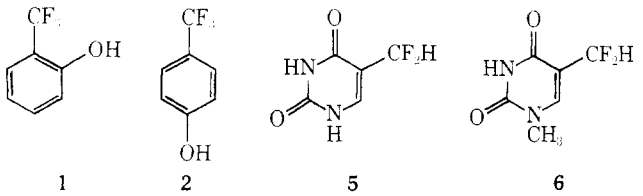
Reactant	Conditions	Product	Ref
α-CF_3-propionic acid	Aqueous base	Methylmalonic acid	14
α-CF_3-α-OH-propionic acid	Aqueous base	No reaction	14
1,1,1-F_3-2,2-di(4-X-phenyl)-ethane (X = F, Cl)	EtOH–KOH	Et-di(4-X-phenyl)acetate	*a*
4(6)-CF_3-indole-2-CO_2Et	Aqueous base	Indole-2,4(6)-di(CO_2H)	*b*
3-CF_3-tyrosine	Aqueous base	3-CO_2H-tyrosine	15
2-CF_3-tyrosine	Aqueous base	No reaction	15
2-CF_3-benzimidazole	*o*-Phenylene-diamine	2,2′-Bis(benzimidazole)	16
N,N′-Diphenyldifluoro-methylenediamine	Aqueous base	*N,N*′-Diphenylurea	*c*
Ethyl *N*-perfluoropropyl-carbamate	Aqueous base	Ethyl *N*-perfluoropropionyl-carbamate	*d*
2-F-7-MeO-9-CF_3-fluorene	MeOH–KOH	2-F-4-MeO-fluorene-9-CO_2Me	*e*
o(*p*)-CF_3-phenol	Aqueous base	*o*(*p*)-CO_2H-phenol	8
m-CF_3-phenol	Aqueous base	No reaction	8
α-Fluorooxaloacetate	Asp-Glu transaminase	Oxaloacetate	18
Fluorofumarate	Fumarate hydratase	Oxaloacetate	19
5-CF_3-deoxyuridylate	Thymidylate synthetase	Deoxyuridylate-5-CONH-enzyme	20
5-CF_3-uracils	Aqueous base	5-CO_2H-uracils	1

[a] R. Mechoulan, S. Cohen, and A. Kaluszynen, *J. Org. Chem.*, **21**, 801 (1956). [b] J. Bornstein, S. Leone, W. Sullivan, and O. Bennett, *J. Amer. Chem. Soc.*, **79**, 1745 (1957). [c] K. Petrow and A. Neimyschewa, *Zh. Obshch. Khim.*, **29**, 2169 (1959); *Chem. Abstr.*, **54**, 10912 (1960). [d] R. Dannley and R. Taborsky, *J. Org. Chem.*, **22**, 77 (1957). [e] S. Cohen, *J. Amer. Chem. Soc.*, **79**, 1499 (1957).

C–F bond is one of the stronger covalent bonds known, due in large part to the high charge density associated with the fluorine atom. The high electronegativity of fluorine makes it unlikely that positive fluorine will be eliminated in compounds in which fluorine has replaced hydrogen. The size of the fluorine atom is very close to that of the hydrogen atom (1.35 *vs.* 1.1 Å), minimizing consideration of structural size in the design of fluorinated compounds.

The utility of studying biologically active fluorine compounds in understanding mechanisms of biological reactions has been reviewed;[5] however, the reactions discussed here provide a potentially more useful tool in the elucidation of such mechanisms.

The reactivity of trifluoromethyl groups in most cases has been attributed to hyperconjugative effects,[6,7] to hydrogen bonding effects,[7,8] and to direct displacement (S_N2) reactions.[9] In Table I are shown some of the reactions which involve unusually reactive C–F bonds and which will provide some of the arguments for the mechanisms to be proposed. In this paper are described the hydrolyses of *o*- and *p*-hydroxybenzotrifluoride (**1** and **2**), 1-trifluoromethyl-2-(4-hydroxyphenyl)ethylene (**3**), 5-difluoromethyluracil (**5**), and 1-methyl-5-difluoromethyluracil (**6**), as well as a mechanism which accounts for the reactivity of such carbon–fluorine bonds.



