2-Methyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-4(3H)-quinazolone (2).—A mixture of 2-methyl-4-oxo-4H-3,1-benzoxazine (16.1 g, 0.1 mole) and 4-(3-aminopropyl)-1-phenylpiperazine (21.9 g, 0.1 mole) was heated at 175–180° in a wax bath for 1 hr and dissolved in MeOH. The MeOH solution was treated with dry HCl to give a salt, yield 36.8 g. The salt was recrystallized (aqueous MeOH–HCl), yield 32.9 g, mp 250–251°. A 5-g sample of the salt was converted to the free base, yield 3.9 g. The free base was recrystallized (aqueous AcMe), mp 104–105°.

Method B is exemplified in the following experiment.

4-[3-(2-Amino-5-chlorobenzamido)propyl]-1-phenylpiperazine.—To 1-(3-aminopropyl)-4-phenylpiperazine (87.6 g, 0.4 mole) in 100 ml of C_6H_6 was added 6-chloroisatoic anhydride (79.0 g, 0.4 mole); the mixture was heated on a steam bath for 1 hr after CO_2 evolution had subsided. About 250 ml of Et_2O was added to the mixture and the insoluble solid was collected, yield 132.9 g (92.8%), mp 184–150°. A sample was recrystallized (aqueous DMF), mp 152–155°.

6-Chloro-2-phenyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-4(3H)-quinazolone (16).—A suspension of 4-[3-(2-amino-5-chlorobenzamido)propyl]-1-phenylpiperazine (52 g, 0.14 mole) in 500 ml of $CHCl_3$ was treated with C_6H_5COCl (19.8 g, 0.14 mole) as usual to give the corresponding benzamide of mp 199.5–200.5°, yield 43.8 g. The above benzamide (43.8 g, 0.092 mole) in 250 ml of Ac_2O was refluxed for 16 hr. The solvent was removed *in vacuo* and the residue was crystallized (aqueous AcMe), mp 126–131°.

(6) All melting points are corrected and were determined with a Büchi melting point apparatus. Ir spectra were determined with a Perkin-Elmer Model 237 spectrophotometer. Titrations were carried out with a Sargent Model D recording titrator. All analytical samples had ir spectra compatible with their assigned structures. The analytical samples gave values for C, H, N, and HCl within 0.4% of the theoretical values.

meta-Substituted Benzenesulfonylureas as Hypoglycemic Agents

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The literature during the past decade on the synthesis and hypoglycemic activity of substituted benzenesulfonylureas is very extensive but contains very few *meta*-(mono)substituted derivatives.[2,3] The present note describes the synthesis and screening for hypoglycemic activity of such *meta*-substituted benzenesulfonylureas wherein the substituents are Cl, F, Me, or CF_3. These have been obtained by the treatment of the corresponding *meta*-substituted benzenesulfonylthioureas with H_2O_2 under alkaline conditions.[4] The sulfonylthioureas were synthesized by the interaction of the benzenesulfonamides and appropriate isothiocyanates in Me_2CO under alkaline conditions.[5] The requisite benzenesulfonamides were prepared from the benzenesulfonyl chlorides which in turn were obtained by diazotization of the corresponding anilines followed by the action of SO_2 in glacial AcOH.[6]

The relevant data for new *meta*-substituted benzenesulfonylthioureas and the sulfonylureas are given in Tables I and II, respectively.

Pharmacology.—All the benzenesulfonylureas have been evaluated for their hypoglycemic activity in normal healthy rabbits. The animals were fasted 18–20 hr prior to the oral administration of 50 mg/kg of the test compounds. Blood sugar was estimated by Somogyi's method[7] using Nelson's reagent[8] and the activity at different intervals up to 7 hr is given in Table II as per cent change in blood sugar.

Twelve out of 21 compounds were almost inactive. Significant activity was shown by three compounds (**34**, **41**, and **45**), and in all these three compounds R′ was *n*-propyl. The order of activity in relation to the substituent R was $CH_3 > Cl > F > CF_3$ while that with regard to the alkyl group R′ was $n\text{-}C_3H_7 > i\text{-}C_3H_7 > C_6H_{11} > n\text{-}C_4H_9 > i\text{-}C_4H_9 > C_2H_5 > CH_2CH{=}CH_2$.

