Substituted Sulfonyl Piperazines

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In view of reports in the literature on the anticonvulsant action of various sulfonyl piperazines and of certain substituted 1-sulfonyl-4-β-aminoethylpiperazines as antishock agents, a series of mono- and disulfonyl β-aminoethylpiperazines have been prepared. The compounds were obtained, in most cases, by a modified Schotten-Bauman reaction. The carbobenzyloxy blocking group was employed in the preparation of the monosubstituted compounds and was removed by catalytic hydrogenation without cleavage of the sulfonyl group.

A LARGE NUMBER of 1,4-unsymmetrically substituted sulfonyl piperazines has been prepared for various purposes. Among them are 1-ethylsulfonyl-4-ethylpiperazine (1), a compound active in the treatment of hemorrhagic or heat shock, and 1-diethylsulfonyl-4-(2′-thiazoyl)piperazine (2), active as an anticonvulsant. Jacob and Suau (3) later found that 1-substituted sulfonyl-4-β-aminoethylpiperazines were useful in the treatment of hemorrhagic and traumatic shock. The presence of a β-aminoethyl group in other piperazine compounds has, in general, provided compounds with pharmacological activity, varying from adrenergic (4) to curarimimetic (5). This agrees with many of the known antihistamines, antispasmodics, and local anesthetics in which the ethylene group between oxygen and nitrogen or nitrogen and nitrogen provides the most active compounds. This suggested that the activity of sulfonyl piperazines could possibly be enhanced by inserting a β-aminoethyl group between the sulfonyl group and the piperazine nucleus. It also appeared desirable to prepare 1-β-aminoethylpiperazines containing two sulfonyl groups. The present investigation is intended to make available for testing various arylsulfonyl compounds.

DISCUSSION

The methods which have been employed in the preparation of the disubstituted arylsulfonyl compounds have generally involved the treatment of 1-β-aminoethylpiperazine with two equivalents of an arylsulfonyl chloride in aqueous media with an inorganic base to neutralize the liberated hydrogen chloride, or in alcoholic media with pyridine as the hydrogen chloride acceptor. The second procedure was more time-consuming and did not give good yields. The products, which are described in Table I, were obtained in a good state of purity either as the free base or as the sodium salt. They also gave correct carbon-hydrogen analyses after one recrystallization. It was noted that the carbon-hydrogen analyses for 1-benzenesulfonyl-4-β-benzenesulfonamidoethylpiperazine also would be the same for the monosulfonated compound and differentiation was not possible by treating the compound with dilute acid. However, the calculated nitrogen content of the two compounds was different. The product obtained gave a correct nitrogen analysis which proved that it was disubstituted.

It was also decided to prepare the monosulfonated β-aminoethylpiperazines, i.e., 1-arylsulfonyl-4-β-aminoethylpiperazine. It is necessary, therefore, to have a blocking group present on one of the nitrogens of the piperazine ring, prior to the introduction of the β-aminoethyl group, which can be removed by a nonhydrolytic procedure.

The blocking group selected for investigation was carbobenzyloxy, since it may be cleaved from the piperazine nitrogen by catalytic hydrogenation. 1-Carbobenzyloxypiperazine was prepared by a method based on that of Goldman (6), which in turn was modified by Foye and Fedor (7). The amino group of β-aminoethyl chloride, in turn, was protected with a benzoyl group prior to its reaction with 1-carbobenzyloxypiperazine. 1-Carbobenzyloxy - 4 - β - benzamidoethylpiperazine was readily prepared and the blocking group was removed by catalytic hydrogenation in a manner similar to the one reported by Goldman and Williams (8). The hydrogenation was successfully carried out using hydrogen and 10% palladium-on-charcoal in refluxing alcohol.

The desired 1-arylsulfonyl-4-β-benzamidoethylpiperazine was obtained by shaking the 1-β-benzamidoethylpiperazine with the appropriate arylsulfonyl chloride in water with sodium hydroxide or sodium carbonate to neutralize the liberated hydrogen chloride. Hydrolysis of the benzoyl blocking group with acid also cleaved the arylsulfonyl group. The compounds obtained in this manner are shown in Table I. The equation illustrates the synthesis of 1-benzenesulfonyl-4-β-benzamidoethylpiperazine.

