Experimental

Cupric Bromide with Chalcone in Methanol.—2′-Hydroxide-5′-methyl-4-methoxychalcone, m.p. 98° (0.5 g.), and cupric bromide (1.2 g.) were taken in methanol (40 ml.). In one experiment it was kept overnight. In another experiment it was refluxed for 2 hr. After dilution with water the solid which separated was crystallized from ethanol–acetic acid. It was unchanged chalcone.

Cupric Bromide with β-Methylumbelliferone in Methanol. β-Methylumbelliferone, m.p. 184° (1 g.), cupric bromide (2.5 g.) were taken in methanol (50 ml.) and kept overnight. In another experiment it was refluxed for 2 hr. After dilution with water the solid which separated was crystallized from ethanol–acetic acid. It was unconverted β-methylumbelliferone.

Cupric Bromide with Chalcone in Dioxane. (a) In Cold.—The chalcone (0.5 g.) and cupric bromide (1.2 g.) in dioxane (30 ml.) were kept overnight. On dilution with water and crystallization from ethanol–acetic acid original chalcone was obtained.

(b) In Hot.—The chalcone (0.5 g.) and cupric bromide (1.2 g.) in dioxane (30 ml.) were refluxed for 2 hr. The mixture as diluted with water and the solid which separated was crystallized from ethanol–acetic acid, m.p. 165°. Mixed melting point of the bromo compound m.p. 165° with 3-bromo-6-methyl-4′-methoxyflavanone, gave no depression. Compound m.p. 165° on treatment with ethanolic sodium hydroxide solution gave a flavone derivative identical with 6-methyl-4′-methoxyflavone, m.p. 168°.

Cupric Bromide with β-Methylumbelliferone in Dioxane. (a) In Cold.—β-Methylumbelliferone (1 g.) and cupric bromide (2.5 g.) were kept overnight in dioxane (50 ml.). The mixture was diluted with water and the solid separated was crystallized from ethanol–acetic acid. It was unconverted β-methylumbelliferone.

(b) In Hot.—β-Methylumbelliferone (1 g.) and cupric bromide (2.5 g.) in dioxane (50 ml.) were refluxed for 2 hr. The mixture was diluted with water and the solid obtained was fractionally crystallized from acetic acid. 3,6-Dibromo-, m.p. 274°, and 3,8-dibromo-4-methylumbelliferone, m.p. 248°, were the products. Identity was shown by a mixed melting point with the authentic samples.

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Organic Fluorine Compounds. XXVIII. Reaction of Sulfonic- and Mixed Sulfonic-Carboxylic Acid Anhydrides with Anhydrous Hydrogen Fluoride

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The generalization of the method of Colson and Fredenhagen provides an easy preparation of acyl fluorides from the corresponding acid anhydrides or acyl chlorides and anhydrous hydrogen fluoride.[1]

The method has now been extended to the preparation of sulfonyl fluorides. Sulfonyl chlorides generally do not react with anhydrous hydrogen fluoride at or below room temperature to give the corresponding sulfonyl fluorides. At elevated temperatures and under pressure, however, the reaction probably takes place.

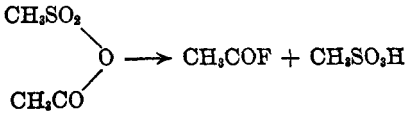
Sulfonic acid anhydrides react with anhydrous hydrogen fluoride to give the corresponding sulfonyl fluorides

$$(RSO_2)_2O + HF \longrightarrow RSO_2F + RSO_3H$$

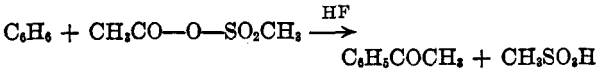
Both aliphatic and aromatic sulfonic acid anhydrides react with equal ease. The separation of the sulfonyl fluorides from the by-product sulfonic acids can be achieved by water washing and subsequent vacuum distillation. The following sulfonyl fluorides (all known from literature) have been prepared.

Boiling points and infrared spectra are identical with compounds described in literature.[2,3]

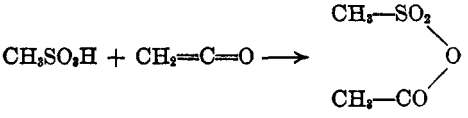
Mixed anhydrides of carboxylic and sulfonic acid, as acetic methanesulfonic anhydride, gave in reactions with anhydrous hydrogen fluoride only acyl fluorides and sulfonic acids (Table II).



When the mixed acetic sulfonic anhydrides are treated with aromatic hydrocarbons in the presence of anhydrous hydrogen fluoride, acid-catalyzed Friedel-Crafts acylation only takes place.



Acetic sulfonic anhydrides were prepared according to Baroni[4] by the interaction of the corresponding sulfonyl halides with silver acetate. The reaction of ketene with the appropriate sulfonic acids gives only low yields of mixed anhydrides.



Experimental

Sulfonic acid anhydrides were prepared according to methods of Khorona[5] and Field,[6] acetic sulfonic anhydrides according to Baroni.[4]

Preparation of Acetic Sulfonic Anhydrides with Ketene.—Alkylsulfonic acid (1 mole) in liquid sulfur dioxide solution was placed into a 250-ml. flask and 1 mole of ketene gener-

(1) Part XXVII, G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).

(2) W. Davis and J. H. Dick, *J. Chem. Soc.*, 483 (1932).

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(4) A. Baroni, *Atti Accad. Naz. Lincei*, **17**, 1081 (1933) *Chem. Abstr.*, **28**, 1661 (1934).