N-*m*-Tolylsulfonyl-N′-*n*-propylurea (**41**) was found to be the most potent in the series, showing blood sugar reduction of 22.0% in rabbits and of 30.4% in rats after 5 hr. It was also tested along with tolbutamide at 25 and at 100 mg/kg in both species and was found to be slightly less potent than tolbutamide. Crossover tests confirmed this. The LD_{50} (oral) in albino mice for **41** was 2.0 g/kg (for tolbutamide 2.6 g/kg).

Experimental Section[9]

***m*-Chlorobenzenesulfonamide.**—*m*-Chloroaniline (25.5 g, 0.2 mole) in 80 ml of concentrated HCl and 200 ml of H_2O was diazotized with $NaNO_2$ (18 g in H_2O, 50 ml) at 0–5°. This diazotized solution was slowly added with stirring to 200 ml of saturated (30%) SO_2 solution in glacial AcOH containing $CuCl_2$ (4 g) and concentrated HCl (15 ml) at 5–10°. The mixture was stirred for 30 min and was allowed to stand for 3 hr at room temperature. The oily layer of *m*-chlorobenzenesulfonyl chloride was then separated and added to 200 ml of 25% NH_4OH. It was stirred for 3 hr and left overnight. Excess NH_3 was then removed by heating on a water bath. The solid that separated on cooling was filtered off and crystallized (H_2O), 12.6 g (33%), mp 145–146° (lit.[10] mp 148°). *Anal.* ($C_6H_6ClNO_2S$) N.

Similarly prepared were *m*-fluorobenzenesulfonamide in 22.3% yield, mp 131–133° (lit.[11] mp 129–130°); *m*-tolylsulfonamide in 33.4% yield, mp 111–112° (lit.[12] mp 108°); and *m*-(α,α,α-trifluoromethyl)benzenesulfonamide in 49% yield, mp 123° (lit.[13] mp 121–122°).

N-*m*-Fluorobenzenesulfonyl-N′-*n*-propylthiourea (10).—*m*-Fluorobenzenesulfonamide (3.5 g, 0.02 mole) was dissolved in Me_2CO (35 ml). To this solution were added aqueous NaOH (0.8 g in 5 ml) and *n*-propyl isothiocyanate (2.45 ml, 0.024 mole) and the mixture was refluxed for 3 hr. The solvent was then removed and the residue was diluted with H_2O (50 ml). The solution was decolorized, filtered, acidified with HCl, and crystallized to obtain the desired compound.

All the benzenesulfonylthioureas were prepared by the above procedure and are listed in Table I.

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(12) Farbwerke Hoechst A.-G., German Patent 974,062 (1960); *Chem. Abstr.*, **56**, 4679*i* (1962).

(3) J. R. Geigy, A.G., Swiss Patent 377,801 (1964); *Chem. Abstr.*, **62**, 9066*h* (1965).

(4) M. H. Shah, M. Y. Mhasalkar, V. M. Patki, and C. V. Deliwala, *J. Sci. Ind. Res.* (India), **18B**, 202 (1959).

(5) S. Petersen, *Ber.*, **83**, 551 (1950).

(6) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *ibid.*, **90**, 841 (1957).

(7) M. Somogyi, *J. Biol. Chem.*, **160**, 69 (1945).

(8) N. Nelson, *ibid.*, **153**, 375 (1944).

(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(10) C. Paal, *Ber.*, **34**, 2748 (1901).

(11) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).

(12) J. J. Griffen, *Am. Chem. J.*, **19**, 173 (1897); through the "Dictionary of Organic Compounds," I. Heilbron and H. M. Bunbury, Ed., Eyre and Spottiswoode, London, 1953, p 518.

(13) L. M. Yagupolskii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **29**, 552 (1959); *Chem. Abstr.*, **54**, 3564*h* (1960).

