[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF SMITH KLINE & FRENCH LABORATORIES]

The Synthesis of Some Potential Hypoglycemic Agents[1]

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The synthesis and biological test results of several *p*-substituted phenylsulfonylureas are described.

The clinical effectiveness of *N*-(*p*-tolylsulfonyl)-*N'*-*n*-butylurea (tolbutamide) and *N*-(*p*-chlorophenylsulfonyl) - *N'* - *n* - propylurea (chlorpropamide) as oral antidiabetic agents prompted a search for similar agents with fewer side effects and of greater potency. A large number of substituted sulfonylureas has been reported[2] but the range of substituents attached to the aromatic nucleus has been fairly limited. Consequently, it was decided to prepare a group of *p*-substituted phenylsulfonylureas in which emphasis was placed on fluorinated substituents. In the past similar modifications have often proved beneficial in other classes of drugs.

In general, these sulfonylureas (Table I) were prepared from the corresponding sulfonamides and an alkylisocyanate in the presence of a basic catalyst.

The sulfonamides (Table II), in turn, were usually obtained by chlorosulfonation of an appropriately substituted benzene derivative followed by treatment with ammonia.

Although *p*-dimethylaminobenzenesulfonamide has been prepared by several investigators[3] it was found to be most conveniently prepared by treating sulfanilamide and potassium carbonate in dimethylformamide with two moles of methyl iodide. In this manner, 45–50% yields of pure sulfonamide were consistently obtained. Oxidation of this sulfonamide with aqueous hydrogen peroxide yielded N^4,N^4-dimethylsulfanilamide N^4-oxide. Efforts to prepare the corresponding sulfonylurea either by treatment of the sulfonamide *N*-oxide with isocyanate or by oxidation of *N*-(*p*-dimethylaminophenylsulfonyl)-*N'*-*n*-alkylurea with aqueous peroxide were unsuccessful. In all cases only starting material or decomposition products were isolated.

It was also shown that *p*-acetylbenzenesulfon-

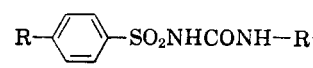
(1) This work was presented in part at the Third Delaware Valley Regional Meeting of the American Chemical Society in Philadelphia, Pa., February 25, 1960.

(2) E. Haack, *Arzneimittel-Forsch.*, **8**, 444 (1958); H. Ruschig *et al.*, *Arzneimittel-Forsch.*, **8**, 448 (1958); F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958); and D. R. Cassady *et al.*, *J. Org. Chem.*, **23**, 923 (1958).

(3) C. H. Andrewes, H. King, and J. Walker, *Proc. Roy. Soc. (London)*, **133B**, 20 (1946); P. Grammaticakis, *Bull. soc. chim. France*, **1954**, 92; and W. D. Kumler, *J. Am. Chem. Soc.*, **68**, 1184 (1946).

TABLE I

ARYLSULFONYLUREAS

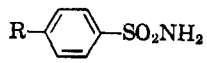


R	R'	Yield, %	Recryst. Solvent	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3SO_2	*n*-C_4H_9	56.6	95% C_2H_5OH	183–184	$C_{12}H_{18}N_2O_5S_2$	43.10	5.43	8.38	43.32	5.54	8.14
CH_3SO_2	*n*-C_3H_7	68.8	95% C_2H_5OH	201–202	$C_{11}H_{16}N_2O_5S_2$	41.23	5.03	8.74	41.26	5.26	8.74
CH_3CO	*n*-C_4H_9	43.6[a]	Toluene	148–149	$C_{13}H_{18}N_2O_4S$	52.33	6.08	9.39	52.55	6.29	9.14
CH_3CO	*n*-C_3H_7	38.0[a]	Toluene	150–153	$C_{12}H_{16}N_2O_4S$	50.69	5.67	9.85	50.66	5.57	9.29
CF_3S	*n*-C_4H_9	75.5	60% CH_3OH	119–120	$C_{12}H_{15}F_3N_2O_3S_2$	40.44	4.24	7.86	40.55	4.53	8.10
CF_3S	*n*-C_3H_7	71.5	60% CH_3OH	137–138.5	$C_{11}H_{13}F_3N_2O_3S_2$	38.59	3.83	8.18	38.79	4.00	8.19
CF_3SO_2	*n*-C_4H_9	45.3[a]	Aq. Acet.	138	$C_{12}H_{15}F_3N_2O_5S_2$	37.11	3.89	—	36.88	4.02	—
							S, 16.51			S, 16.27	
CF_3SO_2	*n*-C_3H_7	21.2[a]	Aq. Acet.	148	$C_{11}H_{13}F_3N_2O_5S_2$	35.29	3.50	—	35.43	3.30	—
							S, 17.13			S, 17.37	
CF_3O	*n*-C_4H_9	54.5	60% CH_3OH	107–109	$C_{12}H_{15}F_3N_2O_4S$	42.35	4.44	8.23	42.37	4.66	8.29
CF_3O	*n*-C_3H_7	58.5	70% CH_3OH	123–124	$C_{11}H_{13}F_3N_2O_4S$	40.49	4.02	8.59	40.62	4.30	8.75
CF_3	*n*-C_4H_9	61.6	Toluene	122–124	$C_{12}H_{15}F_3N_2O_3S$	44.44	4.66	8.64	44.64	4.61	8.56
CF_3	*n*-C_3H_7	71.0	Toluene	144–146	$C_{11}H_{13}F_3N_2O_3S$	42.58	4.22	9.03	42.81	4.49	9.22
$(CH_3)_2N$	*n*-C_4H_9[b]	—[c]	*i*-C_3H_7OH	160–162	$C_{13}H_{21}N_3O_3S$	52.15	7.07	14.04	52.16	7.20	14.33
$(CH_3)_2N$	*n*-C_3H_7	—[c]	*i*-C_3H_7OH	172–173	$C_{11}H_{19}N_3O_3S$	50.50	6.71	14.73	50.60	6.91	14.67

