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Hypoglycemic Activity in a Series of 1-Aryl-3-arylsulphonylureas

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In recent years, there has been widespread interest in sulphonylureas because of the hypoglycemic activity of some members of this class.[1-13] Two sulphonylureas are now in clinical use in the United States of America for the treatment of diabetes mellitus: 1-*n*-butyl-3-(4-tolylsulphonyl)urea (tolbutamide) and 1-(4-chlorobenzenesulphonyl)-3-*n*-propylurea (chlorpropamide). These, and most of the synthetic analogues that have been prepared, are members of the 1-alkyl-3-arylsulphonylurea family. During the course of a search for more effective hypoglycemic agents, we have synthesized and screened a number of 1-aryl-3-arylsulphonylureas. Only a few studies have been published concerning the hypoglycemic properties of this class of compound,[5, 10] despite the fact that several 1-aryl-3-arylsulphonylureas have been known for some time.[14, 15]

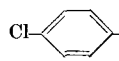
Synthesis

Two general methods were employed for the preparation of these compounds. The first, Method A, involves the reaction between an arylsulphonamide (I) and a substituted phenylisocyanate (II) in a mixture of triethylamine and dimethylformamide at 25°.[16] This procedure is convenient for the preparation of those sulphonylureas in which the required phenylisocyanates are readily available.

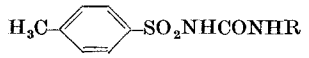
* Presented before the Division of Medicinal Chemistry, 135th Meeting of the American Chemical Society, Boston, Mass., April 6, 1959, Abstracts, p. 148.

† For preceding paper see McLamore, W. M., Fanelli, G. M., P'an, S. Y. and Laubach, G. D. *Ann. N.Y. Acad. Sci.*, **74**, 443 (1959).

Table I.

R	Method	Yield, %	m.p., °C	Formula	Analyses, %					
					Calcd.			Found		
					C	H	N	C	H	N
1-Aryl-3-(4-chlorobenzenesulphonyl)ureas 										
C_6H_5	A	87	179–181	$C_{13}H_{11}ClN_2O_3S$	50·24	3·57	9·02	50·47	3·67	9·51
4-BrC_6H_4	B	47	241(d.)	$C_{13}H_{10}BrClN_2O_3S$	40·07	2·59	7·19	39·92	2·52	7·31
4-ClC_6H_4[a]	A	77	182–183	$C_{13}H_{10}Cl_2N_2O_3S$	45·23	2·92	8·13	45·26	2·90	8·32
4-FC_6H_4	B	67	183–184	$C_{13}H_{10}FClN_2O_3S$	47·49	3·07	8·52	47·71	3·12	8·30
4-IC_6H_4	B	92	243(d.)	$C_{13}H_{10}ClIN_2O_3S$	36·51	2·40	6·55	36·34	2·48	6·29
3,4-$(Cl)_2C_6H_3$[a]	B	73	184–185	$C_{13}H_9Cl_3N_2O_3S$	41·12	2·39	7·38	41·32	2·12	7·55
4-$CH_3C_6H_4$	B	98	176–177	$C_{14}H_{13}ClN_2O_3S$	51·77	4·03	8·63	51·39	3·91	8·83
2-$CH_3OC_6H_4$	B	75	165–166	$C_{14}H_{13}ClN_2O_4S$	49·34	3·85	8·22	49·00	3·81	8·43
3-$CH_3OC_6H_4$	B	92	158–160	$C_{14}H_{13}ClN_2O_4S$	49·34	3·85	8·22	49·73	3·89	8·24
4-$CH_3OC_6H_4$	B	98	173–174	$C_{14}H_{13}ClN_2O_4S$	49·34	3·85	8·22	49·41	3·99	8·38
3,4-$(CH_3)_2C_6H_3$	B	62	169–170	$C_{15}H_{15}ClN_2O_3S$	53·17	4·46	8·27	53·04	4·57	8·46
2,4-$(CH_3O)_2C_6H_3$	B	54	167–168	$C_{15}H_{15}ClN_2O_5S$	48·58	4·08	7·56	48·36	4·07	7·32
2,5-$(CH_3O)_2C_6H_3$	B	95	152–154	$C_{15}H_{15}ClN_2O_5S$	48·58	4·08	7·56	48·74	4·29	7·55
3,4-$(CH_3O)_2C_6H_3$	B	64	160–161	$C_{15}H_{15}ClN_2O_5S$	48·58	4·08	7·56	48·59	4·02	7·33
5-Cl-2-$CH_3OC_6H_3$	B	88	129–130	$C_{14}H_{12}Cl_2N_2O_4S$	44·81	3·22	7·47	45·15	3·26	7·73
2-CH_3O-5-$CH_3C_6H_3$	B	25	123–124	$C_{15}H_{15}ClN_2O_4S$	50·77	4·26	7·90	50·86	4·27	7·87
4-CH_3O-2-$CH_3C_6H_3$	B	46	141–142	$C_{15}H_{15}ClN_2O_4S$	50·77	4·26	7·90	50·35	4·29	8·15
4-Cl-2,5-$(CH_3O)_2C_6H_2$	B	89	195–196	$C_{15}H_{14}Cl_2N_2O_5S$	44·45	3·48	6·91	44·48	3·53	6·89
5-Cl-2,4-$(CH_3O)_2C_6H_2$	B	69	182–183	$C_{15}H_{14}Cl_2N_2O_5S$	44·45	3·48	6·91	44·58	3·89	6·91
4-$(CH_3)_2NC_6H_4$	B	53	158–159	$C_{15}H_{16}ClN_3O_3S$	50·92	4·56	11·88	50·71	4·53	11·57

