When treated with hydrogen chloride in ether, a dihydrochloride was obtained. After several recrystallizations from 1-propanol–ethyl acetate and 2-propanol–acetonitrile the product melted at 264–265°. Other catalyst-solvent combinations were inferior to the above.

**1,2,2,6,6-Pentamethyl-4-aminopiperidine (XXII).**—1,2,2,6,6-Pentamethyl-4-piperidone oxime (17 g., 0.092 mole) in 100 ml. of dry tetrahydrofuran was added dropwise during 20 min. to a stirred solution of 8.4 g. (0.22 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran. After maintaining the solution at reflux for 1 hr., it was left at room temperature for 2 days. Most of the solvent was then removed by distillation and ether added to the residue. Potassium hydroxide (10 *N*, 100 ml.) was then cautiously added followed by continuous ether extraction for 24 hr. The ether was removed by distillation through a 2 × 25 cm. column packed with glass helices and the product distilled at 15 mm. The fraction boiling at 97–99° was collected and weighed 11.7 g. (75%) $n^{20}D$ = 1.4813.

**4-Guanido-1,2,2,6,6-pentamethylpiperidine Dinitrate (XXI).**—1-Guanyl-3,5-dimethyl-pyrazole nitrate (9.3 g., 0.046 and 4-mole) amino-1,2,2,6,6-pentamethylpiperidine (3.9 g., 0.023 mole) were fused together at a bath temperature of 110° for 3 hr. Treatment of the cooled melt with 25 ml. of boiling 2-propanol gave 3.95 g. of white crystals m.p. 211–213°. Recrystallization of this material from 75 ml. of acetonitrile gave 2.49 g. (32%) of product, m.p. 212–215° dec. In a capillary evacuated to *ca.* 0.1 mm. and sealed, the m.p. was 227–229° without apparent decomposition.

The analytical sample was prepared by recrystallizing material from an earlier run twice from ethanol. In a sealed evacuated capillary it melted at 225–226°.

**1-(*o*-Bromobenzyl)-2,2,6,6-tetramethylpiperidine (XXV).** *o*-Bromobenzyl chloride[36] (2.0 g., 0.01 mole) and 2,2,6,6-tetramethylpiperidine (2.82 g., 0.02 mole) were heated in a sealed tube for 42 hr. at 145°, 12 hr. at 100°, 10 hr. at 160°, 185–200° for 10 hr., and at 230° for 3 days. The crude reaction mixture was dissolved in ether and basic substances extracted into 6 *N* hydrochloric acid. The aqueous extract was then made basic with 10 *M* potassium hydroxide and the product extracted with four portions of ether. The combined extract was dried over potassium carbonate and the ether distilled. Unchanged tetramethylpiperidine was removed by distillation at 40–60° at 15 mm. The residue which remained was dissolved in ether, filtered, and treated with hydrogen chloride to give 0.8 g. (23%) of white leaflets melting at 207–210°. An analytical sample, 207–209° was prepared by an additional recrystallization from acetone–ether. Some impure hydrochloride from a different run was converted to the free base with aqueous potassium hydroxide. The resulting oily-looking crystals, m.p. 64–70°, were extremely soluble in most organic solvents. Sublimation at 0.1 mm. led to no significant purification. Loose crystals which gave a fairly satisfactory analysis were obtained by washing the crude material with methanol at −8°. The product melted at 72–77°.

***N*-(1,2,2,6,6-Pentamethyl-4-piperidinyl)-1-tosyl-5-pyrrolidone-2-carboxamide (XXIIIb).**—*N*-Tosyl-L-pyrrolid-5-one-2-carbonyl chloride[25] (3.0 g., 0.01 mole) in 10 ml. of chloroform was cooled in an ice bath and treated dropwise with 1,2,2,6,6-pentamethyl-4-aminopiperidine (1.70 g., 0.01 mole). After 40 min. at room temperature, 10 ml. of ethyl acetate was added and the mixture poured into 50 ml. of ether. The precipitated hydrochloride was collected and washed with ether and ligroin. When dry it weighed 4.6 g., m.p. 198–215°. The filtrate deposited an additional 500 mg., m.p. 201–214° dec. As no suitable solvent for purifying this salt could be found, it was dissolved in 50 ml. of water, made basic with 5% sodium bicarbonate and the product extracted into 150 ml. of ether. The solvent was then removed on the steam bath and the residue crystallized from 25 ml. of benzene. The product weighed 3.15 g. (73%) and melted at 198–203°. Two additional recrystallizations from benzene gave analytically pure material, m.p. 208,° $[\alpha]^{26.5}D$ −75.7° (*c* 1, in 1% acetic acid).

**1,2,2,6,6-Pentamethyl-4-(*N*-tosyl-L-α-glutamylamino)-piperidine (XXIV).**—The preceeding compound (14.6 g.) was dissolved in 50 ml. of methanol and stirred vigorously while a solution of 11.1 g. (0.065 mole) of barium hydroxide in the minimum amount of water was quickly added. A thick white precipitate separated immediately. After 10 min. at room temperature the solid was dissolved by the addition of 350 ml. of water. After an additional 15 min., carbon dioxide was bubbled through the solution until the precipitation of barium carbonate appeared to be complete. The *p*H was then adjusted to 8 with ammonium hydroxide and the barium carbonate filtered. Evaporation of the solvent on a rotating evaporator at 15 mm. gave a glassy residue which was dissolved in 220 ml. of acetone. The crystals which separated on standing overnight weighed 13.4 g. (90.5%). After recrystallization from methanol–acetone the melting point was 200–215° dec., $[\alpha]^{26.5}D$ +20.6° (*c* 1, in water). The product from a second run had the same melting point and infrared spectrum but the specific rotation was +27.0°.

NOTE ADDED IN PROOF. Triacetonamine azine (VIa) has been reported previously by R. M. Haines and W. A. Waters, *J. Chem. Soc.*, 3221 (1958).

(36) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2298 (1940).