1 **2** **5** **6**

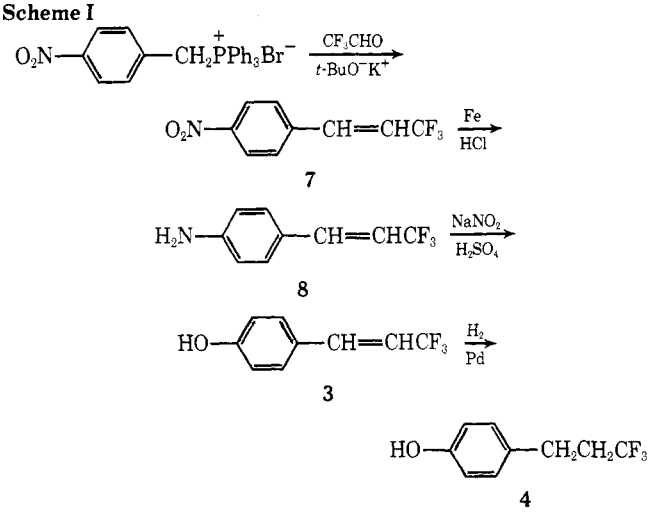
Synthesis of Required Fluorinated Compounds. The study of potentially labile fluorinated compounds required the synthesis of some new derivatives and the methods used necessitated consideration of the possible reactivity of these compounds. 5-Difluoromethyluracil was prepared as described by Mertes, *et al.*,[10] and 1-methyl-5-difluoromethyluracil could be prepared similarly using sulfur tetrafluoride. 5-Fluoromethyluracil and 1-methyl-5-fluoromethyluracil could not be prepared by halogen exchange from the corresponding chloromethyluracils[11] using silver fluoride or potassium fluoride in acetonitrile or dimethylformamide or by treatment of the hydroxymethyluracils with sulfur tetrafluoride. Treatment of the hydroxymethyluracils with concentrated hydrofluoric acid as described for the preparation of chloromethyluracils[11] using HCl proved unsuccessful. In all cases, material was obtained which appeared to be polymeric.

The phenols **1** and **2** could be obtained commercially; however, the synthesis of **3** required that the method be compatible with the starting materials employed. The reaction of *p*-hydroxycinnamic acid with sulfur tetrafluoride appeared to be the simplest method; however, the presence of HF in the reaction suggested the possibility of polymerization of the starting compound. Since acyl fluorides are known to be intermediates in the fluorination of carboxylic acids,[12] the possibility also existed that the unprotected phenol would react to cause polymerization.

The alternatives included (a) blocking the phenol, carrying out the fluorination, and then deblocking; (b) condensation to introduce the trifluoromethyl group to a phenol or blocked phenolic system; and (c) condensation to introduce the trifluoromethyl group to a phenyl system which could be transformed to the desired phenol. Consideration of the steps involved, the availability of starting materials, the possibility of side reactions, and the ease of synthesis suggested the use of the third method. The scheme finally used (Scheme I) involved the Wittig condensation between *p*-nitrobenzyltriphenylphosphonium bromide[13] and trifluoroacetaldehyde in dimethylformamide with potassium *tert*-butoxide as base to give 1-trifluoromethyl-2-(4-nitrophenyl)ethylene (**7**). The nitro compound was reduced with powdered iron and HCl and diazotized with sodium nitrite in aqueous sulfuric acid, and the diazonium salt decomposed in hot aqueous sulfuric acid to the desired phenol. Catalytic reduction of the nitro group could not be accomplished without accompanying reduction of the ethylene group.

Hydrolytic products were identified by isolation from reaction mixtures and comparison of physical and spectral data with literature values (see Experimental Section).

Scheme I



Results

The pH–log k_{obsd} profiles for the hydrolyses of **1**, **2**, and **3** are given in Figure 1 and show dependence on ionizable groups with pK values between 8.5 and 8.6. The titrimetrically determined pK values are 8.45, 8.50, and 8.70 for **1**, **2**, and **3**, respectively. The data for all three may be fit by an equation of the form $k_{obsd} = k_r K_a/(K_a + a_H)$, where K_a is the dissociation constant of the phenol, a_H the hydrogen ion activity as measured by the glass electrode, and k_r the first-order rate constant for the hydrolysis. The values of k_r are 4.5×10^{-3}, 3.96×10^{-2}, and 1.27×10^{-2} min^{-1} for **1**, **2**, and **3**, respectively. Compound **4**, prepared by catalytic hydrogenation of **3**, is stable in 1 N NaOH at room temperature for at least 24 hr as is the nitro compound **7**.