1-Aryl-3-(4-tolylsulphonyl)ureas



C_6H_5[a,b,c]	A		169–171							
4-BrC_6H_4	A	88	249–250(d.)	$C_{14}H_{13}BrN_2O_3S$	45·54	3·55	7·59	45·11	3·61	7·57
4-ClC_6H_4	A	69	166–167	$C_{14}H_{13}ClN_2O_3S$	51·77	4·03	8·63	51·55	4·36	8·87
4-FC_6H_4	B	76	172–173	$C_{14}H_{13}FN_2O_3S$	54·53	4·25	9·09	54·78	4·25	9·28
2-IC_6H_4	B		135–136	$C_{14}H_{13}IN_2O_3S$	41·40	3·21	6·90	41·02	3·58	7·13
4-IC_6H_4	B	71	247(d.)	$C_{14}H_{13}IN_2O_3S$	41·40	3·21	6·90	41·09	3·17	6·85
3,4-$(Cl)_2C_6H_3$	B	70	177–179	$C_{14}H_{12}Cl_2N_2O_3S$	46·81	3·37	7·80	47·17	3·08	7·74
4-$CH_3C_6H_4$	B	99	155–156	$C_{15}H_{16}N_2O_3S$	59·19	5·30	9·21	58·64	5·06	9·24
2-$CH_3OC_6H_4$	B	74	190–191	$C_{15}H_{16}N_2O_4S$	56·23	5·03	8·75	56·04	5·10	8·64
3-$CH_3OC_6H_4$	B	76	165–166	$C_{15}H_{16}N_2O_4S$	56·23	5·03	8·75	56·19	4·95	8·59
4-$CH_3OC_6H_4$[b]	B	98	159–160	$C_{15}H_{16}N_2O_4S$	56·23	5·03	8·75	56·16	5·03	8·76
3-$CF_3C_6H_4$	B	67	134–135	$C_{15}H_{13}F_3N_2O_3S$	50·27	3·66	7·82	50·32	3·85	8·01
3,4-$(CH_3)_2C_6H_3$	B	50	159–160	$C_{16}H_{18}N_2O_3S$	60·37	5·70	8·80	60·62	5·62	8·84
2,4-$(CH_3O)_2C_6H_3$	B	93	175–176	$C_{16}H_{18}N_2O_5S$	54·85	5·18	8·00	54·68	5·18	8·01
2,5-$(CH_3O)_2C_6H_3$	B	78	179–180	$C_{16}H_{18}N_2O_5S$	54·85	5·18	8·00	54·54	5·16	7·92
3,4-$(CH_3O)_2C_6H_3$	B	76	156–157	$C_{16}H_{18}N_2O_5S$	54·85	5·18	8·00	54·84	5·07	7·99
5-Cl-2-$CH_3OC_6H_3$	B	77	157–158	$C_{15}H_{15}ClN_2O_4S$	50·92	3·99	7·92	50·77	4·38	7·98
2-CH_3O-5-CH_3-C_6H_3	B	41	122–123	$C_{16}H_{18}N_2O_4S$	57·48	5·43	8·38	57·21	5·63	8·53
4-CH_3O-2-$CH_3C_6H_3$	B	42	179–180	$C_{16}H_{18}N_2O_4S$	57·48	5·43	8·38	57·55	5·17	8·40
4-Cl-2,5-$(CH_3O)_2C_6H_2$	B	50	189–190	$C_{16}H_{17}ClN_2O_5S$	49·93	4·45	7·28	50·34	4·54	7·34
5-Cl-2,4-$(CH_3O)_2C_6H_2$	B	94	171–173	$C_{16}H_{17}ClN_2O_5S$	49·93	4·45	7·28	50·28	4·53	7·24
4-$(CH_3)_2NC_6H_4$[d]	B	73	164–165	$C_{16}H_{19}N_3O_3S$	57·65	5·75	12·61	57·83	5·59	12·41