# 2-Sulfobenzoic Acid Esters. I. 2-Sulfamyl Derivatives

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*Received December 1, 1961*

Improved syntheses of 2-sulfamylbenzoic acid esters and a number of substituted derivatives are described. Isomeric sulfamylbenzoates and carbamyl and sulfonyl analogs have also been prepared.

This paper describes some new general methods of synthesis of sulfamylbenzoates, and the preparation of a number of derivatives and related compounds. Our work was prompted by the discovery in these laboratories that certain compounds of this type possessed marked anticonvulsant activity.[1]

The known methyl and ethyl esters of 2-sulf-

(1) Unpublished results. We are indebted to Dr. A. Kandel and coworkers for carrying out the pharmacological examination of these compounds. The study of these compounds was prompted by the biological activity displayed by a related series of compounds (Part II of this series) kindly supplied to us by Dr. Glenn H. Hamor of the University of Southern California.

amylbenzoic acid (I) can be prepared in high yield by passing hydrogen chloride into a refluxing solution of saccharin in the appropriate alcohol.[2] However, application of this technique to the synthesis of the isopropyl ester gives less than 2% yield of product.

Two general procedures have been devised (Fig. 1) which not only facilitate the synthesis of the various esters, including those which could only be poorly prepared by the direct route described above, but also allow the synthesis of *N*-alkylsulfamyl compounds. It is not possible to prepare these latter substances by alkylation of I, because under the influence of base, I is immediately converted to saccharin.

For the preparation of the sulfamylbenzoates by route (a) (Fig. 1.), sulfobenzoic anhydride is heated with phosphorus pentachloride, giving a mixture of the two dichlorides.[3] Warming of this mixture with the appropriate alcohol gives the carboxylic ester, II. There was no evidence of sulfonic ester formation, even when an excess of the alcohol was employed. Treatment of II with excess *anhydrous* ammonia gives I in over-all yields of 40–60% (based on sulfobenzoic anhydride). Reaction of the sulfonyl chloride with *aqueous* ammonia leads only to saccharin.

Sulfobenzoic acid can also be used as the starting material in this sequence, but the yield of mixed dichlorides is much lower than when the anhydride is used.

The sequences of reactions can be modified, as shown in route (b), Fig. 1. Sulfobenzoic anhydride

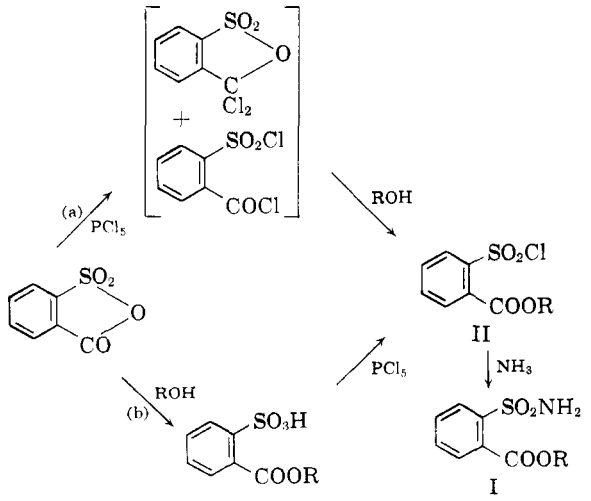



Figure 1

readily reacts with alcohols to give the carboxylic esters. Subsequent treatment with phosphorus pentachloride gives the sulfonyl chloride II, which is then carried through as shown.

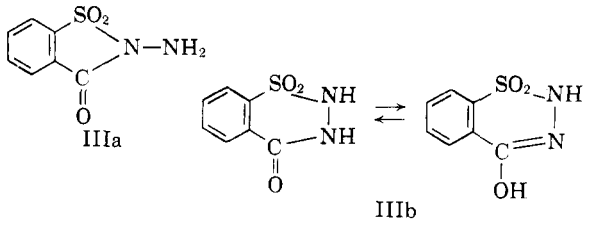
(2) I. Remsen and A. R. L. Dohme, *Am. Chem. J.*, **11**, 345 (1889); C. Fahlberg and R. List, *Ber.*, **20**, 1603 (1887).

(3) R. List and M. Stein, *Ber.*, **31**, 1649 (1898); I. Remsen *Am. Chem. J.*, **30**, 247 (1903); I. Remsen, *ibid.*, **18**, 791 (1896).

By either route, it is unnecessary to isolate or purify any of the intermediates.

The sulfamyl *N*-alkyl derivatives (compounds 6 and 7) are prepared by substituting the appropriate amine for ammonia in the last step. The sulfamyl *N*-acetyl derivatives (compounds 5 and 6) are prepared by refluxing the sulfamylbenzoates with acetic anhydride.

Attempts to prepare a sulfhydrazide analoge, by reaction of II (R = isopropyl) with hydrazine, led instead to a substance whose analysis corresponds to IIIa or IIIb.




The product has been assigned structure IIIb on the basis of its solubility in dilute base, and the marked similarity of its infrared spectra to that of phthalazine-1,4-dione.

Several of the isomeric sulfamylbenzoates were also prepared for comparative purposes. In the *meta* series, only the ethyl ester had previously been reported.[4] The *meta* methyl and isopropyl sulfamylbenzoates (Table I, compounds 8 and 9) are obtained by reaction of the dichloride with the appropriate alcohol, followed by treatment with anhydrous ammonia. The methyl ester[5] of the *para* isomer (compound 10) is prepared by brief reflux of a methanolic solution of *n*-sulfamylbenzoic acid containing a mineral acid catalyst. For the synthesis of the isopropyl ester (compound 11), prolonged heating under pressure was necessary.

Attempts to prepare *t*-butyl esters of the isomeric sulfamylbenzoic acids by the above procedures, or by reaction of the acid chlorides with *t*-butyl alcohol in the presence of acid scavengers, were unsuccessful.

The results of our attempts to synthesize aromatic esters of 2-sulfamylbenzoic acid will be described in Part III of this series.

