molecular weights of metals dissolved gallium in boiling mercury to the extent of 0.7855%. However, he did not attempt to determine the solubility. Puschin, Stepanovic and Stajic[2] investigated the mutual solubilities by means of freezing point lowering and concluded that the metals are at their freezing points either insoluble or very slightly soluble in one another. Davies and Keeping,[3] in a study of the magnetic susceptibility of some amalgams, made an amalgam containing 0.2436% gallium at 18.9°. Gilfillan and Bent,[4] on the basis of freezing point lowering, concluded that at the freezing points the solubility of gallium in mercury is about 0.13%, while that of mercury in gallium is immeasurably small.

In view of the uncertainty in these data, it was decided to determine the mutual solubilities at 35° and at 100° by the following direct method: The liquids were mixed and allowed to equilibrate. Weighed samples were removed from each layer and the gallium dissolved out by hydrochloric acid. The remaining mercury was weighed. Our results indicate that the solubilities are considerably greater than had been thought.

Experimental.—The gallium was obtained from the Aluminum Co. of America and was said to be better than 99.95% gallium. This high purity was confirmed by qualitative spectrographic analysis. The mercury was purified by washing with nitric acid and water, drying and distilling.

Gallium wets glass and oxidizes rapidly when exposed to air. It was found, however, that when it is placed under a weakly acidic (with HCl) solution of gallium chloride its surface apparently remains free of oxide and it no longer wets glass. It was felt that the presence of this film of oxide may have caused previous investigators to obtain low results for the solubility. Therefore, the gallium was always kept under such a solution.

Weighed portions of the metals (approximately 3.5 g. Ga and 7.0 g. Hg) were placed in a glass tube under the gallium chloride solution and allowed to equilibrate, with frequent shaking, in a bath maintained at constant temperature.

The interface between the two phases could not be seen. In order to locate it, a steel shot of somewhat smaller diameter than the tube was added and forced to the bottom of the mixture of metals by means of a small glass rod. When released the shot rose to what was assumed to be the interface. That the shot would stop at the interface is reasonable in view of the densities which are: Hg = 13.6, Fe = 7.5 and Ga = 5.9.

Several small samples were taken from each layer and weighed. (Samples were removed from the lower mercury-rich layer through a stopcock on the lower end of the tube, and from the upper layer by means of a pipet.) To these, concentrated HCl was added to dissolve the gallium. As soon as all of the gallium had dissolved as indicated by the discontinuance of gas evolution, the solution was decanted from the mercury, which was quickly dried with filter paper and reweighed. Gallium reacts only slowly with hydrochloric acid and the gallium-rich samples required several days for complete reaction even when heated on a water-bath. In spite of this long time, that no mercury dissolved was proved by spectrographic analysis of the acid solution.

Furthermore, the validity of the method of analysis was demonstrated by applying it to a mercury–gallium mixture of known composition.

The results are given in Table I. In order to eliminate the possibility that the metals were simply dispersed in one another, two of the determinations were made after the metals had stood in contact for approximately two months. These are indicated in the table by an asterisk.

(2) N. A. Puschin, S. Stepanovic and V. Stajic, *Z. anorg. Chem.*, **209**, 329 (1932).

(3) W. G. Davies and E. S. Keeping, *Phil. Mag.*, [7] **7**, 145 (1929).

(4) E. S. Gilfillan, Jr., and H. E. Bent, THIS JOURNAL, **56**, 1661 (1934).

TABLE I

LIQUID–LIQUID EQUILIBRIA DATA FOR THE SYSTEM GALLIUM MERCURY

Run no.	Layer rich in	Wt. of sample, g.	Wt. of mercury, g.	Hg, %	Ga, %
		At 35°			
1	Hg	0.4671	0.4615	98.8	1.2
2	Hg	.4659	.4594	98.6	1.4
3	Hg	.4083	.4036	98.8	1.2*
4	Hg	.7873	.7774	98.7	1.3*
5	Ga	.3138	.0189	6.0	94.0
6	Ga	.2022	.0135	6.7	93.3
7	Ga	.3687	.0241	6.6	93.4*
8	Ga	.1007	.0067	6.7	93.3*

Average: mercury-rich layer, 98.7% Hg; gallium-rich layer, 6.5% Hg. In terms of atom per cent.: solubility of gallium in mercury is 3.6% and solubility of mercury in gallium is 2.0%.