1-Aryl-3-benzenesulphonylureas

$C_6H_5SO_2NHCONHR$

4-BrC_6H_4	A	71	245	$C_{13}H_{11}BrN_2O_3S$	43·95	3·12	7·89	43·87	3·25	7·66
4-ClC_6H_4	A	63	222–223	$C_{13}H_{11}ClN_2O_3S$	50·25	3·54	9·02	50·17	3·51	9·04
4-FC_6H_4	B	75	162–163	$C_{13}H_{11}FN_2O_3S$	53·05	3·77	9·52	53·06	3·99	9·50
4-IC_6H_4	B	60	158–159	$C_{13}H_{11}IN_2O_3S$	38·90	2·76	6·98	38·59	2·90	6·86
3,4-$(Cl)_2C_6H_3$	B	63	167–168	$C_{13}H_{10}Cl_2N_2O_3S$	45·23	2·92	8·12	45·19	2·98	7·90
2-$CH_3OC_6H_4$	A	67	173–174	$C_{14}H_{14}N_2O_4S$	54·90	4·61	9·15	54·91	4·64	9·09
4-$CH_3OC_6H_4$	B	63	139·5–140·5	$C_{14}H_{14}N_2O_4S$	54·90	4·61	9·15	55·37	4·75	9·34
4-$(CH_3)_2NC_6H_4$	B	47	120–121	$C_{15}H_{17}N_3O_3S$	56·40	5·37	13·16	56·56	5·75	13·01

[a] Reference 15. [b] Prepared by Chemerda, J. and Tull, J. Belgian Patent 860,631. [c] Reference 10. [d] Reference 5.

Method A

$$\underset{\text{(I)}}{ArSO_2NH_2} + \underset{\text{(II)}}{Ar'N=C=O} \longrightarrow \underset{\text{(III)}}{ArSO_2NHCONHAr'}$$

A new method, Method B, was developed because of the limited number of isocyanates commercially available. In this procedure, diphenylcarbamoyl chloride (IV) is condensed with the anilines (V), and the products (VI) (1-aryl-3,3-diphenylureas) are treated in dimethylformamide with the sodium salts of various sulphonamides (VII). The desired sulphonylureas (VIII) are soluble in dilute bases and can thus be readily separated from the

Method B

$$\underset{\text{(IV)}}{(C_6H_5)_2NCOCl} + \underset{\text{(V)}}{Ar'NH_2} \longrightarrow \underset{\text{(VI)}}{(C_6H_5)_2NCONHAr}$$

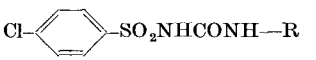
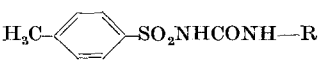
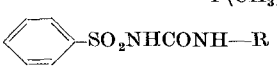
$$\underset{\text{(VI)}}{(C_6H_5)_2NCONHAr'} + \underset{\text{(VII)}}{ArSO_2\overset{\ominus}{N}H.\overset{\oplus}{N}a} \longrightarrow \underset{\text{(VIII)}}{ArSO_2NHCONHAr'} + \underset{\text{(IX)}}{(C_6H_5)_2NH}$$

by-product, diphenylamine (IX). The sulphonylureas which are prepared with difficulty by the older methods are now readily accessible by this procedure. Method B gives high yields of the desired product in most cases; low yields in a few cases can be attributed to the fact that no effort was made to purify the commercially available anilines. The compounds prepared are described in Table I.

