of 18.8 g. (0.1 mole) of 3,4-dichlorophenyl isocyanate and 8.1 g. (0.1 mole) of ethylene chlorohydrin was charged into a stoppered erlenmeyer flask and held at 80° for 6 hr. On cooling, the sirup crystallized. Recrystallization from heptane gave small colorless granules, yield 97.5%.

C. 2-Thiocyanoethyl 3,4-Dichlorocarbanilate (42).—A solution of 44.0 g. (0.14 mole) of 2-bromoethyl 3,4-dichlorocarbanilate and 14.5 g. (0.15 mole) potassium thiocyanate in 100 ml. of acetone was refluxed for 16 hr. Acetone was distilled while adding 100 ml. of water dropwise during the distillation. On cooling, the product solidified and was removed by filtration. Recrystallization from chlorobenzene gave fine white granules, yield 51.8%.

D. Propyl 3,4-Dichlorothiolcarbanilate (62).—A solution of 18.8 g. (0.1 mole) of 3,4-dichlorophenylisocyanate and 7.6 g. (0.1 mole of propyl mercaptan in 150 ml. of heptane was stirred at 50° using 3 drops of triethylamine as catalyst. The product began to separate at once. After standing 1 hr., it was filtered. Recrystallization from dilute methanol gave fine white needles, yield 70.8%.

E. Propyl 3,4-Dichlorothionocarbanilate (72).—The method is essentially procedure B using equimolar amounts of 3,4-dichlorophenyl isothiocyanate and propanol. Fine colorless needles crystallized from heptane, yield 92.2%.

F. Propyl 3,4-Dichlorodithiocarbanilate (77).—Same as procedure D using equimolar amounts of 3,4-dichlorophenyl isothiocyanate and propyl mercaptan. Fine colorless needles crystallized from heptane, yield 93.7%.

Acknowledgment.—The authors are indebted to John L. O'Sullivan and Ottmar S. Kring for the analyses and to Paul D. McDonald for the bacteriostatic screening.

The Synthesis of Some New Sulfonylureas

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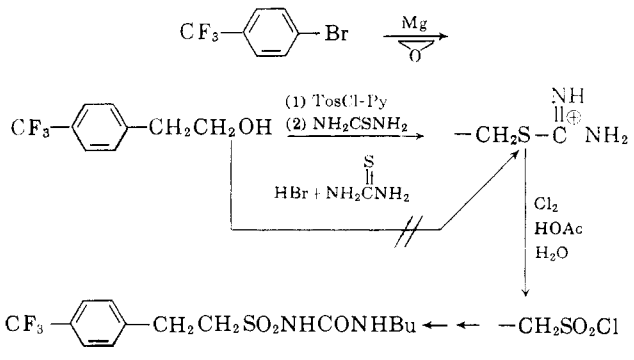
The synthesis of some new sulfonylureas is described. Two compounds have been found whose high hypoglycemic activity is surprising in view of what has previously been known regarding structure–activity relationships in this area.

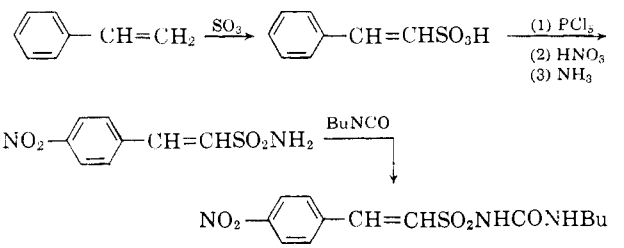
Although certain sulfonylureas have proven to be clinically useful oral antidiabetic agents,[1] recent reports describing the high rate of development of resistance to these[2] prompted us to search for related agents which might be active in such patients. Toward this end, we have synthesized some new sulfonylureas. Table I lists the sulfonylureas prepared.

The starting benzyl- and phenethylsulfonyl chlorides were prepared by reaction of the corresponding benzyl- and phenethyl halides with thiourea,[3] followed by chlorination of the resulting thiuronium salts in aqueous acetic acid.[3] 2-(*p*-Trifluoromethylphenyl)-ethanol was not converted to the thiuronium salt on heating with concentrated hydrobromic acid and thiourea.[4] The tosylate, however, reacted readily.

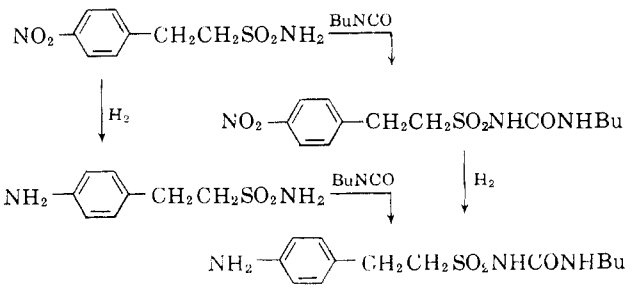


The sulfonamides were prepared by reaction of the sulfonyl chlorides with anhydrous ammonia. Table II lists the new sulfonamides.