For comparative purposes, several new arylsulfonylpiperazine compounds were prepared. When a basic aqueous-alcoholic solution of 1-carbobenzyloxypiperazine was treated with various arylsulfonyl chlorides at room temperature a good yield, in most cases, of 1-carbobenzyloxy-4-arylsulfonylpiperazines resulted. Hydrogenation by the previously described procedure gave the 1-arylsulfonylpiperazines shown in Table II. When the catalytic hydrogenation procedure was employed for the removal of the carbobenzyloxy group from 1-

Received August 16, 1960, from the Massachusetts College of Pharmacy, Boston, and the Division of Pharmacy, South Dakota State College, Brookings.
Accepted for publication October 6, 1960.
Presented to the Scientific Section, A.PH.A., Washington, D. C., meeting, August 1960.
† Fellow of the American Foundation for Pharmaceutical Education, 1959–1960.
The authors are indebted to Dr. N. Sperber of the Schering Research Laboratories for carrying out and providing the results of a pharmacodynamic screening of the compounds.

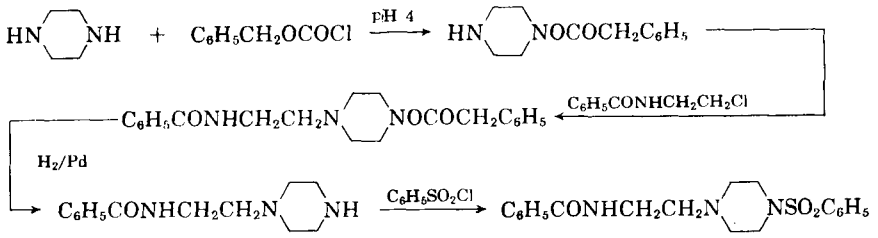
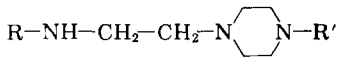


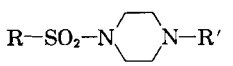
TABLE I.—SUBSTITUTED β-AMINOETHYL PIPERAZINES



R	R'	M.p.,[a] °C.	Formula	Analyses, % Calcd.	Found[b]
Benzoyl	CBzO[c]	104–105	$C_{21}H_{25}N_3O_3$	C, 68.65	68.86
				H, 6.86	6.88
Benzoyl	Benzenesulfonyl	235–239	$C_{19}H_{23}N_3O_3S$	C, 61.09	60.85
				H, 6.21	6.01
Benzoyl	*p*-Nitrobenzene sulfonyl	210–212	$C_{19}H_{22}N_4O_5S$	C, 54.69	54.85
				H, 5.28	5.65
p-Nitrobenzene-sulfonyl	*p*-Nitrobenzene-sulfonyl	207–209	$C_{18}H_{21}N_5O_8S_2$	C, 43.29	43.00
				H, 4.24	4.14
p-Aminobenzene-sulfonyl	*p*-Aminobenzene-sulfonyl	206–207	$C_{18}H_{25}N_5O_4S_2$	C, 49.18	49.07
				H, 5.73	5.87
p-Toluenesulfonyl	*p*-Toluenesulfonyl	160–162	$C_{20}H_{27}N_3O_4S_2$	C, 54.90	55.12
				H, 6.22	6.29
Benzenesulfonyl	Benzenesulfonyl	144–146	$C_{18}H_{23}N_3O_4S_2$	C, 52.86	52.90
				H, 5.67	5.73
				N, 10.27	9.95

[a] The melting points were taken on a Fisher-Johns block and are uncorrected. [b] The analyses were carried out by Weiler and Strauss, Oxford, England, and by Geller Laboratories, Bardonia, N. Y. [c] CBzO = carbobenzyloxy.