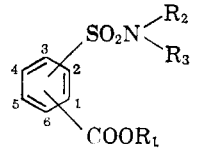
The 4-chloro-2-sulfamylbenzoic acid ester is prepared by diazotization of the corresponding 4-amino compound[6] under carefully controlled conditions. When the diazotization is carried out in the customary manner, *i.e.*, in the cold with slow addition of one equivalent of sodium nitrite, the compound isolated in high yield is a diazo coupling product whose analysis corresponds to the structure IVa or IVb (Fig. 2). Similar coupling products of

(4) W. Steinkopf, *et al.*, *J. prakt. Chem.*, **117**, 1 (1927).

(5) W. Scheele, M. Fredenhagen, and T. Timm, *Kunststoffe*, **39**, 109 (1949); *Chem. Abstr.*, **43**, 5995 (1949).

(6) First prepared by G. H. Hamor and M. Janfaza. Thesis of M. Janfaza, 1957, School of Pharmacy, University of Southern California. Our synthesis of this compound will be discussed in Part II of this series.

TABLE I. SULFAMYLBENZOIC ACID ESTERS



| No. | Position of Substituents | $R_1$ | $R_2$ | $R_3$ | M.P. | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1,2 | Me | H | H | 122–124[a] | 44.64 | 4.22 | 44.60 | 4.51 |
| 2 | 1,2 | Et | H | H | 80–82[b] | 47.15 | 4.84 | 47.10 | 4.81 |
| 3 | 1,2 | *i*-Pr | H | H | 72–75 | 49.37 | 5.39 | 49.57 | 5.55 |
| 4 | 1,2 | $C_2H_5SO_2C_2H_4$ | H | H | 115–117 | 41.11 | 4.70 | 41.11 | 4.70 |
| 5 | 1,2 | *i*-Pr | Ac | H | 117–122 | 50.51 | 5.30 | 50.41 | 5.62 |
| 6 | 1,2 | *i*-Pr | Ac | Me | oil[c] | 52.16 | 5.72 | 52.01 | 5.73 |
| 7 | 1,2 | *i*-Pr | Me | Me | oil[d] | 53.12 | 6.32 | 52.82 | 6.42 |
| 8 | 1,3 | Me | H | H | 129–131 | 44.64 | 4.22 | 44.50 | 4.25 |
| 9 | 1,3 | *i*-Pr | H | H | 101–103 | 49.37 | 5.39 | 49.59 | 5.55 |
| 10 | 1,4 | Me | H | H | 181–183[e] | 44.64 | 4.22 | 44.78 | 4.32 |
| 11 | 1,4 | *i*-Pr | H | H | 133.5–136 | 49.37 | 5.39 | 49.60 | 5.63 |

[a] Lit.,[2] m.p. 124–125°. [b] Lit.,[2] m.p. 83°. [c] $n^{25}D$ 1.5264. [d] $n^{23}D$ 1.5197. [e] Lit.,[5] m.p. 181–182°.

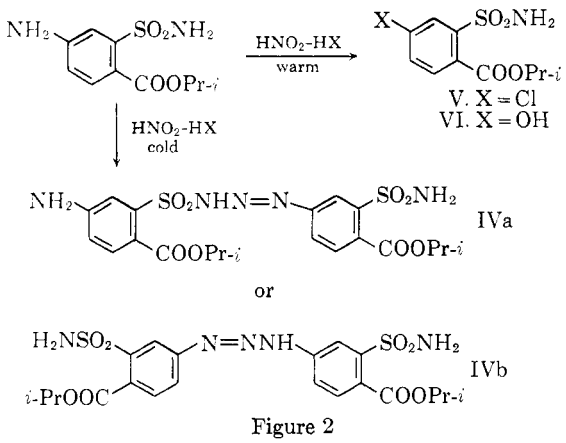



Figure 2

amines and sulfonamides have been reported previously.[7] When, however, the diazotization is carried out rapidly, using an excess of nitrous acid at room temperature, the chloro derivative V is obtained in high yield.

The 4-hydroxy-2-sulfamylbenzoic acid ester is prepared using similar diazotization conditions followed by hydrolysis in strongly acidic solution.

The 4-methyl-5-chloro-2-sulfamylbenzoate (VIII) is prepared from 5-methyl-4-chlorosulfanilic acid utilizing the procedure developed for the synthesis of the unsubstituted sulfamylbenzoates (Fig. 3).

Isopropyl 4-methyl-2-sulfamylbenzoate (VII) is prepared by reductive dehalogenation of the sulfanilic acid and thence *via* the sequence shown in Fig. 3.

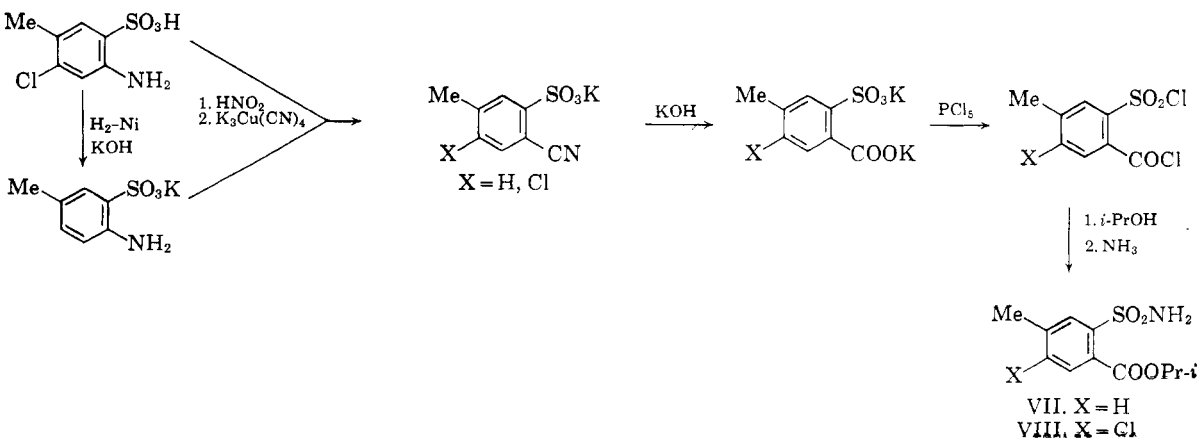
The isomeric 5-methyl-2-sulfamylbenzoate (compound 15) is similarly prepared from 4-methyl-5-chlorosulfanilic acid.