In the synthesis of the styrene sulfonamides, the procedure of Bordwell[5] was employed.



The sulfonylureas were prepared by the reaction of the sulfonamide with butyl isocyanate in aqueous acetone containing one equivalent of base; the use of organic bases in nonaqueous systems gave poorer yields. The amino-substituted sulfonylurea was prepared both by reaction of the isocyanate with the aminosulfonamide and by reduction of the nitrosulfonylurea. The products were identical.



The 4-cyano-, carboxy-, carboxamido-, carbethoxy-, and acetamidophenethylsulfonylureas were most con-

(1) Particularly 1-*n*-butyl-3-(4-tolylsulfonyl)-urea (tolbutamide) and 1-(4-chlorobenzenesulfonyl)-3-*n*-propylurea (chlorpropamide).

(2) D. E. Delawter and J. M. Moss, *J. Am. Med. Assoc.*, **181**, 89 (1962); R. A. Camerini-Davalos and A. Marble, *ibid.*, **181**, 176 (1962); Editorial, *ibid.*, **181**, 131 (1962).

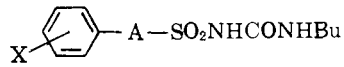
(3) General procedure of T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **58**, 1348 (1936). We found that in the preparation of the sulfonyl chlorides, the use of aqueous acetic acid as solvent gave better yields and more consistent results than the aqueous system recommended by these authors.

(4) General procedure of D. F. Lee, B. Saville, and B. R. Trego, *Chem. Ind.* (London), **27**, 868 (1960).

(5) F. G. Bordwell, C. M. Suter, J. M. Hollbert, and C. S. Rondestvedt, *J. Am. Chem. Soc.*, **68**, 139, 1778 (1946).

TABLE I

SULFONYLUREAS

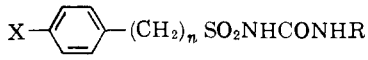


X	A	M.p., °C.	Yield, %[a]	Calcd. C	Calcd. H	Found C	Found H
4-Cl	$-CH_2-$	180–181	62	47.29	5.62	47.44	5.47
4-NO_2	$-CH_2-$	193.5–194.5	50	45.70	5.43	45.81	5.40
H	$-CH_2CH_2-$	159–161[b]	53				
4-NO_2	$-CH_2CH_2-$	153–155	59	47.40	5.81	47.47	5.80
2-NO_2	$-CH_2CH_2-$	154–156	40	47.40	5.81	47.35	5.69
4-NH_2	$-CH_2CH_2-$	129–131	55	52.15	7.07	52.22	7.01
4-$AcNH_2$	$-CH_2CH_2-$	206 dec.	47	52.77	6.79	53.04	7.03
4-CN	$-CH_2CH_2-$	143–148 dec.	45	54.35	6.19	54.09	6.46
4-$CONH_2$	$-CH_2CH_2-$	197–199 dec.	55	51.36	6.47	51.58	6.42
4-COOEt	$-CH_2CH_2-$	127–130 dec.	60	53.91	6.79	53.65	6.53
4-COOH	$-CH_2CH_2-$	172–174 dec.	48	51.20	6.14	51.14	6.15
4-CF_3	$-CH_2CH_2-$	158–159	37	47.72	5.43	47.87	5.59
H	$-CH=CH-$	128–130[c]	33	55.30	6.43	55.24	6.30
4-NO_2	$-CH=CH-$	190–190.5	30	47.70	5.23	47.73	5.23

[a] Based on sulfonamide. [b] Lit.[9] m.p. 164–166°. [c] Lit.[10] m.p. 127–128°.

veniently prepared from the 4-aminosulfonamide ($NH_2 \rightarrow CN \rightarrow COOH \rightarrow COCl \rightarrow CONH_2$, COOEt) followed by reaction with butyl isocyanate, rather than by a similar conversion of 4-aminophenethylsulfonylurea.

Ruschig[6] has reported that in compounds of the type A, optimum activity is present when $n = 0$ (X = H).