The hydrolysis of 1-methyl-5-difluoromethyluracil to 1-methyl-5-formyluracil shows a pH–log k profile similar to the ones for the phenols (Figure 2). However, results obtained with the trifluoro analog of this compound[1] indicate that the data are probably best fit by an equation of the form $k_{obsd} = k_{OH}K_w/(K_a + a_H) + k_{OH'}[OH^-]K_a/(K_a + a_H)$, where k_{OH} and $k_{OH'}$ are the second-order rate constants for the reaction of hydroxide ion with the neutral and ionized pyrimidines, respectively, K_w is the autoprotolysis constant of water, and K_a is the dissociation constant of the N-3 proton. Unlike the case with 1-methyl-5-trifluoromethyluracil, $k_{OH'}$ appears to be too small to measure so that the second term of the equation may be ignored and the value obtained for k_{OH} is 7.3×10^3 M^{-1} min^{-1} with $K_a = 1.75 \times 10^{-9}$ (pK_a = 8.76). The hydrolysis of this compound was run in D_2O to check the possibility of the hydrolyses of these fluorine compounds occurring *via* a carbene pathway, with the expectation that if such a mechanism were operative, deuterium would be incorporated into the aldehyde proton. However, mass spectral analysis showed the product to contain less than 0.5% deuterated aldehyde.

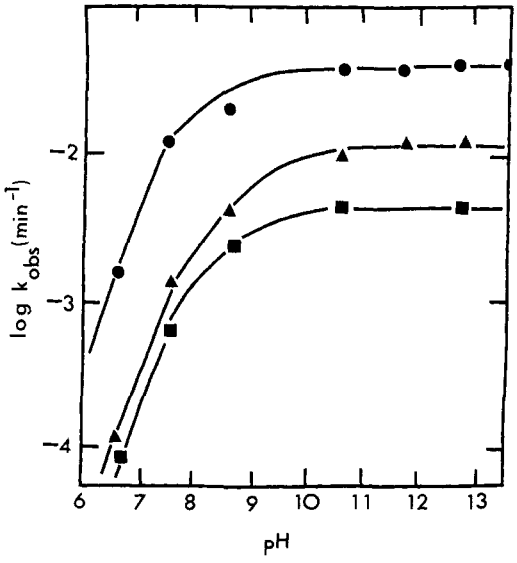


Figure 1. The pH–log k_{obsd} profiles for the hydrolyses of **1** (▲), **2** (●), and **3** (■) at 30°.

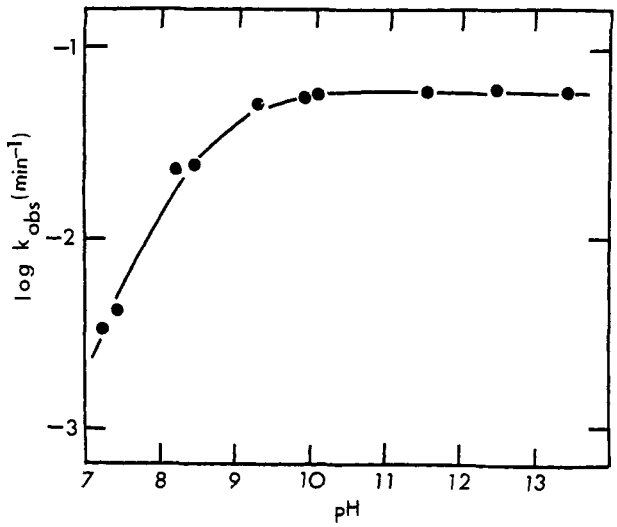


Figure 2. The pH–log k_{obsd} profile for the hydrolysis of 1-methyl-5-difluoromethyluracil (**6**) at 30°.