To study further the effect of structural variation on biological activity, two analogs of I were prepared in which the sulfamyl group was replaced by the carbamyl and by the sulfonyl group.

Attempts to prepare the carbamyl analog (IX) *via* phthalamic acid led only to phthalimide (Fig. 4). The compound was finally prepared using a procedure similar to that described earlier for the sulfamylbenzoate series (route b, Fig. 1).

(7) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, 1944, p. 587.

Figure 3



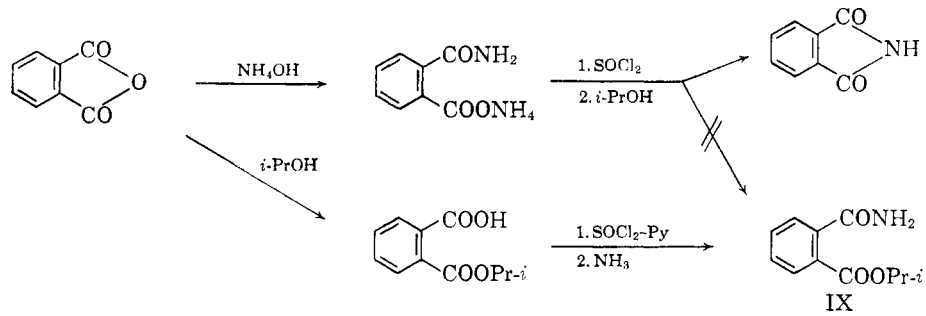
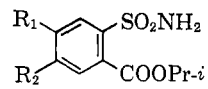



Figure 4

TABLE II. RING SUBSTITUTED 2-SULFAMYLBENZOIC ACID ESTERS




| No. | $R_1$ | $R_2$ | M.P. | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| 12 | Cl | H(V) | 142–144 | 43.24 | 4.36 | 43.53 | 4.59 |
| 13 | HO | H(VI) | 167.5–168.5 | 46.32 | 5.05 | 46.44 | 5.14 |
| 14 | Me | H(VII) | 90–92 | 51.34 | 5.88 | 51.04 | 6.07 |
| 15 | H | Me | 85–87 | 51.34 | 5.88 | 50.88 | 5.98 |
| 16 | Me | Cl(VIII) | 152–155 | 45.28 | 4.84 | 45.38 | 5.15 |

The methylsulfonyl analog X is readily prepared as outlined in Fig. 5.

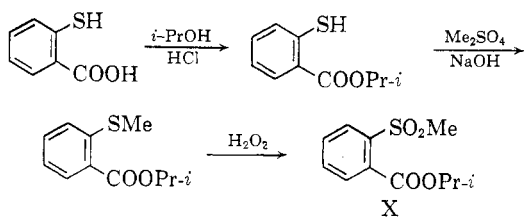



Figure 5

**Structure–Activity Relationships.**[1]—In mice, the otherwise unsubstituted *o*-sulfamylbenzoates were the most potent anticonvulsants, as indicated by their effect on prevention of maximal electric shock. The *meta* isomer was much less potent, and the *para* isomer was essentially devoid of activity. In the *ortho* series, the isopropyl ester was the most potent, and the methyl and ethyl esters were much less potent in that order. Substitution on the sulfamyl group markedly increased undesirable side effects.

The carbamyl and methylsulfonyl analogs showed weak but similar activity.

## Experimental[8]

**2-Sulfamylbenzoic Acid Esters. A. From Saccharin at Atmospheric Pressure (Compounds 1, 2, and 4).**—Gaseous hydrogen chloride was passed into a suspension of 0.1 mole of saccharin in 75 ml. of the appropriate alcohol, while cooling, until the alcohol was saturated. The mixture was then heated on the steam bath until the saccharin dissolved (2–6 hr.). The excess alcohol was removed by heating *in vacuo*. On treatment of the residue with ethyl acetate, unchanged saccharin separated and was removed by filtration. The ethyl acetate was removed *in vacuo*, and the residual solid was recrystallized from the appropriate alcohol and water. By this procedure the methyl ester (compound 1) was prepared in 74% yield, the ethyl ester (compound 2) in 48% yield, and the ethylsulfonylethyl ester (compound 4) in 25% yield. Under these conditions the isopropyl ester (compound 3, I) was formed in about 2% yield. After most of this work was completed, it was found that by the use of 5 ml. of methanesulfonic acid in place of the hydrogen chloride, and a reflux period of 18 hr., a 90% yield of I was obtained.

**B. From Saccharin under Pressure (Compound 3).**—A cooled suspension of 18.6 g. of saccharin in 70 ml. of isopropyl alcohol was saturated with hydrogen chloride, then heated in a closed vessel at 100°. The reaction is readily followed by noting the disappearance of the suspended saccharin. After 4 days, the reaction mixture was worked up as above to give a 70% yield of compound 3.

**C. From Sulfobenzoic Anhydride *via* the Dichloride (Route a).**—A mixture of 72.5 g. (0.395 mole) of *o*-sulfobenzoic anhydride[9] and 104.0 g. (0.5 mole) of phosphorus pentachloride was gently warmed on the steam bath until the reaction mixture became fluid, and then heated at reflux for 6 hr. The phosphorus oxychloride was removed by heating *in vacuo*, then the residual oil was taken up in ether and rinsed with ice water to remove unreacted phosphorus pentachloride. The solvent was removed *in vacuo*, leaving 84.5 g. (90% yield) of a thin oil that solidified on cooling, m.p. 53–59°. The reported melting point[3] for the mixture of *o*-chlorosulfonylbenzoyl chloride (m.p. 40°) and 1,1-dichlorosulfobenzoic anhydride (m.p. 79–80°) is m.p. 20–21°. The crude mixture was used in the next step.

