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.

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6-Chloro- and 6-Bromopenicillanic Acids

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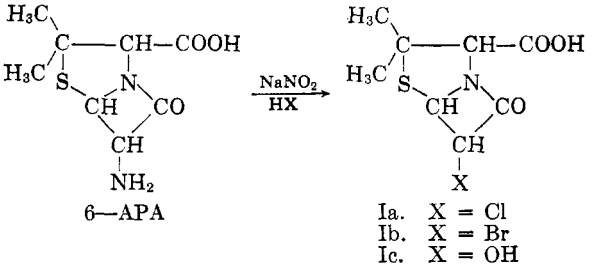
6-Aminopenicillanic acid (6-APA), firstly named "penicin" by Sakaguchi and Murao[1] who reported hydrolysis of penicillin G by an enzyme present in *Penicillium chrysogenum*, became available in large amounts in 1959 when Batchelor, *et al.*,[2] described the isolation of 6-APA from penicillin fermentation 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-

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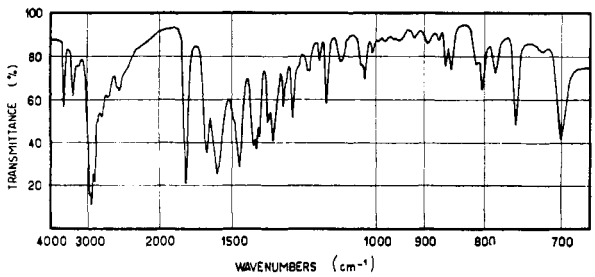

Figure 1

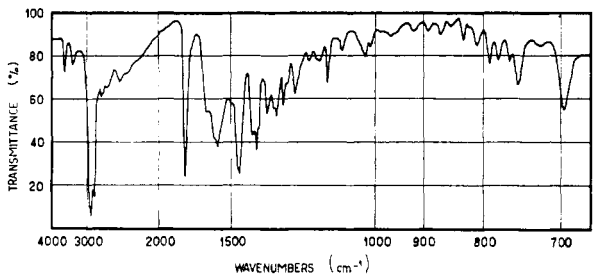

Figure 2

tallization of its dibenzylethylenediamine salts. The substitution of the amino group on a β-lactam ring with a hydroxy group is likely to decrease further the stability of 6-APA, so that it was quite impossible for us to isolate any amount of compound Ic.

Acids Ia and Ib are useful starting compounds for further investigations on the 6-APA chemical behavior. Ia and Ib, in the form of their dibenzylethylenediamine (DED) salts, are devoid of microbiological activity against *M. pyogenes aureus* 209 P [m.i.c./γ ml.: Penicillin G = 0.05; 6-APA = 5; Ia (DED − salt) > 100; IIa (DED − salt) > 100].

Experimental

6-Chloropenicillanic Acid (Ia).—A solution of 6.5 g. of 6-APA in 100 ml. of 1 *N* hydrochloric acid was cooled to 0–2° and a solution of 2.5 g. of sodium nitrite in 20 ml. of water was added dropwise. One hour after the completion of the addition, the temperature was allowed to rise to 15–18° and the separated oil extracted with ethyl ether. The organic layer was dried over sodium sulfate and the ether evaporated *in vacuo* at room temperature. The oily residue, 4.5 g., showed in the infrared spectrum bands at 1725 cm.$^{-1}$ (C=O stretching of carboxylic group) and at 1770 cm.$^{-1}$ (C=O stretching of β-lactam fused to thiazolidine ring) in agreement with the structure of Ia.

This oil, which decomposed under distillation, was dissolved in ethyl ether and treated with an ether solution of dibenzylethylenediamine; 5.5 g. of Ia dibenzylethylenediamine salt was obtained, which, after several crystallizations from aqueous ethanol, melted at 159–160°; $[\alpha]_D$ +154.4 (*c* 0.5%, in methanol). The infrared spectrum is reported in Fig. 1.

Anal. Calcd. for $C_{32}H_{40}Cl_2N_4O_6S_2$: C, 54.00; H, 5.67; N, 7.88; S, 9.01; Cl, 9.97. Found: C, 53.75; H, 6.19; N, 7.65; S, 8.99; Cl, 10.24.

6-Bromopenicillanic Acid (Ib).—was prepared essentially in the same way described for Ia, starting from 4.32 g. of 6-APA dissolved in 50 ml. of 2.5 *N* sulfuric acid containing 10.4 g. of sodium bromide and adding dropwise a solution of 2.12 g. of sodium nitrite in 10 ml. of water. The oily residue (4.88 g.) showed infrared bands at 1770 and 1725 cm.$^{-1}$, confirming for Ib the supposed structure. On treatment of Ib with an ether solution of dibenzylethylenediamine, 3.4 g. of crude Ib dibenzylethylendiamine salt was obtained, which, recrystallized from aqueous ethanol, melted at 164–165°; $[\alpha]_D$ +140.9 (*c* 0.5%, in methanol). The infrared spectrum is reported in Fig. 2.

Anal. Calcd. for $C_{32}H_{40}Br_2N_4O_6S_2$: C, 48.00; H, 5.03; N, 6.99; S, 8.00; Br, 19.96. Found: C, 48.17; H, 5.11; N, 7.28; S, 7.85; Br, 19.90.

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Alkylfluorophenylcarbinols with Choleretic Activity

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p-Tolylmethylcarbinol, a component of the essential oil of *Curcuma domestica*, is known to show potent choleretic activity,[1] and the same properties have been found in several of its homologs[2] and in similar heterocyclic carbinols.[3] It is also known that methyl groups can be replaced by halogens without qualitatively affecting pharmacological activity. Hence, it was of interest to investigate whether alkylfluorophenylcarbinols would likewise display choleretic activity; fluorine radicals were preferred to other halogens since the solidity of the C—F bonds in aromatic molecules renders biochemical dehalogenation more difficult. We now report the preparation, for biological evaluation, of a wide series of such fluorinated carbinols, by reaction of the appropriate alkylmagnesium bromide or iodide with *o*-, *m*-, and *p*-fluorobenzaldehyde; in this series, only methyl-*p*-fluorophenylcarbinol was known.[4] All the carbinols thus obtained in 80–90% yield, were colorless oils with an aromatic odor that was pronounced for the lower terms and less marked for the higher terms. Several arylalkyl-

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