A

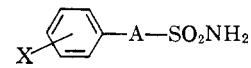
When $n = 1$ activity is destroyed; when $n = 2$ only minimal activity is observed.[6a] He and many others have also described the effect of modifying X when $n = 0$. Some examples of substituents which produce high hypoglycemic activity in such compounds are X = 4-NH_2[6] and 4-CF_3,[7] whereas when X = NO_2, the compounds are inactive.[6]

The relative hypoglycemic activities of the sulfonylureas which we have prepared are presented in Table III.[8]

Surprisingly, in the phenethyl series, when X = 4-NO_2 or 4-CN, highly potent compounds result,

TABLE II

ARALKYLSULFONAMIDES

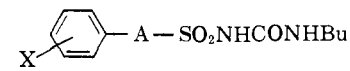


X	A	Yield, %[a]	M.p., °C.
4-NO_2	$-CH_2CH_2-$	85	118–121[b]
2-NO_2	$-CH_2CH_2-$	44	125–127
4-CN	$-CH_2CH_2-$	52	105–108
4-$AcNH_2$	$-CH_2CH_2-$	33	159–160
4-$CONH_2$	$-CH_2CH_2-$	81	197–199
4-COOEt	$-CH_2CH_2-$	87	103–110
4-COOH	$-CH_2CH_2-$	99	232–235 dec.
4-CF_3	$-CH_2CH_2-$	84	110–113
4-NO_2	$-CH=CH-$	82	188–190[c]

[a] Based on sulfonyl chloride. [b] Lit.[11] m.p. 120.5–122°. [c] Lit.[5] m.p. 193–194°.

TABLE III

HYPOGLYCEMIC ACTIVITY[a]



X	A	Relative activity (guinea pigs)
4-Cl	....	4+[b]
4-CF_3	....	4+[c]
4-NH_2	....	4+[d]
4-NO_2	....	0[e]
H	$-CH_2-$	0[e]
4-Cl	$-CH_2-$	0
4-NO_2	$-CH_2-$	0
H	$-CH_2CH_2-$	+
4-NO_2	$-CH_2CH_2-$	4+
2-NO_2	$-CH_2CH_2-$	0
4-NH_2	$-CH_2CH_2-$	0
4-AcNH	$-CH_2CH_2-$	0
4-CN	$-CH_2CH_2-$	4+
4-$CONH_2$	$-CH_2CH_2-$	0
4-COOEt	$-CH_2CH_2-$	0
4-COOH	$-CH_2CH_2-$	0
4-CF_3	$-CH_2CH_2-$	0
H	$-CH=CH-$	0[f]
4-NO_2	$-CH=CH-$	0

[a] See ref. 8. [b] Chlorpropamide; has propyl in place of butyl group. [c] Lit.[7] value. [d] Lit.[6] value; carbutamide. [e] See ref. 6. [f] See ref. 10.

(6) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, and R. Weyer, *Arzneimittel-Forsch.*, **8**, 448 (1958).

(6a) The referee has called our attention to a paper by B. Hockfelt and A. Jonsson, *J. Med. Pharm. Chem.*, **5**, 231 (1962), which appeared after our paper had been completed, describing certain results conflicting with those obtained by Ruschig, *et al.* Our test results confirm those of Ruschig.

(7) B. Blank, F. A. Farina, J. F. Kerwin, and H. Saunders, *J. Org. Chem.*, **26**, 1551 (1961); H. L. Yale and F. Sowinski, *ibid.*, **25**, 1824 (1960).

(8) Male guinea pigs weighing 110–150 g. were fasted for 18 hr. prior to and during testing. The compounds were administered orally at various doses (12.5 to 100 mg./kg.). After a predetermined time of peak-effect the blood was analyzed for glucose with the aid of a Technicon Auto-analyzing Unit using the modified method of W. S. Hoffman, *J. Biochem.*, **120**, 51 (1937). The relative hypoglycemic activities in Table III refer to relative potency as compared to chlorpropamide, which is designated as 4+, with a descending scale ending in zero which is assigned to compounds without hypoglycemic activity. A more comprehensive report on the hypoglycemic activity in various species will be given in a separate publication.

(9) G. Korger, H. Wagner, and W. Aumüller, German Patent 1,032,734 (1958).

(10) W. M. McLamore and G. D. Laubach, U. S. Patent 2,979,437 (1961). This patent claims that styrenesulfonylureas as a class have hypoglycemic activity. The two styrene derivatives that we have tested (Table III) showed no significant activity.

(11) E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Am. Chem. Soc.*, **62**, 2099 (1940).

whereas when X = 4-NH_2 or 4-CF_3, the compounds have very little hypoglycemic activity. In view of what has previously been known regarding structure–activity relationships in this area, the high activity of the 4-nitro and 4-cyano compounds is most surprising. The remarkable specificity of these modifications can be seen further from the fact that the 2-nitrophenethyl and 4-nitrostyryl compounds are inactive.