TABLE I
meta-SUBSTITUTED BENZENESULFONYLTHIOUREAS
m-$RC_6H_4SO_2NHCSNHR'$

No.	R	R'	Crystn solvent[a]	% yield[b]	Mp, °C[c]	Formula	Analyses
1	Cl	C_2H_5	A	80	108–110	$C_9H_{11}ClN_2O_2S_2$	N, S
2	Cl	C_3H_5	A	76	99–100	$C_{10}H_{11}ClN_2O_2S_2$	N
3	Cl	*n*-C_3H_7	A	78	119–120	$C_{10}H_{13}ClN_2O_2S_2$	N, S
4	Cl	*i*-C_3H_7	A	78	115–116	$C_{10}H_{13}ClN_2O_2S_2$	N, S
5	Cl	*n*-C_4H_9	A	86	105–107	$C_{11}H_{15}ClN_2O_2S_2$	N, S
6	Cl	*i*-C_4H_9	A	72	81–82	$C_{11}H_{15}ClN_2O_2S_2$	N, S
7	Cl	C_6H_{11}	A	86	134–135	$C_{13}H_{17}ClN_2O_2S_2$	N, S
8	F	C_2H_5	A	81	137–138	$C_9H_{11}FN_2O_2S_2$	N
9	F	C_3H_5	A	72	95–96	$C_{10}H_{11}FN_2O_2S_2$	N, S
10	F	*n*-C_3H_7	A	75	132–134	$C_{10}H_{13}FN_2O_2S_2$	N
11	F	*i*-C_3H_7	A	80	98–100	$C_{10}H_{13}FN_2O_2S_2$	N, S
12	F	*n*-C_4H_9	A	79	104–105	$C_{11}H_{15}FN_2O_2S_2$	N, S
13	F	*i*-C_4H_9	A	84	97–98	$C_{11}H_{15}FN_2O_2S_2$	N, S
14	F	C_6H_{11}	A	72	153–154	$C_{13}H_{17}FN_2O_2S_2$	N, S
15	CH_3	C_2H_5	A	73	113–115	$C_{10}H_{14}N_2O_2S_2$	N, S
16	CH_3	C_3H_5	A	70	103–105	$C_{11}H_{14}N_2O_2S_2$	N
17	CH_3	*n*-C_3H_7	B	76	101–102	$C_{11}H_{16}N_2O_2S_2$	N, S
18	CH_3	*i*-C_3H_7	B	81	112–114	$C_{11}H_{16}N_2O_2S_2$	N, S
19	CH_3	*i*-C_4H_9	A	70	85–87	$C_{12}H_{18}N_2O_2S_2$	N, S
20	CH_3	C_6H_{11}	A	72	130–131	$C_{14}H_{20}N_2O_2S_2$	N, S
21	CF_3	C_2H_5	A	80	108–110	$C_{10}H_{11}F_3N_2O_2S_2$	N, S
22	CF_3	C_3H_5	A	79	91–93	$C_{11}H_{11}F_3N_2O_2S_2$	N
23	CF_3	*n*-C_3H_7	A	92	106–107	$C_{11}H_{13}F_3N_2O_2S_2$	N, S
24	CF_3	*i*-C_3H_7	A	92	105–106	$C_{11}H_{13}F_3N_2O_2S_2$	N, S
25	CF_3	*n*-C_4H_9	A	90	83–84	$C_{12}H_{15}F_3N_2O_2S_2$	N, S
26	CF_3	C_6H_{11}	B	80	120–121	$C_{14}H_{17}F_3N_2O_2S_2$	N, S

[a] A, C_6H_6 + *n*-C_6H_{14}; B, C_6H_6; C, EtOH + C_6H_6; D, EtOH. [b] Yields reported are the results of a single experiment and are calculated on material melting not lower than 3° below the highest melting point obtained. [c] Melting points are capillary melting points and are uncorrected.