TABLE II.—SUBSTITUTED SULFONYL PIPERAZINES



R	R'	M.p.,[a] °C.	Formula	Analyses, % Calcd.	Found[b]
p-Toluene	CBzO[c]	145–147	$C_{19}H_{22}N_2O_4S$	C, 60.93	60.72
				H, 5.92	5.89
p-Toluene	H	103–105	$C_{11}H_{16}N_2O_2S$	C, 55.00	54.76
				H, 6.72	6.50
p-Toluene	Benzyl	121–123	$C_{18}H_{22}N_2O_2S$	C, 65.45	65.66
				H, 6.71	7.05
p-Nitrobenzene	CBzO	155–156	$C_{18}H_{19}N_3O_6S$	C, 53.33	53.41
				H, 4.73	4.75
p-Aminobenzene	H	210–213	$C_{10}H_{15}N_3O_2S$	C, 49.99	50.39
				H, 6.23	6.25

[a, b, c] See footnotes, Table I.

carbobenzyloxy - 4 - *p* - nitrobenzenesulfonylpiperazine it was found, as expected, that the nitro group was also reduced to an amino group. In one case the arylsulfonylpiperazine was further treated with α-chlorotoluene to give the 1-arylsulfonyl-4-benzylpiperazine.

Antishock and anticonvulsant tests have not been completed with these compounds. However, two of the compounds, 1-β-benzenesulfonamidoethyl-4-benzenesulfonylpiperazine, and 1-β-(*p*-aminobenzenesulfonamidoethyl)- 4- *p* - aminobenzenesulfonylpiperazine were inactive in a general pharmacodynamic screen and central nervous system test carried out at the Schering Research Laboratories.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns block and are uncorrected. Analyses were obtained from the Weiler and Strauss Microanalytical Laboratory, Oxford, England, and from Geller Laboratories, Bardonia, N. Y.

N-Benzoyl-β-chloroethylamine.—This compound was prepared by the procedure of Brintzinger, Pfannstiel, and Daddebusch (9). An 85% yield of white needles was obtained which melted at 105–106° as previously reported (9).

1-Carbobenzyloxypiperazine.—This compound was prepared by the procedure of Goldman and

Williams (6). A 45% yield of colorless product was obtained which boiled at 160–165° (2 mm.). The reported boiling point (6) is 158–161° (1.4 mm.).

1 - Carbobenzyloxy - 4 - β - benzamidoethylpiperazine.—A mixture of N-benzoyl-β-chloroethylamine (5.5 Gm., 0.03 mole), sodium carbonate (12 Gm.), and 1-carbobenzyloxypiperazine (6.6 Gm., 0.03 mole) in xylene (100 ml.) was refluxed for 6 hours or until carbon dioxide no longer was evolved from the reaction mixture. The excess sodium carbonate and the sodium chloride formed during the reaction were removed by filtration, and the xylene was removed by vacuum distillation. The residue was recrystallized from isopropyl alcohol to yield 9.8 Gm. (89%) of 1-carbobenzyloxy-4-β-benzamidoethylpiperazine; m.p. 104–105°.

1 - Benzenesulfonyl - 4 - β - benzamidoethylpiperazine.—In a 300-ml. three-neck flask equipped with a hydrogen inlet tube, a mechanical stirrer, and a reflux condenser was placed 3.7 Gm. (0.01 mole) of 1 - carbobenzyloxy - 4 - β - benzamidoethylpiperazine and 1 Gm. of 10% palladium-on-charcoal in 100 ml. of ethanol. The mixture was stirred and heated by an oil bath at 85° while hydrogen was bubbled in continuously. After 6 hours, when the evolution of carbon dioxide had ceased, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. A chilled aqueous solution of the residue was treated with 1.8 Gm. (0.01 mole) of benzenesulfonyl chloride and 4.0 ml. of 4 *N* sodium hydroxide. After stirring for 3 hours at room temperature, the mixture was cooled and filtered, yielding 2.1 Gm. (57%) of white crystals. The product was first recrystallized from water and then from ethanol to give white needles melting at 235–239°.

1 - *p* - Nitrobenzenesulfonyl - 4 - β - benzamidoethylpiperazine.—The hydrogenation procedure was identical with the one described for the previous preparation. A chilled aqueous solution of the residue was treated with 2.2 Gm. (0.01 mole) of *p*-nitrobenzenesulfonyl chloride and 4.0 ml. of 4 *N* sodium hydroxide. After stirring for 6 hours at room temperature, the mixture was cooled and concentrated under reduced pressure. The product was recrystallized from an alcohol-water mixture to yield 1.8 Gm. (64%) of pale yellow crystals; m.p. 210–212°.