A solution of 5 g. (0.021 mole) of the mixed *o*-sulfobenzoic acid dichlorides in 25 ml. of isopropyl alcohol was heated at 45° for 2 hr. The solution was concentrated under reduced pressure and the oily residue of crude isopropyl 2-chlorosulfonylbenzoate (II) was dissolved in ether and poured into a saturated solution of ammonia in ether and left at room temperature for 2 days. Some ammonia salt of saccharin separated and was removed by filtration. The filtrate was concentrated to give 2.65 g. (52%) of an oil which solidified on cooling and which was recrystallized from isopropanol–water to give compound 3.

**D. From Sulfobenzoic Anhydride *via* Alcoholysis (Route b).**—A suspension of 36.8 g. (0.2 mole) of *o*-sulfobenzoic anhydride in 70 ml. of isopropyl alcohol was heated until all

(8) All melting points corrected. The analyses were performed by D. Rolston and her staff of these laboratories.

(9) Eastman Organic Chemicals, Rochester, N. Y.

of the solid dissolved and then for an additional 20 min. The solution was concentrated under reduced pressure to give 48.8 g. of a pale yellow sirup which crystallized on standing to give the isopropyl *o*-sulfobenzoate, a very hygroscopic solid, m.p. 35–45°. The ester was heated with 104 g. (0.5 mole) of phosphorus pentachloride for 2.5 hr. on a steam bath and then the phosphorus oxychloride was removed under reduced pressure. The residue was dissolved in ether, rinsed with ice water several times, dried with magnesium sulfate, and concentrated to give 46.7 g. (89%) of isopropyl 2-chlorosulfonylbenzoate as a yellow oil. The oil was treated with ammonia as described before to give compound 3, identical with that prepared by the other routes.

**m-Sulfamylbenzoic Acid Esters (Compounds 8 and 9).**—These esters were prepared from the commercially available[9] *m*-chlorosulfonylbenzoyl chloride by a procedure essentially identical with that described for the 2-sulfamylbenzoic acid esters (method c). The methyl ester (compound 8) was prepared in 51% yield, the isopropyl ester in 72% yield.

**p-Sulfamylbenzoic Acid, Methyl Ester (Compound 10).**—A suspension of 6 g. (0.03 mole) of *p*-sulfamylbenzoic acid[9] in 35 ml. of methanol containing 0.5 ml. of concd. sulfuric acid was refluxed overnight. The dark solution was cooled and a solid separated. The ester was recrystallized from methanol–water, 5.3 g. (88% yield).

**p-Sulfamylbenzoic Acid, Isopropyl Ester (Compound 11).**—Hydrogen chloride was bubbled into a suspension of 20.1 g. of *p*-sulfamylbenzoic acid[9] in 50 ml. of isopropyl alcohol for 15 min. The suspension was then heated at 70° in a pressure bottle for 2 days. The solid remaining at the end of this period was separated by filtration, and 14 g. of starting material was recovered. The filtrate was concentrated under reduced pressure providing 5 g. (20%) of crude material, m.p. 132–135°. The solid was dissolved in ethyl acetate and washed with 5% sodium carbonate and then with water. It was then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The solid residue was recrystallized from methanol–water, 2 g. (8% yield).

**2-(*N*,*N*-Dimethylsulfamyl)benzoic Acid, Isopropyl Ester (Compound 7).**—A mixture of 48.8 g. (0.2 mole) of isopropyl 2-sulfobenzoate, prepared as described earlier, and 104 g. (0.5 mole) of phosphorus pentachloride was heated on the steam bath for 2.5 hr. The phosphorus oxychloride was removed under reduced pressure. For further purification the oil was dissolved in toluene and the toluene then removed by distillation, then the oil was dissolved in ether and the ethereal solution rinsed with water, dried, filtered, and concentrated to give 46.7 g. (89%) of *o*-(chlorosulfonyl)benzoic acid, isopropyl ester, isolated as a yellow oil.

A solution of 8.75 g. (0.033 mole) of the sulfonylchloride in ether was added to an excess of a solution of dimethylamine in ether. The reaction was very vigorous.

The resulting suspension was left at room temperature for 12 hr., then concentrated under a nitrogen stream. The residue was extracted with ethyl acetate. The solvent was then distilled out and an oil was obtained which failed to crystallize. It was redissolved in ethyl acetate, rinsed with water and 5% solution of sodium bicarbonate, dried, and chromatographed through a column of neutral alumina (Woelm, nonalkaline, activity grade No. 1) using benzene as the eluting solvent. The product was a viscous oil, $n^{23}D$ 1.5197.

**2-(*N*-Acetylsulfamyl)benzoic Acid, Isopropyl Ester (Compound 5).**—A suspension of 8.05 g. (0.033 mole) of *o*-sulfamylbenzoic acid, isopropyl ester in 40 ml. of acetic anhydride was refluxed for 2 hr.; the solid dissolved after 10 min. The excess acetic anhydride was eliminated under reduced pressure leaving a clear oily residue which crystallized on standing and was recrystallized from isopropyl alcohol–water 7.85 g. (82%).

**2-(*N*-Acetyl-*N*-methylsulfamyl)benzoic Acid, Isopropyl Ester (Compound 6).** A solution of isopropyl 2-chlorosulfonylbenzoate in ether was converted to the 2-(*N*-methylsulfamyl)benzoate by reaction with a solution of methylamine in ether, in the same manner as already described for compound 7. The product was an oil. This oil was chromatographed over neutral alumina, using benzene as eluent, and the fractions having the same refractive index ($n^{24}D$ 1.5293) were combined. Since the analysis of this oil was slightly off, it was converted to the *N*-acetyl derivative. A solution of 4.0 g. (0.0155 mole) of 2-(*N*-methylsulfamyl)-benzoic acid isopropyl ester in 10 ml. of acetic anhydride was refluxed for 2 hr. The solution was concentrated under reduced pressure, and the residue dissolved in benzene and passed through a chromatography column (Woelm nonalkaline alumina). The fractions having the same refractive index were combined, 3.7 g. (80%) of a colorless oil.