TABLE II
meta-SUBSTITUTED BENZENESULFONYLUREAS
m-$RC_6H_4SO_2NHCONHR'$

No.	R	R'	Crystn solvent[a]	% yield[b]	Mp, °C[c]	Formula	Analyses	Change in blood sugar (mg %) after oral administration to rabbits: 1.5 hr	3 hr	5 hr	7 hr
27	Cl	C_2H_5	B	78	145–146	$C_9H_{11}ClN_2O_3S$	N, S	Nil	Nil	−3.2	−4.2
28	Cl	C_3H_5	B	85	124–125	$C_{10}H_{11}ClN_2O_3S$	N, S	−2.0	−7.5	−11.2	−12.0
29	Cl	*i*-C_3H_7	A	92	146–147	$C_{10}H_{13}ClN_2O_3S$	N, S	−2.2	−3.9	−6.9	−12.4
30	Cl	*i*-C_4H_9	A	84	116–117	$C_{11}H_{15}ClN_2O_3S$	N, S	−8.5	−11.7	−14.3	−11.3
31	Cl	C_6H_{11}	A	91	148–150	$C_{13}H_{17}ClN_2O_3S$	N, S	−6.9	−9.0	−15.5	−13.2
32	F	C_2H_5	B	90	166–167	$C_9H_{11}FN_2O_3S$	N, S	−2.7	−4.2	−6.9	−8.1
33	F	C_3H_5	B	92	145–146	$C_{10}H_{11}FN_2O_3S$	N, S	+7.1	+5.3	+2.8	Nil
34	F	*n*-C_3H_7	B	88	160–161	$C_{10}H_{13}FN_2O_3S$	N, S	−3.2	−9.9	−12.1	−16.3
35	F	*i*-C_3H_7	B	83	153–154	$C_{10}H_{13}FN_2O_3S$	N, S	+3.0	−12.5	−15.3	−9.0
36	F	*n*-C_4H_9	B	88	129–130	$C_{11}H_{15}FN_2O_3S$	N, S	+3.0	−8.0	−7.5	−1.5
37	F	*i*-C_4H_9	A	96	134–135	$C_{11}H_{15}FN_2O_3S$	N, S	+8.6	+4.6	Nil	−8.1
38	F	C_6H_{11}	A	86	173–174	$C_{13}H_{17}FN_2O_3S$	N, S	−2.0	−2.9	Nil	Nil
39	CH_3	C_2H_5	B	80	147–148	$C_{10}H_{14}N_2O_3S$	N	−2.1	−5.1	−7.0	−9.3
40	CH_3	C_3H_5	B	77	129–131	$C_{11}H_{14}N_2O_3S$	N, S	Nil	−3.5	−5.6	−6.3
41	CH_3	*n*-C_3H_7	A	82	114–115	$C_{11}H_{16}N_2O_3S$	N, S	−8.8	−13.5	−22.0	−20.0[d]
42	CH_3	*i*-C_3H_7	A	67	154–155	$C_{11}H_{16}N_2O_3S$	N, S	−4.2	−10.1	−16.6	−11.3
43	CF_3	C_2H_5	C	98	162–163	$C_{10}H_{11}F_3N_2O_3S$	N, S	Nil	−1.5	−2.0	−2.0
44	CF_3	C_3H_5	C	86	150–151	$C_{11}H_{11}F_3N_2O_3S$	N, S	+6.4	+1.4	Nil	−3.1
45	CF_3	*n*-C_3H_7	D	97	140–141[e]	$C_{11}H_{13}F_3N_2O_3S$	N	−6.2	−8.1	−19.8	−13.0
46	CF_3	*i*-C_3H_7	D	87	144–145	$C_{11}H_{13}F_3N_2O_3S$	N, S	−4.0	−7.4	−10.0	−3.5
47	CF_3	C_6H_{11}	D	95	132–134[f]	$C_{14}H_{17}F_3N_2O_3S$	N	−7.6	−9.1	−12.3	−12.2

[a–c] See corresponding footnotes in Table I. [d] Blood sugar came to near fasting level at end of 24-hr period. [e] Lit.[3] mp 144.5–145.5°. [f] Lit.[3] mp 133°.

N-*m*-Fluorobenzenesulfonyl-N'-*n*-propylurea (34).—N-*m*-Fluorobenzenesulfonyl-N'-*n*-propylthiourea (2.76 g, 0.01 mole) was dissolved in 0.5 *N* NaOH (50 ml) and 30% H_2O_2 (8 ml) was added dropwise. The temperature was maintained at 45–55° during the addition. It was then allowed to stand at about 40° for 30 min. The reaction mixture was then acidified to pH 2.5–3 and the white solid was collected by filtration, washed (H_2O), and crystallized (C_6H_6).

All the benzenesulfonylureas were prepared as described above and are listed in Table II.

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