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TABLE I
PREPARATION OF SULFONYL FLUORIDES FROM SULFONIC ACID ANHYDRIDES

Sulfonyl fluoride	B.p., °C.	% yield	S, % Calcd.	S, % Found	F, % Calcd.	F, % Found
Methanesulfonyl	122–123	91	32.68	32.79	19.36	19.28
Ethanesulfonyl	134–135	95	28.59	28.70	16.94	16.87
Benzenesulfonyl	90–91/14 mm.	93	20.01	20.19	11.86	11.80
p-Toluenesulfonyl	113/16 mm.	90	18.40	18.56	10.90	10.78

TABLE II

Acetic sulfonic acid anhydride	Acyl fluoride obtained	% yield
Acetic methanesulfonic	Acetyl	87
Acetic ethanesulfonic	Acetyl	86
Acetic benzenesulfonic	Acetyl	91
Acetic *p*-toluenesulfonic	Acetyl	92

ated as described by Hurd[7] was introduced into the acid maintaining the temperature at −15 to −10°. The reaction mixture was then fractionated in vacuum. Yields obtained were less than 10%. Acetic anhydride was always formed in substantial amounts due to disproportionation of mixed anhydride.

Reaction of Sulfonic Acid Anhydrides with Anhydrous Hydrogen Fluoride.—Sulfonic acid anhydride (1.0 mole) was mixed (Teflon-coated magnetic stirrer) with 30 g. (1.5 moles) of anhydrous hydrogen fluoride at −10° in a fused silica or polyolefin reaction flask. The reaction mixture, protected in the usual way from atmospheric moisture, was stirred for 2 hr. at 0° under a silica or plastic reflux condenser. It was allowed to warm to room temperature and stirred there for another hour. The reaction mixture was then washed with cold water, the organic layer separated, dried, and fractionated in vacuum. Yields of sulfonyl fluorides obtained are summarized in Table I.

Reaction of Acetic Sulfonic Anhydride with Anhydrous Hydrogen Fluoride.—Acetic sulfonic anhydride (0.3 mole) was mixed with 0.3 mole of hydrogen fluoride at −10° in a polyethylene flask. The reaction mixture was then allowed to stand at 10° for 6 hr. Fractionation of the mixtures yielded acetyl fluoride (b.p. 20–21°, identified by infrared spectrum) in high yields (see Table II).

Reaction of Acetic Methanesulfonic Anhydride with Hydrogen Fluoride in the Presence of Benzene.—Into a vigorously stirred mixture of 0.2 mole of acetic methanesulfonic anhydride and 0.5 mole of benzene 0.25 mole of hydrogen fluoride was added at 0°. Stirring was continued for an additional hour at 20°. The reaction mixture was then washed three times with 50 ml. of water, dried over sodium sulfate and fractionated. A 5-g. sample of acetophenone was obtained (20% yield), identified by its physical data and infrared spectrum.

(7) C. D. Hurd, *Org. Syn.*, Coll. Vol. I, 330, 1956.

6-Chloro- and 6-Bromopenicillanic Acids

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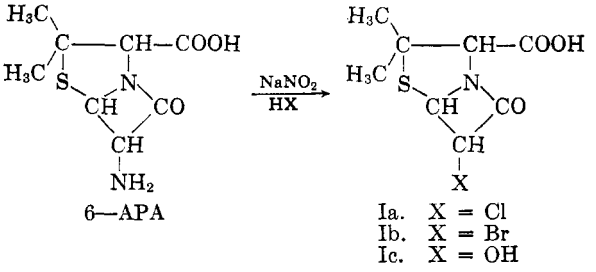
6-Aminopenicillanic acid (6-APA), firstly named "penicin" by Sakaguchi and Murao[1] who reported hydrolysis of penicillin G by an enzyme present in *Penicillium chrysogenum*, became available in large amounts in 1959 when Batchelor, *et al.*,[2] described the isolation of 6-APA from penicillin fermentation broths grown in absence of precursors. Since then 6-APA has been subjected to reaction with a number of acid chlorides or acid anhydrides in order to obtain new "synthetic" penicillins.[3,4]

We are now investigating the chemical behavior of 6-APA and, as a part of our research program, we wish to report the transformation of 6-APA into 6-chloro- and 6-bromopenicillanic acids.



6-APA may be easily diazotized at 0–2° in diluted hydrochloric acid or hydrobromic acid; 6-APA structure, whose β-lactam ring is generally easily hydrolized,[5] is not affected in the above diazotization conditions and Ia or Ib was isolated in good yields.

Only a few examples of the substitution of the amino group of an amino acid or an amino alcohol with a halogen atom through a diazotization in hydrohalogenic acid have been reported.[6–9]

An attempt to replace the amino group of 6-APA with a hydroxy group (Ic) failed. By diazotizing 6-APA in diluted acetic, tartaric, or sulfuric acids a compound was obtained which gave low values when assayed as a β-lactam.[10] No free or esterified hydroxyl groups were detected in this compound, nor was it possible to purify the reaction product by chromatography on alumina or by fractional crys-

(1) K. Sakaguchi and S. Murao, *J. Agr. Chem. Soc. (Japan)*, **23**, 411 (1950); *Chem. Abstr.*, **45**, 1197 (1951).

(2) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, and G. N. Rolison, *Nature*, **183**, 257 (1959).

(3) A. Gourevitch, G. A. Hunt, and J. Lein, *Antibiot. Chemotherapia*, **10**, 121 (1960).

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(5) F. R. Batchelor, "Chemistry of Penicillin," Princeton University Press, 1949.

(6) H. Felkin, *Compt. rend.*, **234**, 2203 (1952).

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(8) S-C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **76**, 6054 (1954).

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, p. 395.

(10) J. P. Alicino, *Anal. Chem.*, **33**, 648 (1961).