**1,2,3-Benzothiadiazin-4(3*H*)-one 1,1-Dioxide (III).**—A solution of 1.5 g. (0.05 mole) of hydrazine in ether was added to an etheral solution of 6.6 g. (0.025 mole) of 2-chlorosulfonylbenzoic acid isopropyl ester. The resulting mixture was left in the refrigerator for 2 days during which time a yellow oil separated. The volatile materials were removed under a nitrogen stream leaving an oil. This oil was treated again with excess ether–hydrazine, and the resulting oil now solidified on cooling. The solid (a hydrazine salt) was soluble in water; on acidification of the aqueous solution a white solid separated. It was recrystallized from ethyl acetate–hexane, to give 1.8 g. (36% yield) of the product, m.p. 212–215°.[10]

*Anal.* Calcd. for $C_7H_6N_2O_3S$: C, 42.42; H, 3.05; N, 14.14. Found: C, 42.59; H, 3.43; N, 14.39.

**Isopropyl 4-chloro-2-sulfamylbenzoate (Compound 13).**—Isopropyl 4-amino-2-sulfamylbenzoate[6] (0.0051 mole) was dissolved in 5 cc. of 3:1 hydrochloric acid and cooled to 15°. To this was added at once a solution of 0.35 g. (0.0051 mole) of sodium nitrite in 10 cc. of water. A pale yellow solution resulted. After stirring at 15° for 2 to 10 min., the solution was poured as rapidly as the temperature rise permitted into a solution of 0.6 g. of cuprous chloride in 10 cc. of concd. hydrochloric acid at 60–70°. Considerable foaming occurred. The mixture was heated at 85° and then cooled and the solid filtered and rinsed with water. The resulting cream-colored solid was recrystallized from isopropyl alcohol–hexane (80% yield).

**Diazo Coupling Product. IV.**—To a suspension of 1 g. of 4-amino-2-sulfamyl benzoic acid, isopropyl ester[6] in 10 ml. of 2% sodium bicarbonate, was added 1 g. of concd. sulfuric acid; this mixture was cooled in an ice bath and to it was added a solution of 0.35 g. of sodium nitrite in 10 ml. of water, keeping the temperature at 5°. The color of the solution changed to yellow. The solution was warmed to room temperature and, after the addition of 1 ml. of concd. hydrochloric acid, the mixture was heated on a steam bath for 1.5 hr. A solid separated during this time and was filtered, m.p. 184–187° dec. It was recrystallized from acetonitrile–water, m.p. 212–213° dec., 0.4 g.

*Anal.* Calcd. for $C_{20}H_{25}N_5O_8S_2$: C, 45.60; H, 4.25; N, 13.60. Found: C, 46.03; H, 4.06; N, 13.25.

**Isopropyl 4-Hydroxy-2-sulfamylbenzoate (Compound 13).**—Isopropyl 4-amino-2-sulfamylbenzoate (1 g.) was diazotized as described under the preparation of compound 12. The diazonium solution was added to a boiling solution of 4 cc. of concd. sulfuric acid in 20 cc. of water. After boiling for 5 min., the mixture was chilled and the solid filtered, m.p. 160–165°, 0.25 g. The filtrate was extracted with ether and ethyl acetate giving an additional 0.1 g., m.p. 160–163°.

The solids were combined and extracted with hot benzene. Addition of hexane to the chilled filtrate gave crystals, m.p. 153–155°. The benzene-insoluble solid was dissolved in hot water, and reprecipitated on chilling, giving a small amount of orange crystals, m.p. 167.5–168.5°. The analysis and infrared spectra of both were identical. The yield of the higher melting crystals was 20%. Attempts to carry out the reaction on a larger scale have been unsuccessful.

(10) H. A. Offe, W. Siefken, and G. Domagk, *Z. Naturforsch.*, **7b**, 446 (1952); *Chem. Zentr.*, **124**, 553 (1953) list a sulfobenzoic acid hydrazide, m.p. 210°, which is probably the same compound.

**5-Chloro-4-methyl-2-sulfamylbenzoic Acid, Isopropyl Ester (VIII).**—A mixture of 20.7 g. (0.1 mole) of 6-amino-4-chloro-3-methyl-benzenesulfonic acid (Antara Chemicals) (54% purity) and 5.3 g. (0.05 mole) of sodium carbonate in 300 ml. of water was warmed until bubbling had ceased. The dark solution was diluted to 400 ml., chilled to 20°, and to this was then added a solution of 6.9 g. (0.1 mole) of sodium nitrite in 40 ml. of water. After further cooling to 10°, 35 g. of concd. sulfuric acid was added, and stirring and cooling were continued for 30–35 min.; the solid that separated was filtered, the solid diazonium salt was stirred with cold water and filtered again. The diazonium salt was suspended in ice water and added to a solution of 6.5 g. of cuprous cyanide and 13 g. of potassium cyanide in 125 ml. of water, to give a red-brown solution which was heated for 30 min. at 70–80°. On cooling, 10 g. of a tan granular precipitate was obtained; another 2 g. of the salt of 4-chloro-3-methyl-6-cyanobenzenesulfonic acid was obtained by addition of salt to the filtrate.

The solid was suspended in 50 ml. of 10% sodium hydroxide and heated at reflux for 2 hr. On acidification, 7 g. (4% yield) of a tan precipitate separated, 4-methyl-5-chloro-2-sulfobenzoic acid, sodium salt.

This sodium salt (6.6 g.) was converted to the corresponding dichloride, on heating with phosphorus pentachloride, in a manner similar to that described earlier. The dichloride was obtained, m.p. 63–68°, 5.75 g. (82% yield).