[a] Yield based on sulfonamide actually consumed. [b] This compound has been recently reported by S. Onisi, *J. Pharm. Soc. (Japan)*, **79**, 559 (1959). [c] In the preparation of this urea, varying amounts of unreacted starting material were always isolated.

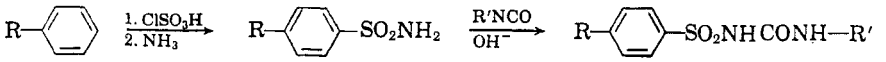
TABLE II

SUBSTITUTED BENZENESULFONAMIDES[a]



R	Yield, %	M.P.	Recrystal. Solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3SO_2	81.6	244–246	95% C_2H_5OH	$C_7H_9NO_4S$		[b]				
CH_3CO	46.6[c]	173–176	*i*-C_3H_7OH	$C_8H_9NO_3S$		[d]				
CF_3S[e]	71.2	160–162	50% C_2H_5OH	$C_7H_6F_3NO_2S_2$	32.68	2.35	5.45	33.04	2.49	5.37
						S, 24.93			S, 25.14	
CF_3SO_2[f]	79.5	142	Toluene	$C_7H_6F_3NO_4S_2$	29.06	2.09	4.84	29.33	2.40	4.73
CF_3O[g]	59.6	144–145	Toluene	$C_7H_6F_3NO_3S$	34.86	2.51	5.81	34.98	2.91	5.92
CF_3[h]	29.8	177–179	Toluene	$C_7H_6F_3NO_2S$	37.33	2.69	6.22	37.71	3.20	6.29
$(CH_3)_2N$[i]	49.8	209–211	Acetone	$C_8H_{12}N_2O_2S$		[j]				
$(CH_3)_2N$[i] ↓ O	77.0	173–174 dec.	CH_3OH-$(C_2H_5)_2O$	$C_8H_{12}N_2O_3S$	44.43	5.59	12.95	44.18	5.76	12.83

[a] The sulfonamides listed were prepared by direct chlorosulfonation unless otherwise stated. [b] H. Burton and P. F. Hu, *J. Chem. Soc.*, **1949**, 604. [c] Yield based upon sulfonamide actually consumed. [d] H. Burton and P. F. Hu, *J. Chem. Soc.*, **1949**, 178, ref. 4, and experimental section. [e] The immediate precursor, trifluoromethylthiobenzene, prepared as described by L. M. Yagulpolsky and M. S. Marents, *J. Gen. Chem.* (*U.S.S.R.*) (Eng. Trans.), **24**, 885 (1954). [f] Obtained by treating a refluxing acetic acid solution of *p*-trifluoromethylthiobenzenesulfonamide with 30% hydrogen peroxide and quenching the reaction after four hours with ice and water. [g] Trifluoromethoxybenzene synthesized as described by N. N. Yarobenko and A. S. Vasileva, *J. Gen. Chem.* (*U.S.S.R.*), **28**, 2502 (1958). [h] Prepared from *p*-trifluoromethylaniline by the method described in ref. 5. [i] Synthesis described in experimental. [j] Ref. 3.



amide was most easily made by the controlled oxidation of *p*-ethylbenzenesulfonamide as indicated by Wolf.[4]

The synthesis of *p*-trifluoromethylbenzenesulfonamide from *p*-trifluoromethylaniline was carried out according to the method of Meerwein *et al.*[5] for the synthesis of *p*-nitrobenzenesulfonamide.