Experimental[12]

Thiuronium Bromides. General Procedure.[3]—A mixture of 0.1 mole of aralkylbromide, 0.11 mole of thiourea, and 100 ml. of alcohol was heated at reflux for 1 hr. The solution was then concentrated, *in vacuo*, until a solid started to separate, and then cooled. The thiuronium bromide precipitated and was filtered. The following new compounds were prepared: S-(*p*-nitrophenethyl)-thiuronium bromide, m.p. 195–196° (98% yield) and S-(*o*-nitrophenethyl)-thiuronium bromide, m.p. 147–149° (99% yield). All of the other thiuronium bromides, prepared the same way, were known compounds. These salts were recrystallized from 2-propanol or 2-propanol–ether.

Sulfonyl Chlorides. General Procedure.[3]—Chlorine gas was passed into a solution of 0.1 mole of thiuronium salt in 250 ml. of 50% aqueous acetic acid (maintained at 15°) for 1.5 hr. The sulfonyl chloride separated and was filtered and then washed with cold water. The following new compound was prepared: 2-(*o*-nitrophenethyl)sulfonyl chloride, m.p. 69–71°, 70% yield. The other sulfonyl chlorides are known compounds.

Sulfonamides. General Procedure.—Anhydrous ammonia was passed into a solution of 0.1 mole of sulfonyl chloride in 500 ml. of benzene for 45 min. The mixture was then concentrated and the residue was treated with 500 ml. of water. The product was insoluble and was filtered and washed thoroughly with water, then recrystallized from alcohol-water. The yields and physical constants of the new sulfonamides are listed in Table II. The other sulfonamides are known compounds.

Sulfonylureas. General Procedure.—A solution of 0.1 mole of *n*-butyl isocyanate in 10 ml. of acetone was added dropwise with stirring and cooling to a solution of 0.1 mole of the sulfonamide in a mixture of 100 ml. of *N* sodium hydroxide and 100 ml. of acetone. After the isocyanate was all added, the solution was maintained at 0° for 1 hr. and at room temperature for 2 hr. The acetone was removed under reduced pressure and any butylurea that separated was filtered off. On acidification of the filtrate, the sulfonylurea separated and was recrystallized from ethanol or ethanol–water. The yields and physical constants of the new products are listed in Table I.

2-(*p*-Trifluoromethylphenyl)-ethylsulfonamide.—The Grignard reagent was prepared from 100 g. (0.44 mole) of *p*-bromobenzotrifluoride (Pierce Chemical Company) and 10.7 g. (0.44 mole) of magnesium in ether by standard procedures. A cold solution of 26 g. (0.44 mole) of ethylene oxide in ether was slowly added to the well stirred Grignard reagent, maintained at 10°. The resulting red-brown solution was allowed to warm up to room temperature, then dry benzene was added and the ether was distilled out. The solution was heated at reflux (pot temperature 65°) for 2 hr., then it was cooled and poured into cold dilute hydrochloric acid. The organic layer was dried, concentrated, and the product was distilled, b.p. 125–130° (27 mm.), $n^{25}D$ 1.4629; yield 43 g.

A solution of this alcohol (24.0 g., 0.13 mole) in pyridine was slowly added to a chilled solution of 24.8 g. (0.13 mole) of *p*-toluenesulfonyl chloride in pyridine, while the temperature was maintained at 0 to 5°. The solution was stirred for 10 hr. at room temperature. Most of the pyridine was then removed *in vacuo;* the remaining solution was then poured into dilute hydrochloric acid and the oil that separated was extracted with ether. Evaporation gave 22.4 g. (50%) of crude tosylate. This was used without further purification.

A solution containing 8 g. (0.023 mole) of the tosylate and 2.5 g. (0.032 mole) of thiourea in 50 ml. ethanol was refluxed for 18 hr. The solvent was distilled out; the residual tacky thiuronium tosylate on stirring with ether was transposed to a white powdery solid, yield 4.7 g. (56%), m.p. 136–140°. The thiuronium tosylate was dissolved in 50 ml. of 50% aqueous acetic acid and cooled to 5°. Chlorine was bubbled through the solution at a rapid rate, while maintaining the temperature below 10°. A solid soon precipitated. Chlorine was passed in until the exothermic reaction ceased. The solid sulfonyl chloride was filtered and rinsed with water, 2.9 g., m.p. 62–64°.

Ammonia was bubbled through a solution of the sulfonyl chloride in ether. The ether was then distilled off and the residual white solid was stirred with dilute hydrochloric acid. The sulfonamide was obtained in 83.5% yield, m.p. 110–113°, and converted to the sulfonylurea (Table I) by the general procedure already described.