The dichloride was dissolved in 25 ml. of isopropyl alcohol and heated at 45–50° for 30 min.; the solution was concentrated under reduced pressure and the residual oil solidified on standing, m.p. 78–80°; this yellow solid, isopropyl 4-methyl-5-chloro-2-chlorosulfonylbenzoate, was dissolved in ether, poured into ammonium saturated ether and ammonia was bubbled through for 10 min. The excess ammonia and ether were eliminated by blowing nitrogen over the suspension; the residual solid was extracted with ethyl acetate. Concentration provided a solid, m.p. 79–140°.

On chromatographing over neutral alumina (Woelm) using benzene as solvent, this solid separated into the desired product, isopropyl 5-chloro-4-methyl-2-sulfamylbenzoate (VIII) (compound 16), (1.7 g., 24% over-all yield based on sulfobenzoic acid), and unchanged isopropyl 5-chloro-4-methyl-2-sulfonylbenzoate, m.p. 92–94°.

*Anal.* Calcd. for $C_{11}H_{12}Cl_2O_4S$: C, 42.45; H, 3.89. Found: C, 42.36; H, 4.02.

**4-Methyl-2-sulfamylbenzoic Acid, Isopropyl Ester.**—A solution of 41 g. (purity 54%) (0.1 mole) of 6-amino-4-chloro-3-methylbenzenesulfonic acid (Antara Chemicals) in a mixture of 12 g. of potassium hydroxide, 400 ml. of water, and 25 ml. of methanol, was reduced using several grams of Raney nickel.[11] The theoretical amount of hydrogen was absorbed. The suspension was filtered and the filtrate concentrated under reduced pressure; 1.7 g. of starting material was recovered. Upon further concentration, 17 g. (75% yield), of a white solid was obtained, 6-amino-3-methylbenzenesulfonic acid, potassium salt.

To a solution of this salt in 100 ml. of water was added 6.9 g. (0.1 mole) of sodium nitrite; the temperature was kept at 10° while sulfuric acid (20 ml.) was added; almost immediately a cream-colored solid separated and after 30 min. of stirring, the suspension was filtered, the solid suspended in water and filtered again. This solid, diazonium salt, was added to a solution of 6.5 g. of cuprous cyanide and 13 g. of potassium cyanide in 50 ml. of water. The resulting brown solution was kept at 70–80° for 30 min. and concentrated under reduced pressure; on cooling a dark yellow solid separated, the 6-cyano-3-methyl-benzenesulfonic acid, potassium salt. This salt was dissolved in 65 ml. of 10% sodium hydroxide and refluxed for 5 hr.; on acidification, some starting material separated and was removed. On concentration and chilling, there was obtained 12 g. (48%) of 4-methyl-2-sulfobenzoic acid, potassium salt.

This solid (0.0485 mole) was mixed with 30 g. of phosphorus pentachloride (0.145 mole) and heated at 90° for 3 hr. The phosphorus pentachloride was removed under reduced pressure. The residue was dissolved in ether, the ethereal solution rinsed with ice water, dried over magnesium sulfate, and concentrated to give 5.6 g. (45%) of 4-methyl-2-chlorosulfonylbenzoyl chloride. The oil was dissolved in 25 ml. of isopropyl alcohol and heated at 55° for 45 min. The resulting solution was concentrated under reduced pressure to give isopropyl 4-methyl-2-chlorosulfonylbenzoate as an oil. This oil was dissolved in ether and treated with excess ammonia for 3 days. The suspension was filtered and the filtrate concentrated, giving 2.8 g. (50% yield) of an oil that crystallized on standing and was recrystallized from isopropyl alcohol–water, 1.9 g. (34% yield). Further dilution of the filtrate after separating 4-methyl-2-sulfamylbenzoic acid, isopropyl ester, gave a small sample of 4-methyl-5-chloro-2-sulfamylbenzoic acid, isopropyl ester.

**5-Methyl-2-sulfamylbenzoic Acid, Isopropyl Ester (Compound 15.).**—This compound was prepared from 6-amino-3-chloro-4-methylbenzene sulfonic acid (Antara Chemicals) in 7% over-all yield by exactly the same procedures as was the 4-methyl isomer.

**Isopropyl Phthalamate. X. A. Attempt *via* Phthalamic Acid.**—Ammonium phthalamate,[12] 20 g., was added portionwise and with stirring to 75 g. of thionyl chloride. Vigorous bubbling resulted, with formation of a thick suspension and mild heat evolution. The suspension was stirred 8 hr., then diluted with some benzene and filtered. The precipitate was washed with water and dried, and corresponded to a quantitative yield of phthalimide.

**b. Synthesis *via* Isopropyl Hydrogen Phthalate.**—A 90-g. sample of phthalic anhydride (0.607 mole) and 40 g. of isopropyl alcohol (0.67 mole) were refluxed until all of the anhydride had dissolved, and then for an additional 8 hr. The solution was poured into a mixture of 55 cc. of 40% sodium hydroxide and ice, and the resulting clear solution was extracted with ether. Evaporation of this extract gave 5 g. of an oil, undoubtedly the diisopropyl ester. The aqueous solution was acidified, and then extracted with chloroform. After drying and evaporation, 92 g. (71%) of hard, white crystalline isopropyl hydrogen phthalate was obtained, m.p. 78.5–80.5°.

The ester (44 g., 0.212 mole) was dissolved in 300 cc. of benzene containing 20 g. (0.2 mole) of triethylamine and the solution was cooled to 5°. To this was added 23.8 g. (0.2 mole) of thionyl chloride, the temperature being maintained at less than 15° by external cooling. After the addition was complete, the suspension was stirred at room temperature for 4 hr., then the amine hydrochloride was filtered off (24 g.). To this filtrate was added some ethereal ammonia to remove any traces of unchanged acids present, and the solution was filtered again.

The filtrate was evaporated giving 37.5 g. of an oil that crystallized on stirring, m.p. 80–90°. The brown solid was heated and triturated with isopropyl ether, and was thereby transposed to a white solid, m.p. 109–110°. After recrystallization from benzene–hexane there was obtained 7.1 g. (16% yield) of the phthalamate as tan needles, m.p. 109.5–110.5°. From the filtrate there could be obtained an additional 8 g. of impure phthalamate.