1 - *p* - Toluenesulfonyl - 4 - carbobenzyloxypiperazine.—To a solution of 10.24 Gm. (0.04 mole) of 1-carbobenzyloxypiperazine and 7.7 Gm. (0.04 mole) of *p*-toluenesulfonyl chloride in 100 ml. of an ethanol-water mixture was added a few pellets of sodium hydroxide. The mixture was shaken for 3 hours, allowed to stand overnight, and the white precipitate was collected. Recrystallization from ethanol yielded 5.1 Gm. (34%) of 1-*p*-toluenesulfonyl - 4 - carbobenzyloxypiperazine; m.p. 145–147°.

1-*p*-Toluenesulfonylpiperazine.—A solution containing 3.74 Gm. (0.01 mole) of 1-*p*-toluenesulfonyl-4-carbobenzyloxypiperazine in ethanol was hydrogenated in an analogous manner to that previously described. The product obtained after evaporation of the alcohol was recrystallized from a methanol-water mixture. A yield of 1.3 Gm. (54%) of 1-*p*-toluenesulfonylpiperazine was obtained; m.p. 103–105°.

1 - *p* - Toluenesulfonyl - 4 - benzylpiperazine.—A mixture of 1-*p*-toluenesulfonylpiperazine (1.2 Gm., 0.005 mole), sodium carbonate (1 Gm.), and α-chlorotoluene (0.63 Gm., 0.005 mole) in xylene (50 ml.) was refluxed for 6 hours. The excess sodium carbonate and the sodium chloride were removed by filtration, and the xylene evaporated under reduced pressure. Recrystallization from methanol yielded 1.2 Gm. (75%) of pale brown platelets melting at 121–123°.

1 - *p* - Nitrobenzenesulfonyl - 4 - carbobenzyloxypiperazine.—To a solution of 10.24 Gm. (0.04 mole) of 1-carbobenzyloxypiperazine and 8.86 Gm. (0.04 mole) of *p*-nitrobenzenesulfonyl chloride in 100 ml. of ethanol was added a few pellets of sodium hydroxide. A small amount of heat was applied to the mixture to initiate the reaction. The mixture was shaken for 2 hours, and after refrigeration overnight, the white precipitate was collected. Recrystallization from ethanol yielded 14.3 Gm. (96%) of 1 - *p* - nitrobenzenesulfonyl - 4 - carbobenzyloxypiperazine; m.p. 155–156°.

1-*p*-Aminobenzenesulfonylpiperazine.—A solution containing 6 Gm. (0.015 mole) of 1-*p*-nitrobenzenesulfonyl-4-carbobenzyloxypiperazine in ethanol was hydrogenated in an analogous manner to that already described. The product obtained after evaporation of the solvent was recrystallized from ethanol. A yield of 3 Gm. (75%) of product was obtained which melted at 210–213°.

1 - β - (*p* - Nitrobenzenesulfonamidoethyl) - 4 - *p*-nitrobenzenesulfonylpiperazine.—To 6.43 Gm. (0.05 mole) of 1-β-aminoethylpiperazine[1] and 22.2 Gm (0.1 mole) of *p*-nitrobenzenesulfonyl chloride in 100 ml. of water was added sufficient sodium hydroxide to maintain an alkaline pH. The mixture was stirred for 8 hours, acidified with dilute hydrochloric acid, and the precipitate collected. Recrystallization from an ethanol-acetone mixture yielded 13 Gm. (52%) of pale yellow needles which melted at 207–209° (decompn.).

1 - β - (*p* - Aminobenzenesulfonamidoethyl) - 4-*p*-aminobenzenesulfonylpiperazine.—To a solution of 10 Gm. of stannous chloride dihydrate in 10 ml. of concentrated hydrochloric acid was slowly added 2.5 Gm. (0.005 mole) of 1-β-(*p*-nitrobenzenesulfonamidoethyl) - 4 - *p* - nitrobenzenesulfonylpiperazine. The reaction temperature was kept at 25–30° by cooling with water. After the addition was complete, and the reaction mixture had been stirred for 2 hours at room temperature, it was poured into a cold solution of 4 *N* sodium hydroxide. The resulting white precipitate was collected on a filter and recrystallized from an ethanol-water mixture. A yield of 1.8 Gm. (82%) of crystalline solid was obtained which melted at 206–207°.