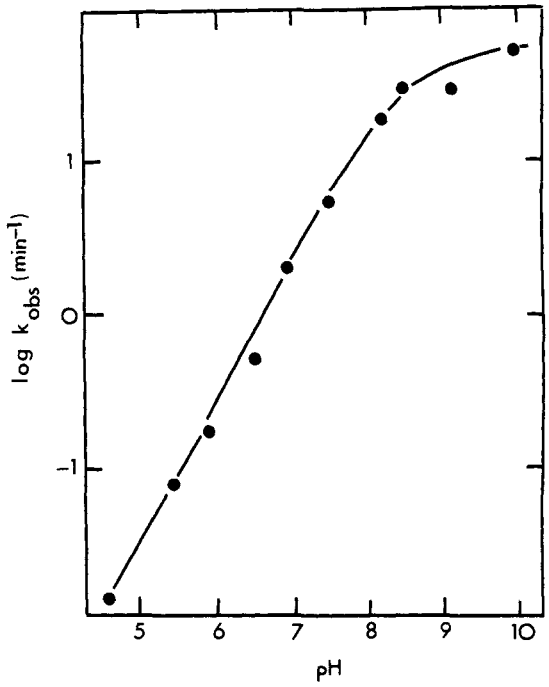


Figure 3. The partial pH–log k_{obsd} profile for the hydrolysis of 5-difluoromethyluracil (**5**) at 30°.

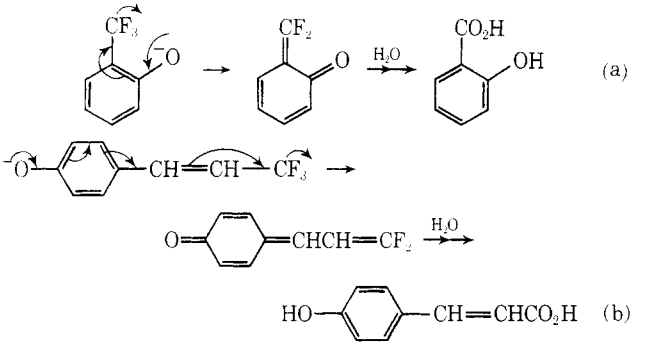
Although a complete profile for the hydrolysis of the parent pyrimidine was not obtained, the data indicated the dependence of rate on an ionizable group of approximate pK = 8.5 with an associated first-order rate constant of approximately 30 min^{-1} at 30° (Figure 3).

Discussion

The data for the hydrolysis of **1** and **2** are consistent with a mechanism in which the *o*- and *p*-phenolate anions

assist in the displacement of fluoride ion to give difluoroquinone methide intermediates (Scheme II). The complete inertness of *m*-hydroxybenzotrifluoride toward vigorous hydroxide treatment[8] substantiates the involvement of the oxyanions of **1** and **2** and provides a strong argument against the kinetically equivalent direct displacement of fluoride from the neutral species of **1** and **2** in an SN2-type displacement.

Scheme II



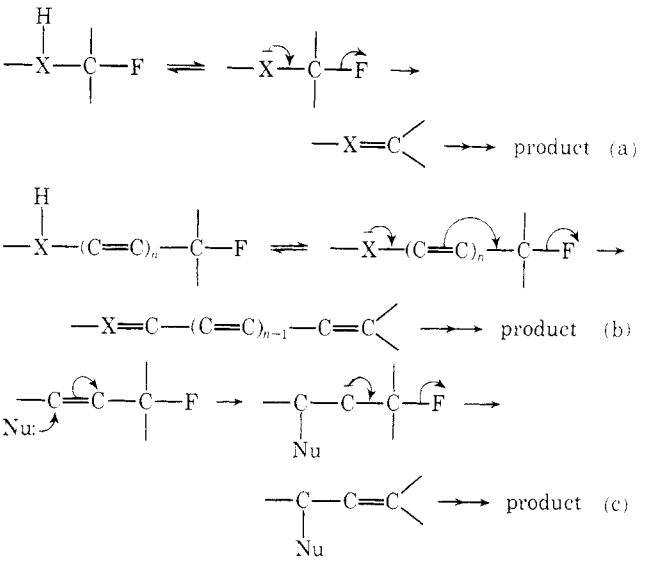
The data for the hydrolysis of the vinylogous derivative **3** to *p*-coumaric acid provide further verification of this postulate. A mechanism in accord with the data and which is analogous to that shown for **1** and **2** involves assistance of the phenolate anion through the π system with the formation of the reactive difluoro intermediate (Scheme IIb). When the double bond was reduced to give **4**, the trifluoromethyl group was stable in 1 *N* NaOH for 24 hr, demonstrating that transmission of the effect of the phenolate anion of **3** through the conjugated system is required for fluoride displacement.

To test for the possibility of a mechanism involving hydroxide ion attack on the ethylene group of neutral **3** in a Michael-type reaction, the nitro compound **7** was studied. However, **7** was found to be stable in 1 *N* NaOH indicating that such a mechanism probably is not operative in these compounds.