***p*-Acetamidophenethyl Sulfonamide.**—A solution of 0.025 mole of *p*-aminophenethyl sulfonamide[11] in 10 ml. of glacial acetic acid and 10 ml. of acetic anhydride was refluxed for 0.5 hr., and then poured into 500 ml. of water. The product was extracted with methylene chloride; the extract was dried and evaporated to give 2.6 g. of crude product, m.p. 153–154°. Recrystallization from a small amount of hot water gave pure material, 1.5 g., m.p. 159–160°. The compound showed a strong characteristic carboxyl absorption at 6.02 μ in the infrared.

N-Butyl-N′-(*p*-aminophenethyl)sulfonylurea.—A solution of 0.0304 mole of N-butyl-N′-(*p*-nitrophenethyl)sulfonylurea in 100 ml. of water and 30.4 ml. of *N* sodium hydroxide was hydrogenated over 10% palladium-on-carbon catalyst at 3.5 kg./cm.^{2} and 25°. The theoretical amount of hydrogen was absorbed in 1 hr. The catalyst was filtered; on acidification of the filtrate with acetic acid the product precipitated. Recrystallization from ethanol–water gave the pure product, 5.0 g., m.p. 129–131°. This material was identical with the sulfonylurea prepared by the reaction of *p*-aminophenethyl sulfonamide[11] with butyl isocyanate.

***p*-Cyanophenethyl Sulfonamide.**—A concentrated aqueous solution containing 3.72 g. (0.0539 mole) of sodium nitrite was added dropwise to a mixture of 10.8 g. (0.0539 mole) of *p*-aminophenethyl sulfonamide[11] in 22.4 ml. of concentrated hydrochloric acid, maintained at 0°. The resultant suspension was stirred at 0° for an additional 5 min. and then added dropwise and with stirring to a solution containing 4.83 g. (0.0539 mole) of cuprous cyanide, 10.5 g. (0.162 mole) of potassium cyanide, and 27.2 g. (0.324 mole) of sodium bicarbonate in 200 ml. of water, maintained at −5 to 0°. The mixture was stirred at 5° for an additional 1.5 hr. and then filtered. The brown residue was dried and recrystallized from ethyl acetate–hexane to give the product (Table II). It showed a strong characteristic nitrile absorption at 4.5 μ in the infrared. This compound was converted to the sulfonylurea (Table I) by the standard procedure.

***p*-Carboxyphenethyl Sulfonamide.**—*p*-Cyanophenethyl sulfonamide (2.5 g., 0.012 mole) was dissolved in 50 ml. of 10% sodium hydroxide and heated at reflux for 2 hr. The solution was cooled and acidified to give the acid (Table II). The product showed a strong characteristic carboxyl absorption at 5.9 μ in the infrared. This sulfonamide was converted to the sulfonylurea (Table I) by the standard procedure.

***p*-Carboxamidophenethyl Sulfonamide.**—The acid (4.3 g., 0.019 mole) was heated with 50 ml. of thionyl chloride for 1 hr. The volatile material was removed *in vacuo*, and the acid chloride crystallized as a tan solid, 4.1 g. (88% yield), m.p. 104–107°. Ammonia was bubbled into a solution of the acid chloride (2.0 g., 0.008 mole) in 200 ml. of methylene chloride. The solvent was distilled off and the residue crystallized. The compound showed a strong characteristic amide absorption at 6.0 μ in the infrared. The amide (Table II) after recrystallization from hot water was converted to the sulfonylurea (Table I) by the standard procedure. An attempt to prepare this amide by acid-catalyzed hydrolysis of the nitrile failed.

***p*-Carbethoxyphenethyl Sulfonamide.**—Pyridine (0.64 g., 0.008 mole) was added to a solution of 2.0 g. (0.007 mole) of the acid chloride (previously described) in 50 ml. of anhydrous ethanol. After refluxing for 30 min., the volatile materials were removed *in vacuo*. The residual oil crystallized on stirring with water. It showed a strong characteristic ester absorption at 5.85 μ in the infrared. The sulfonamide (Table II) was converted to the sulfonylurea (Table I) by the standard procedure. Attempts to prepare this ester directly from the nitrile (*via* an imino ester intermediate) failed.

Acknowledgment.—We wish to thank Mrs. Minerva F. Kormendy for preparing some of the intermediates.

(12) All melting points are corrected. Analyses were carried out by Mrs. D. Rolston and her staff of these laboratories. All infrared absorption spectra were recorded on a Perkin-Elmer Infracord as mineral oil mulls.