		At 100°			
1	Hg	0.8370	0.8258	98.6	1.4
2	Hg	.8200	.8090	98.6	1.4
3	Hg	.8518	.8400	98.6	1.4
4	Ga	.2133	.0183	8.5	91.5
5	Ga	.2944	.0250	8.5	91.5
6	Ga	.5042	.0443	8.8	91.2

Average: mercury-rich layer, 98.6% Hg; gallium-rich layer, 8.6% Hg. In terms of atom per cent.: solubility of gallium in mercury is 3.9% and solubility of mercury in gallium is 3.2%.

In view of the small increase in solubility with temperature, it is doubtful that a critical solution temperature exists in this system at one atmosphere pressure.

The low mutual solubilities of these metals are not surprising in view of the large difference in their internal pressures. Taking the boiling point of gallium as 2300°K. as given by Harteck[5] and using the Hildebrand rule[6] for estimating internal pressures one computes 38,800 atm. for mercury and 196,000 atm. for gallium.

(5) P. Harteck, *Z. physik. Chem.*, **134**, 1 (1928).

(6) J. H. Hildebrand, "Solubility of Non-Electrolytes," second edition, Reinhold Publishing Corp., New York, N. Y., 1936, p. 103.

GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA RECEIVED SEPTEMBER 5, 1950

Some Fluorine Containing Isosteres of Sulfa Drugs

BY AUGUST SVEINBJORNSSON AND CALVIN A. VANDERWERF

Investigation of the effect on the chemotherapeutic properties of various medicinals produced by the substitution of fluorine atoms for other groups in the molecule has been extended by the herein reported study of the synthesis and bacteriostatic action of a number of analogs of familiar sulfa drugs in which the amino group is replaced by the isosteric fluorine atom. Several *p*-fluorobenzamides have also been synthesized, as compounds of considerable interest from a bacteriological standpoint because of their relationship to *p*-aminobenzoic acid.

Experimental

***p*-Fluorobenzenesulfonamide.**—This compound, m.p. 123.1–124.0°, was prepared in 92% yield from *p*-fluorobenzenesulfonyl chloride and ammonia.

2-(*p*-Fluorobenzenesulfonamido)-pyrimidine.—To a 125-ml. conically shaped flask, equipped with a mechanical

stirrer, a condenser and a dropping funnel, and containing 9.5 g. (0.1 mole) of 2-aminopyrimidine[1] in 30 ml. of dry pyridine, 19.4 g. (0.1 mole) of *p*-fluorobenzenesulfonyl chloride was added with stirring. The mixture was heated at 120° for 2 hours and a solution of 4.4 g. (0.11 mole) of sodium hydroxide in 25 ml. of water was then added slowly with continued heating. The pyridine was removed by distillation under reduced pressure, water being added from time to time to maintain the volume approximately constant. The product which separated was filtered, washed well with water, and air-dried. The yield of pure **2-(*p*-fluorobenzenesulfonamido)-pyrimidine**, m.p. 184.5–185.0°, was 14.6 g. (57.7%).

Anal. Calcd. for $C_{10}H_8O_2N_3SF$: N, 16.6. Found: N, 16.5.

2-(*p*-Fluorobenzenesulfonamido)-thiazole.—This compound was prepared by the method used for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine except that 10.0 g. (0.1 mole) of 2-aminothiazole was substituted for the 2-aminopyrimidine. The crude material was recrystallized from glacial acetic acid to yield 15.5 g. (60.1%) of product melting at 171.2–172.0°,

Anal. Calcd. for $C_9H_7O_2N_2SF$: N, 10.9. Found: N, 10.7.

2-(*p*-Fluorobenzenesulfonamido)-pyridine.—This product was prepared by the method described for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine, except that 9.4 g. (0.1 mole) of 2-aminopyridine was used in place of 2-aminopyrimidine. The crude product (23 g.) was recrystallized repeatedly from glacial acetic acid to give 5.3 g. (21.0%) of pure material, melting at 151.2–151.7°.

Anal. Calcd. for $C_{11}H_9O_2N_2SF$: N, 11.1. Found: N, 11.0.

***p*-Fluorobenzoic Acid.**—This product, m.p. 184.1–184.7°,[2] was prepared in 70% yield from *p*-fluorotoluene[3] according to the directions given by Clark and Taylor[4] for the oxidation of *o*-chlorotoluene to *o*-chlorobenzoic acid.

2-(*p*-Fluorobenzamido)-pyridine.—This compound was prepared from 2-aminopyridine and *p*-fluorobenzoyl chloride[5] by the general method described for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine. The crude material was recrystallized from alcohol–water. The yield of pure product, m.p. 123.6–124.3°, was 62%.