The data for the difluoromethyluracils **5** and **6** do not permit the assignment of reactivity to any ionic species or the assignment of mechanisms; however, with the data from the trifluoromethyluracils,[1] it is possible to postulate the most feasible pathways. The parent pyrimidine **5** is believed to hydrolyze as described for 5-trifluoromethyluracil, with the N-1 and N-3 anions involved in the labilization of fluoride;[1] the hydrolysis of **6** is believed to occur as described for 1-methyl-5-trifluoromethyluracil, with hydroxide ion attacking the 6 position of the heterocycle in a Michael-type reaction to release fluoride. The calculation of a rate constant for the hydrolysis of **5** assuming a second-order process, *i.e.*, hydroxide ion reaction with neutral **5**, gives a value of approximately $6 \times 10^7\ M^{-1}\ min^{-1}$ which is 10^4 times larger than the value for the hydrolysis of **6**, assuming the same mechanism. This indicates that **5** and **6** are hydrolyzing by different means and it seems likely that the mechanisms proposed for trifluoromethyluracil derivatives also are operative with these compounds.

Thus, C–F bond labilization appears to involve either of two general mechanisms. (1) Proton removal is at an atom α to the carbon bearing the fluorine atom with the resultant negative charge, either in a stepwise or concerted manner, aiding in the formation of an intermediate (fluoro)alkene (Scheme IIIa). Depending on the stability of the alkene, it may or may not react with solvent. Similarly, the proton may be situated on an atom such that the negative charge resulting from the ionization of the proton can exert its influence through an extended π system (Scheme IIIb). (2) In the case that the compound is an allylic fluoride incapable of undergoing either of the mechanisms described in (1), it may undergo nucleophilic (Michael-type) attack at the β carbon with assistance by the developing carbanion to give an intermediate similar to those in (1) (Scheme IIIc). In all cases, trifluoromethyl groups give carboxylic acids or derivatives, difluoromethyl groups give aldehydes or ketones, and fluoromethyl groups give alcohols or alkenes.

Scheme III



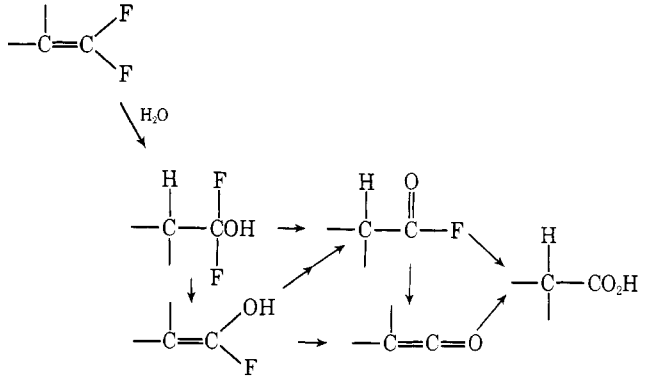
The postulated mechanisms suggest that reactive trifluoromethyl groups should be more stable than difluoromethyl groups which, in turn, would be more stable than fluoromethyl groups. Other factors, such as the effect of varying numbers of fluorine stoms on proton acidity or susceptibility to nucleophiles or on the stability of the intermediates formed, must be considered also; however, the generalization appears to hold for the fluorinated uracil derivatives described here and previously.[1] Indeed, 5-fluoromethyluracil and 1-methyl-5-fluoromethyluracil appear so unstable that they are not isolable (ref 10 and above data).

All of the transformations shown in Table I can be explained then in terms of the mechanisms proposed and the ability of the compounds to form olefinic intermediates appears necessary for reactions to occur. That this is true can be seen in the stability of compounds incapable of such reactions; for example, α-hydroxy-α-trifluoromethylpropionic acid,[14] *m*-hydroxybenzotrifluoride,[8] and 2-trifluoromethyltyrosine[15] are stable, whereas α-trifluoromethylpropionic acid,[14] *o*- and *p*-hydroxybenzotrifluoride,[8] and 3-trifluoromethyltyrosine[15] all are unstable.