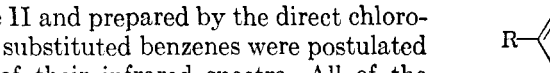
The structure of the unknown sulfonamides listed in Table II and prepared by the direct chlorosulfonation of substituted benzenes were postulated on the basis of their infrared spectra. All of the compounds exhibited a peak in the 12μ region of their infrared spectra which was deemed characteristic of para substitution.[6]

The biological test procedure used was based upon results obtained with tolbutamide and chlorpropamide.

Intact Sprague Dawley male rats from Charles River Breeding Laboratories weighing 250–300 grams were fasted twenty-four hours prior to and during testing and then treated with 100 mg. of the test compound. Water was available at all times. Blood glucose levels were checked using the method of Athanail and Caboud[7] after two hours and again after five hours. In view of the activity shown by tolbutamide and chlorpropamide it was felt that the two-hour sample would reveal hypoglycemic activity if present, and that the five-hour sample would give an indication of duration of activity. The results are shown in Table III.

TABLE III

BLOOD GLUCOSE CHANGES



R	R′	Blood glucose (% change from controls)[a] 2 hr.	5 hr.
CH_3	*n*-Butyl (tolbutamide)	−45	−20
Cl	*n*-Propyl (chlorpropamide)	−42	−40
CH_3SO_2	*n*-Butyl	−22	−14
CH_3SO_2	*n*-Propyl	+ 6	+11
CH_3CO	*n*-Butyl	−28	+ 1
CH_3CO	*n*-Propyl	0	+ 4
CF_3S	*n*-Butyl	−28	+ 5
CF_3S	*n*-Propyl	−15	+14
CF_3SO_2	*n*-Butyl	− 6	+ 6
CF_3SO_2	*n*-Propyl	− 6	+ 2
CF_3O	*n*-Butyl	−16	− 2
CF_3O	*n*-Propyl	−16	+ 8
CF_3	*n*-Butyl	−30	+24
CF_3	*n*-Propyl	−24	−14
$(CH_3)_2N$	*n*-Butyl	− 4	0
$(CH_3)_2N$	*n*-Propyl	− 3	0

[a] Six rats used per group.

EXPERIMENTAL

Preparation of sulfonamides listed in Table II. A solution of the benzene derivative in chloroform was cooled with

(4) J. Wolf, *Pryzemysl. Chem.*, **31**, 417 (1952); *Chem. Abstr.*, **48**, 7581f (1954).

(5) H. Meerwein *et al.*, *Ber.*, **90**, 841 (1957).

(6) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th edition, Wiley, New York, 1956.

(7) G. Athanail and P. G. Caboud, *J. Lab. Clin. Med.*, **51**, 321 (1958).

stirring to 0–5°. To this was added dropwise a 4*M* excess of chlorosulfonic acid at such a rate that the temperature was maintained below 10°. The solution was stirred 1 hr. with cooling (vigorous evolution of hydrogen chloride during this period) and 2 hr. at room temperature. The dark brown reaction mixture was then added dropwise to a stirred mixture of ice and water. The layers were separated and the aqueous solution was extracted twice with chloroform. The combined chloroform layers were evaporated to dryness on a steam bath in the presence of an excess of ammonium carbonate. The residue was suspended in water, filtered, washed with water, dried and recrystallized.

Preparation of sulfonylureas listed in Table I. To a cooled, stirred solution of the sulfonamide in an equivalent amount of 1*N* sodium hydroxide solution was added an equal volume of acetone. To this solution was added dropwise 1 equivalent of the isocyanate dissolved in a small volume of acetone. The addition was controlled so that the temperature of the reaction mixture did not exceed 10°. Stirring was continued for 1 hr. with cooling and for 2 hr. at room temperature. The acetone was removed *in vacuo* at 40° and the aqueous residue was acidified with dilute hydrochloric acid. The cooled acid solution was filtered and the filter cake was washed with water, dried and recrystallized.

p-Acetylbenzenesulfonamide and *p*-trifluoromethylsulfonylbenzenesulfonamide did not react completely under these conditions because of the relative insolubility of their sodium salts in this medium. However, the desired sulfonylureas were conveniently separated from the starting materials by recrystallization.