Anal. Calcd. for $C_{12}H_9ON_2F$: N, 12.9. Found: N, 12.7.

2-(*p*-Fluorobenzamido)-thiazole.—Prepared by the usual method, this compound, m.p. 186.2–186.8° after recrystallization from alcohol–water, was obtained in 75% yield.

Anal. Calcd. for $C_{10}H_7ON_2FS$: N, 12.6. Found: N, 12.5.

2-(*p*-Fluorobenzamido)-pyrimidine.—To a mixture of 2.7 g. (0.028 mole) of 2-aminopyrimidine, 5.4 g. (0.028 mole) of powdered potassium carbonate, and 50 ml. of dry ether contained in a 200-ml. conically shaped 3-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, 4.4 g. of *p*-fluorobenzoyl chloride was added dropwise with stirring. The mixture was heated under reflux on a steam-bath for 3 hours. The solid remaining after removal of the ether and addition of 50 ml. of water was filtered and air dried to give 5.6 g. (91%) of crude material. This was dissolved in benzene, extracted with 5% hydrochloric acid and the benzene solution dried over anhydrous sodium sulfate. Addition of Skellysolve C to the benzene solution gave 4.8 g. (80.0%) of a colorless product, m.p. 224.4–226.0°.

Anal. Calcd. for $C_{11}H_8ON_3F$: C, 60.8; H, 3.7. Found: C, 60.6; H, 3.7.

(1) Obtained through the kindness of the Calco Chemical Division of the American Cyanamid Co.

(2) G. Schiemann and W. Winkelmüller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 299, reported 186°.

(3) B.p. 114–115° at 728 mm. Prepared in 71% yield by diazotization of *p*-toluidine in anhydrous hydrogen fluoride, followed by decomposition of the resulting diazonium fluoride in refluxing hydrogen fluoride.

(4) H. T. Clarke and E. R. Taylor, ref. 2, p. 135.

(5) Prepared by reaction of *p*-fluorobenzoic acid with thionyl chloride.

Discussion.—The compounds were tested *in vitro* as antagonists of the growth of *Staphylococcus aureus*, using Klinger medium and of *Escherichia coli*, using MacLeod medium. The organisms were inoculated, at the peak of their growth curves, into Klett–Summerson tubes containing standard drug concentrations. The tubes were incubated at 37° for 24 hours, and growth was determined by means of a Klett–Summerson photoelectric colorimeter. The minimal effective concentrations necessary to inhibit completely the growth of the organism are shown in Table I. Data for sulfathiazole and sulfasuxadine are added for comparison purposes.

TABLE I

Compound	Minimal effective concentration, *M* *E. coli*	*S. aureus*
p-Fluorobenzenesulfonamide	1×10^{-2}	
2-(*p*-Fluorobenzenesulfonamido)-pyridine	1×10^{-3}	
2-(*p*-Fluorobenzenesulfonamido)-pyrimidine	1×10^{-3}	
2-(*p*-Fluorobenzenesulfonamido)-thiazole	1×10^{-3}	1×10^{-4}
p-Fluorobenzoic acid	1×10^{-2}	1×10^{-2}
p-Fluorobenzamide[a]	1×10^{-1}	1×10^{-2}
Sulfathiazole	1×10^{-4}	4×10^{-6}
Sulfasuxadine	2×10^{-2}	

[a] Prepared by the method of J. H. Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

It is noteworthy that the inhibition of growth on *Escherichia coli* produced by *p*-fluorobenzoic acid was not reversed by its isostere *p*-aminobenzoic acid, but was reversed by tyrosine. The *p*-fluorobenzamides of 2-aminopyridine, 2-aminopyrimidine and 2-aminothiazole were not sufficiently soluble in the media to be tested.

Acknowledgment.—These studies were aided by a contract between the Office of Naval Research, Department of Navy, and the University of Kansas.

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RECEIVED OCTOBER 4, 1950

The Mechanism of Addition of Grignard Reagents to Ketones

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By testing a prediction from a mechanism based on kinetic studies of a model system which did not involve diisopropyl ketone at all, we have succeeded in increasing the yield of addition product in the reaction of *n*-propylmagnesium bromide with diisopropyl ketone from 36[1] to 65%.

This prediction was based on a consideration of the difference between the most probable mechanism for *addition of Grignard reagents to ketones* and the most probable mechanism for *reduction*, which is the principal competing side reaction. From other simple mechanisms which might be assumed to hold for these two processes, one would have predicted either no effect or a lower yield of addition by the new procedure; hence, the

(1) Whitmore and George, THIS JOURNAL, **64**, 1239 (1942).