The mechanism(s) by which the olefinic intermediates are transformed to products is believed to involve alternate addition of nucleophile (or solvent) to the intermediate and elimination of fluoride ion. A possible scheme of hydrolysis is depicted in Scheme IV and, as shown, may involve the intermediacy of acyl fluorides and ketenes in the transformation of a trifluoromethyl group to a carboxylate function, although these intermediates have, as yet, not been detected. An analogous mechanism may be proposed for the reaction of 2-trifluoromethylbenzimidazole with *o*-phenylenediamine to give 2,2′-bis(benzimidazole).[16]

These reactions do not appear to be limited to fluorine compounds strictly as can be seen in the lability of 6-tri-

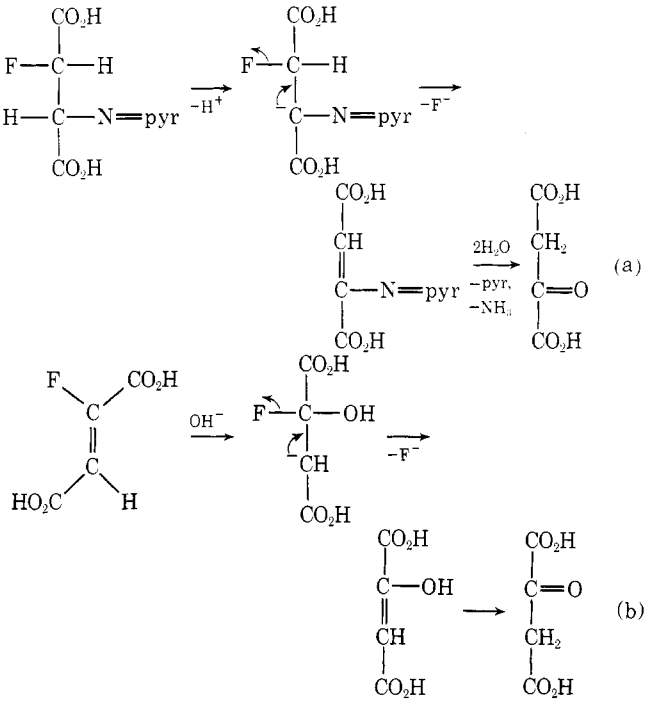
Scheme IV



chloromethylpurine.[17] The mechanism proposed for the hydrolysis of this compound is analogous to those proposed here; however, an important distinction to be made between fluoride and other leaving groups is that the former appears to undergo *facile* displacement only by the mechanisms described here.

One application of C–F heterolytic cleavage reactions would be their use as diagnostic tools in situations where one of the above mechanisms (IIIa–c) is suspected but difficult to verify. For example, an enzyme-catalyzed expulsion of fluoride from a suitably designed analog of a substrate would provide strong evidence for base or nucleophilic catalysis. Similarly, if a mode of catalysis is known, it might be possible to design a fluorine-containing analog which would be converted to a reactive electrophilic species on the active site with all the specificity inherent in enzymic reactions. Both of the above have been demonstrated in the cases of fumarate hydratase,[18] aspartate glutamate transaminase,[19] and thymidylate synthetase.[1,20] The mechanisms for the enzymatic labilization of fluoride ion for some of these examples are given in Scheme V and follow the postulated mechanisms. Further reactions may be envisioned which would be helpful in the determination of modes of catalysis and enzyme catalytic groups.

Scheme V



If the mode of catalysis of an enzyme is known, it may also be possible to design fluorinated inhibitors of that enzyme with a view toward specific irreversible inhibition or specific chemotherapy.

Experimental Section

Ultraviolet absorption spectra were determined on a Cary Model 15 spectrophotometer; infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. Melting points were taken on a Mel-Temp block and all values below 230° are corrected. Rate measurements were made at 30° on a Beckman DU monochromator in conjunction with a Gilford Model 2000 multiple sample absorbance recorder. Hydrolysis rates were monitored spectrophotometrically at 300 nm for **1**, 320 nm for **2** and **3**, and 280 and 290 nm for **5** and **6**, respectively. Buffers utilized were phosphate (pH 6–7.5), borate (pH 8–10), and carbonate (pH 11–12) as the sodium salts. Buffer solutions were 0.2 *M* and ionic strength was maintained at 1.0 *M* with $NaClO_4$. Buffer dilutions up to tenfold showed no apparent effect on the rates. A Radiometer Model 26 pH meter and GK 2021 B combined glass and reference electrode were used for pH measurements; p*K* determinations were made potentiometrically as described by Albert and Serjeant.[21] Mass spectra and deuterium analysis were run on an AEI 902 mass spectrometer equipped with a Mosley 7101 B linear streak recorder. Thin-layer chromatography was run on silica gel GF_{254} (Merck) using ethyl acetate (A), chloroform (B), and chloroform–ethanol (10:7 v/v) (C) as solvent systems. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

o-Hydroxybenzotrifluoride was obtained from Pierce Chemical Co. and *p*-hydroxybenzotrifluoride from PCR, Inc.; both compounds were used without further purification. 5-Difluoromethyluracil was prepared by the method of Mertes, *et al.*[10]