*Anal.* Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32. Found: C, 63.99; H, 6.52.

***o*-Mercaptobenzoic Acid, Isopropyl Ester.**—A suspension of 30.8 g. (0.2 mole) of technical thiosalicylic acid (Eastman Organic Chemicals) in 125 ml. of isopropyl alcohol was heated in a pressure bottle at 65–70° for 3 days. The dark solution was concentrated under reduced pressure and the residual oil was dissolved in hexane to precipitate 3 g. of unchanged starting material. The filtrate was concentrated under reduced pressure and distilled; a single fraction was

(11) H. Kämmerer, L. Horner, and H. Beck, *Ber.*, **91**, 1376 (1958).

(12) E. Chapman and H. Stephen, *J. Chem. Soc.*, 1791 (1925).

obtained, b.p. 106–107°/1.0–1.8 mm., $n^{23}D$ 1.5558, 21.6 g. (55%); this was redistilled to provide an analytical sample, b.p. 90°/0.25 mm., $n^{23}D$ 1.5550.

*Anal.* Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16. Found: C, 60.88; H, 6.14.

**o-Methylmercaptobenzoic Acid, Isopropyl Ester.**—To 19.62 g. (0.1 mole) of *o*-mercaptobenzoic acid isopropyl ester was added 40 ml. of 10% solution of sodium hydroxide (0.1 mole); the oil dissolved and the resulting solution solidified on cooling. To this cold solid was added 13.8 g. (0.11 mole) of methyl sulfate. The reaction was exothermic and a water-insoluble oil was obtained. The reaction mixture was heated in a steam bath for approximately 15 min.; the oil was extracted with ether and the ether solution was dried and then concentrated under reduced pressure to give a crude product, $n^{24}D$ 1.5569; 20.95 g. (99%); a sample of this was distilled to provide an analytical sample, b.p. 136°/1.2 mm., $n^{23}D$ 1.5598.

**2-Methanesulfonylbenzoic Acid, Isopropyl Ester.**—To the solution of 10.5 g. (0.05 mole) of 2-methylmercaptobenzoic acid isopropyl ester in 25 ml. of glacial acetic acid was added 6.25 g. of 30% hydrogen peroxide, keeping the temperature at 10°. The mixture warmed up to 40–50° and was kept at this temperature during the addition of another 6.25 g. of 30% hydrogen peroxide. The mixture was heated at 70–100° for 1 hr. and then concentrated under reduced pressure. A yellow oil was obtained which crystallized on cooling and was recrystallized from ethanol–water, m.p. 86–88°, 8 g. (69%). After drying, the melting point of the analytical sample was 98–100°.

*Anal.* Calcd. for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.83; H, 5.97.

# Syntheses of 1-Aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines Involving Addition of Alkyl Halides to Substituted Epoxides

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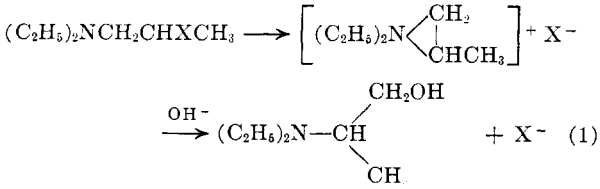
The syntheses of 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines by the reaction of benzhydryl chloride (or bromide) with 1,2-epoxy-3-methoxypropane followed by aminolysis of the resulting 1-halo-2-benzhydryloxy-3-methoxypropane with the appropriate 1-arylpiperazine have been accomplished. These are the first reported examples of this series and are the first instances of the addition of an alkyl halide to a substituted epoxide under mild experimental conditions.

The pharmacological activities of the piperazines, amino ethers, and benzhydryloxy compounds are well recognized. The amino ethers, particularly those of the ethanolamine series, have been used successfully as antihistamines. Their usefulness seems to be enhanced by the introduction of a benzhydryloxy group.[1] In recent years there has been a widespread interest in disubstituted piperazines with respect to their effect on the central nervous system. Among other examples of especially effective compounds to combat hypertension and hypertensive encephalopathy are the 1-aryl-4-(2-methoxyethyl)piperazines and 1-aryl-4-(3-methoxypropyl)piperazines.[2] The interest in the synthesis of 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl) piperazines is, therefore, readily apparent.

Attempts to prepare these ethers from the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine were unsuccessful. Alternatively, benzhydryl ethers may be prepared by the reaction of benzhydrol or its sodium salt with the appropriate halogen derivative.[3] However, it has been shown that, in the preparation and reaction of β-haloamines of this type, rearrangement through an intermediate ethylenimmonium ion occurs as indicated in equation 1.[4]



(1) (a) Robert F. Doerge, *Am. Profess. Pharmacist*, **18**, 1103 (1952). (b) George Rieveschl, Jr., U. S. Patent 2,421,714 (1947).

(2) G. m. b. H. Nordmarke-Werke, British Patent 813,473 (1958).

(3) Yoshi Uyeno *et al.*, Japanese Patent 1529 (1959).

Therefore, another synthetic route was required. Investigation of various possibilities resulted in the discovery that the reaction of the benzhydryl halide with 1,2-epoxy-3-methoxypropane yields 1-halo-2-benzhydryloxy-3-methoxypropane. Further, it was found that this intermediate reacts with the appropriate piperazine to give the desired benzhydryl ether derivative of the substituted piperazine.

Proof that this benzhydryl ether derivative of the substituted piperazine was indeed 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine could be obtained by showing it to be the same product as that obtained from the reaction of benzhydryl halide with the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine. However, an attempt to effect the latter reaction resulted in a product whose infrared spectrum showed that it was not the desired benzhydryl ether.

Consequently, the following series of reactions was carried out to give substantial proof of the structures proposed for the halo-intermediates and for the products of their reactions with 1-aryl-piperazines:

(4) (a) S. D. Doss, *J. Am. Chem. Soc.*, **69**, 2982 (1947); (b) R. H. Reitsems, *J. Am. Chem. Soc.*, **71**, 2041 (1949).