p-Acetylbenzenesulfonamide. To a solution of 123 g. (0.5 mole) of magnesium nitrate hexahydrate dissolved in 600 ml. of water was added 74 g. (0.4 mole) of *p*-ethylbenzenesulfonamide[8] in 600 ml. of acetone. The resulting solution was stirred and heated to 50–55° while 76 g. (0.5 mole) of potassium permanganate was added in portions so that the temperature remained at 50–55°. The mixture was kept at 50–55° for a total of 3 hr. and was then stirred an additional hour at room temperature. The excess permanganate was destroyed by adding 0.5 mole of sodium sulfite and allowing the mixture to stir at room temperature overnight. The mixture was filtered through a Supercel mat and the filter cake was extracted once with hot alcohol. The filtrates were combined and filtered to remove some product. The filtrates were then concentrated to about 700 ml. The solid which precipitated was filtered, combined with the first crop of product and recrystallized from isopropyl alcohol to give 25 g. of *p*-acetylbenzenesulfonamide, m.p. 173–176° (lit. m.p. 178–179°). The isopropyl alcohol filtrate was evaporated and the residue was suspended in water and filtered to give after drying, 24 g. of unchanged *p*-ethylbenzenesulfonamide, m.p. 95°. An additional 3.3 g. of product was recovered by further concentration of the original aqueous filtrate. The yield of *p*-acetylbenzenesulfonamide based upon the amount of *p*-ethylbenzenesulfonamide actually consumed was 46.6%.

p-Dimethylaminobenzenesulfonamide. A suspension of 34.4 g. (0.2 mole) of sulfanilamide and 55.2 g. (0.4 mole) of potassium carbonate in 400 ml. of dimethylformamide was stirred at room temperature while 64.0 g. (0.4 mole) of methyl iodide was added dropwise. After all the methyl iodide had been added, the reaction mixture was heated 1 hr. on a steam bath. The reaction mixture was cooled, poured into 2 l. of water, cooled, and filtered. The yellowish solid was washed with water and recrystallized from acetone. First crop 15.4 g., m.p. 209–211°; second crop 4.4 g., m.p. 207–208° (lit. m.p. 209–211°)[8]; yield 19.8 g. (49.5%).

N^4,N^4-Dimethylsulfanilamide N^4-oxide. A suspension of 20.0 g. (0.1 mole) of *p*-dimethylaminobenzenesulfonamide in 200 ml. of water was stirred and heated on a steam bath. To this was added dropwise 200 ml. of 30% hydrogen peroxide. The cloudy solution was heated an additional 3 hr. after the addition was completed. The pale yellow solution was cooled and the excess peroxide was decomposed by the addition of manganese dioxide. The manganese dioxide was filtered and the filtrate was taken to dryness in a rotary still. The residue was suspended in hot methanol, filtered from insoluble material, and diluted with ether and cooled. A first crop of 11.95 g. of oxide was obtained, m.p. 170° dec. Concentration of the filtrate and further recrystallization of the residue yielded a second crop of 4.7 g., m.p. 168° dec. Total yield was 16.65 g. (77.0%). The analytical sample was purified by further recrystallization from methanol-ether and melted at 173–174° dec.

N-(p-Dimethylaminophenylsulfonyl)-N'-n-butylurea. To a stirred suspension of 20.0 g. (0.1 mole) of *p*-dimethylaminobenzenesulfonamide in 100 ml. of 1*N* sodium hydroxide and 100 ml. of acetone was added 10 g. (0.1 mole) of *n*-butyl isocyanate in 30 ml. of acetone. The mixture was stirred 30 min. at room temperature and then under reflux overnight. The reaction mixture was filtered to give 9.2 g. of starting material, m.p. 207–209°. The filtrate was then distilled *in vacuo* at 40° to remove the acetone. The aqueous residue was cooled and neutralized with acetic acid. The precipitated solid was filtered, washed with water, and suspended in 5% sodium carbonate solution. The insoluble material was filtered off (7.8 g., m.p. 184–199°) and the filtrate was acidified with acetic acid and cooled to give 7.2 g. of urea, m.p. 154–156°. Recrystallization of this material from isopropyl alcohol raised the melting point to 160–162°.

ADDENDUM. While this paper was in press the preparation of *p*-trifluoromethylbenzenesulfonamide and *N*-(*p*-trifluoromethylphenylsulfonyl)-*N'*-*n*-butylurea has been reported.[9]

PHILADELPHIA, PA.

(8) G. Moralli, *Bull. soc. chim. France*, **1953**, 1044.

(9) H. L. Yale and F. Sowinski, *J. Org. Chem.*, **25**, 1824 (1960).