1-Methyl-5-difluoromethyluracil (6) was prepared as described for **5** with modifications. A mixture of 0.5 g of 1-methyl-5-formyluracil[22] and 0.2 ml of H_2O was placed in a stainless steel bomb and cooled to Dry Ice–Me_2CO temperature; 20 g of SF_4 was introduced into the bomb and the vessel was allowed to come to room temperature, after which time it was heated at 100° for 24 hr. After excess gases were vented into a 20% KOH solution, the residue in the bomb was dissolved in 20 ml of MeOH, decolorized with charcoal, and concentrated to 5 ml. Cooling of the solution gave crystals: mp 198–200° dec; yield 0.21 g (38%); tlc in systems A and C showed one spot; uv_{max} (H_2O) 263 nm (ε 11,700) (pH 1), 262 (13,900) (pH 13). *Anal.* ($C_6H_6F_2N_2O_2$) C, H, N.

1-Trifluoromethyl-2-(4-nitrophenyl)ethylene (7). *p*-Nitrobenzyltriphenylphosphonium bromide[13] (2.39 g, 5 mmol) and potassium *tert*-butoxide (0.57 g, 5.1 mmol) were dissolved in 25 ml of anhydrous DMF and the solution was cooled in a salt–ice bath. Into this was distilled trifluoroacetaldehyde from 5 g of trifluoroacetaldehyde hydrate (PCR, Inc.) dropped into a hot (80°) mixture of concentrated H_2SO_4–P_2O_5 (3 ml–5 g). The solution was allowed to come to room temperature and then heated at 100° for 24 hr with stirring. The solution was poured into 100 ml of H_2O and the mixture extracted with $CHCl_3$ (4 × 50 ml). The $CHCl_3$ fraction was dried ($MgSO_4$) and evaporated to a light oil which was dissolved in a minimal amount of EtOAc. The solution was placed on a silica gel column (3 × 40 cm) packed in EtOAc and eluted with EtOAc. The leading uv-absorbing spot was concentrated to an oil which crystallized upon standing as flat yellow needles: mp 80–85°; yield 0.4 g (36%); uv_{max} (EtOH) 287 nm; ν_{max} (KBr) 1540, 1340 (NO_2), 1680 cm^{-1} (aliphatic C=C). *Anal.* ($C_9H_6F_3NO_2$) C, H, N.

1-Trifluoromethyl-2-(4-aminophenyl)ethylene (8). To a mixture of **7** (0.2 g, 1.07 mmol) and 5 ml of H_2O was added 0.5 g of Fe powder followed by 3 ml of concentrated HCl. The flask was fitted with a reflux condensor and heated on a steam bath with occasional swirling to free unreacted **7** from the mixture of Fe and Fe salts. After 15–20 min the mixture was made basic with concentrated KOH and extracted with CH_2Cl_2 (4 × 50 ml). The organic fraction was dried ($MgSO_4$) and evaporated to give a buff-colored solid; 0.15 g (75%); mp 60–65°. The material gave a positive Bratton–Marshall test[23] for diazotizable amine and was used without further purification.

1-Trifluoromethyl-2-(4-hydroxyphenyl)ethylene (3). A solution of 0.15 g of **8** (0.8 mmol) in 2 ml of 5% H_2SO_4 was treated with a solution of 0.02 g of $NaNO_2$ in 4 ml of H_2O by dropwise addition over 5 min at 4°. The solution was allowed to react in the cold for 5 min, after which time excess HNO_2 was destroyed by the addition of 0.2 g of urea. The solution of the diazonium salt was added to 5 ml of a hot 10% H_2SO_4 solution over 5 min and the resulting solution heated for an additional 5 min on a steam bath. After cooling to room temperature, the solution was extracted with $CHCl_3$ (3 × 50 ml); the $CHCl_3$ fraction was dried ($MgSO_4$) and concentrated to an oil. The oil upon sublimation at 0.1–0.2 mm and 80° gave white crystals: mp 65–66°; yield 0.6 g

(66%); uv_{max} (H_2O) 275 (pH 7), 295, 315 nm (shoulder) (pH 13); ν_{max} (KBr) 1660 (C=C), 3350 cm^{-1} (OH). *Anal.* ($C_9H_7F_3O$) C, H.