1 - β - (*p* - Toluenesulfonamidoethyl) - 4 - *p*-toluenesulfonylpiperazine.—A solution of 5 Gm. (0.04 mole) of β-aminoethylpiperazine, 19 Gm. (0.1 mole) of *p*-toluenesulfonyl chloride, 100 ml. of an ethanol-water mixture, and 4 Gm. of sodium hydroxide was shaken for 3 hours at room temperature. The mixture was allowed to stand overnight at room temperature, and after cooling it was acidified with dilute hydrochloric acid. The resulting white solid was collected, dried, and recrystallized from ethanol, yielding 7.3 Gm. (43%) of product; m.p. 160–162°.

[1] Aldrich Chemical Co.

The monohydrated sodium salt of 1-β-(*p*-toluenesulfonamidoethyl) - 4 - *p* - toluenesulfonylpiperazine was obtained by filtration of the precipitate which appeared in the reaction mixture before acidification; m.p. 213-215°.

Anal.—Calcd. for $C_{20}H_{23}N_4NaO_5S_2 \cdot H_2O$: C, 50.20; H, 5.90. Found: C, 49.5; H, 5.9.

1 - β - Benzenesulfonamidoethyl - 4 - benzenesulfonylpiperazine.—This compound was prepared in a manner similar to that described in the previous procedure. A yield of 89% of colorless needles was obtained which melted at 144–146°.

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Prediction of Stability in Pharmaceutical Preparations VIII

Oil-in-Water Emulsion Stability and the Analytical Ultracentrifuge

By EDWARD R. GARRETT†

An oil-in-water emulsion clears in a centrifugal field to form a packed, semirigid "cream." Subsequently, a true oil or continuous phase is spun-out of the "cream." It is shown that rates of emulsion clearing can be stated as a function of the ultracentrifugal r.p.m. and that the rate of clearing under simple gravity can be predicted for the oil-water emulsion as initially constituted. "Bad" emulsion can be differentiated from "good" emulsion by the ready formation of a separate oil phase in the former. In the latter case, an induction period exists before a continuous oil phase is spun out at an accelerating rate, which rate is a function of the centrifugal force.

THE PREDICTION of stability in pharmaceutical preparations has largely dealt with chemical transformations (1, 2). The basic philosophy has been the application of stress or energy to promote decomposition and the following of degradation or of some property of the degradation as a function of time. This function has been linearized and the slopes of such linear plots have been used as estimates of specific rates (k). The reproducibility of such functions at varying degrees of stress would validate their use in prediction of rates under marketing or storage conditions. There are classical relations that describe the variation of such rate parameters with the degree of stress. In the cases previously discussed, a rate at a given temperature is linearized on the basis of it being first, second, etc., order and the apparent rate constant (k) or property proportional to rate constant is correlated with the absolute temperature by means of the Arrhenius expression, which in its logarithmic form is

$$\log k = -(\Delta H_a/2.303\ R)(1/T) + \log P \qquad \text{(Eq. 1)}$$

Thus the accelerated reactions can be used to evaluate the parameters of Eq. 1, i.e., ΔH_a and the resultant quantitative expression may be used to predict specific rates or functions thereof at lower temperatures.

Since the nature of the function is known from the reproducibility among the various accelerated studies, the predicted rate constants may be used in such a function to predict thermal stability at lower temperatures.

The same philosophy may be used in predicting physicochemical stability of pharmaceutical formulations where preservation of the pharmaceutical elegance is of primary interest rather than the integrity of the drug.

A case in point is a colloidal suspension or emulsion. An admirable example of an oil-water emulsion[1] (3, 4) is available commercially. It is a

Received March 27, 1961, from The Research Division, The Upjohn Co., Kalamazoo, Mich.
Accepted for publication June 15, 1961.
Presented in part at Third Annual Industrial Pharmaceutical Research Conference, Land-O-Lakes, Wis., June 1961.
The author is greatly indebted to Mrs. Lillian G. Snyder and Mrs. Kathryn G. Polzin for excellent technical assistance and to Dr. J. A. Fancher for his cooperation in procurement of Lipomul samples and rewarding discussions.
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[1] Marketed as Lipomul I.V. by Upjohn.