1-Trifluoromethyl-2-(4-hydroxyphenyl)ethane (4). A solution of 0.04 g of **3** (0.21 mmol) in 4 ml of absolute EtOH was hydrogenated at room temperature at 1 atm in the presence of 0.01 g of 10% Pd/C. Reduction was complete in 10 min and filtration of the catalyst and removal of solvent gave a quantitative yield of product as a clear oil. The oil was distilled at 75° (bath temperature) and 0.1 mm to give a product which showed no C=C band in the ir; uv_{max} (H_2O) 272 (pH 7), 292 nm (pH 13). *Anal.* ($C_9H_9F_3O$) C, H.

Product Analysis. The phenol (0.05 g) was dissolved in 0.5 ml of 1 *N* NaOH and the solution allowed to stand at room temperature for 12 hr. Uv spectra in base at this time corresponded to those reported for the corresponding hydroxy acids.[24-26] The solutions from **1** and **2** were acidified to pH 1-2 with concentrated HCl and cooled to give crystals. **1** gave salicylic acid, 0.02 g, mp 155-157°; **2** gave *p*-hydroxybenzoic acid, 0.03, g, mp 213-214°. Hydrolyzed **3** was acidified with Dowex 50-X8 (H^- form) to give *p*-coumaric acid, 0.01 g, mp 210-215°; ir spectrum identical with literature spectrum.[27]

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Oxidation of Furans. 2.† Synthesis and Biological Properties of 6-Hydroxy-2*H*-pyran-3(6*H*)-ones and Derivatives

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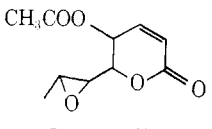
The anticoccidial and *in vitro* antimicrobial properties of a series of 6-hydroxy-2*H*-pyran-3(6*H*)-ones VI and their derivatives VII-XI were investigated. Compounds VI were readily prepared by the peracid oxidation of the appropriate 2-furanmethanols V. Activity was mostly found with compounds substituted with a 4-biphenylyl group and, in particular, **29-47**. The nature of the substituents greatly influenced the degree and type of activity.

In a recent communication,[1] we briefly reported the synthesis of 6-hydroxy-2*H*-pyran-3(6*H*)-ones VI (R^3 = H). These pyran derivatives are chemically related to the naturally occurring antibiotic asperlin I, isolated from *Aspergillus nidulans*,[2] and they were considered to be the most suitable starting materials for the preparation of analogs II of asperlin. Unexpectedly, very good *in vitro* antimicrobial properties were found in compounds of type VI rather than in the analogs II. The present paper will give a more detailed account of the chemistry of 6-hydroxy-2*H*-pyran-3(6*H*)-ones and discuss their biological properties as well as those of their derivatives VII-XI.



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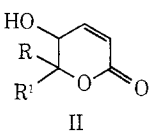

II

† For part 1, see ref 1.

Chemistry. 1. 6-Hydroxy-2*H*-pyran-3(6*H*)-ones VI (R^3 = H). As previously reported, [1] the hydroxypyranones VI (R^3 = H) were prepared by the process depicted in Scheme I; reaction of an aldehyde or ketone III with a furyllithium derivative IV afforded the 2-furanmethanols V which were converted into VI upon treatment with *m*-chloroperbenzoic acid (or occasionally peracetic acid) in chloroform or methylene chloride. Exceptionally the furanmethanol XIII, precursor of compound **65** (Table I), was prepared by reacting the lithium derivatives XII with 2-acetylfuran (Scheme II). In view of their unstability the 2-furanmethanols were used without purification.

2. Derivatives of 6-Hydroxy-2*H*-pyran-3(6*H*)-ones (VII-XI). Most 6-hydroxy-2*H*-pyran-3(6*H*)-ones were found to be sensitive to strong acid or alkaline media‡ and special precautions had to be taken for the preparation of the derivatives VII-XI.

‡In strongly acidic media the 6-hydroxy-2*H*-pyran-3(6*H*)-ones are converted into crotonic acid γ-lactone derivatives, while they dimerize in alkaline media.