Results and Discussion

The 1-aryl-3-arylsulphonylureas were screened pharmacologically by measuring their effect on the blood sugar of fasting rats, after oral administration. The active compounds prepared in this programme are listed in Table II. The most effective hypoglycemic agent is 1-(4-chlorobenzenesulphonyl)-3-(4-dimethylaminophenyl)urea; it is comparable in activity to chlorpropamide. The activities of this compound and its two analogues are

Table II. Hypoglycemic activity of arylsulphonylureas

R	Activity[a] 2 h	Activity[a] 4 h	R	Activity[a] 2 h	Activity[a] 4 h
					
			4-Chlorobenzenesulphonylureas		
n-C_3H_7 (chlorpropamide)	+ + + +	+ + + +	3-$CH_3OC_6H_4$	+ to + +	−
C_6H_5	+ +	+	4-$CH_3OC_6H_4$	+	−
4-FC_6H_4	+ +	−	4-$CH_3C_6H_4$	+	−
4-ClC_6H_4	+ +	+ +	4-$(CH_3)_2NC_6H_4$	+ + + +	+ + + +
4-BrC_6H_4	+	+			
					
			4-Tolylsulphonylureas		
n-C_4H_9 (tolbutamide)	+ +	+	4-BrC_6H_4	+	+
C_6H_5	+ +	+	4-$CH_3OC_6H_4$	+ +	−
4-FC_6H_4	+ + to + + +	−	4-$CH_3C_6H_4$	+	−
4-ClC_6H_4	+	−	4-$(CH_3)_2NC_6H_4$	+	−
					
			Benzenesulphonylureas		
4-FC_6H_4	+ +	+ +	4-ClC_6H_4	+ + +	+ +
4-BrC_6H_4	+ to + +	+	4-$(CH_3)_2NC_6H_4$	+ + + +	+ to + +
4-$CH_3OC_6H_4$	+ to + +	−	3,4-$(Cl)_2C_6H_3$	+ to + +	+ to + +

[a] − No significant change in blood sugar
+ 5 to 10% lowering of blood sugar
+ + 10 to 20% lowering of blood sugar
+ + + 20 to 30% lowering of blood sugar
+ + + + 30 to 40% lowering of blood sugar

X	Activity	
	2 h	4 h
Cl	++++	++++
H	++++	+ to ++
CH_3	+	−

of interest; the differences in their hypoglycemic activities may indicate different rates of metabolic inactivation.

Structure–Activity Correlations

Certain structural requirements for hypoglycemic activity for the 1-aryl-3-arylsulphonylureas were indicated from the structure–activity correlations obtained during this study. With the exception of 1-benzenesulphonyl-3-(3,4-dichlorophenyl)urea, only the 1-aryl-3-arylsulphonylureas in which the 1-aryl group (R; Table II) was unsubstituted or mono-substituted were active. Furthermore, the mono-substituted sulphonylureas in which R was either *ortho-* or *meta*-substituted were inactive, except for 1-(4-chlorobenzenesulphonyl)-3-(3-methoxyphenyl)urea, while the majority of sulphonylureas in which R was *para*-substituted were active. Thus, the compounds in which R was unsubstituted or was mono-substituted in the *para*-position were the most effective in lowering blood sugar.

Physical Measurement Study

A study of certain physical properties of these sulphonylureas was undertaken in the hope of reaching a better understanding of the structure–activity relationships. Several successful studies of this type have been made: e.g. the relationship between pK_a and antibacterial activity of the sulphonamides,[17] a relationship between pK_a and the uricosuric activity in the phenylbutazone series,[18] and the correlation of aqueous solubility of some of the phenylbutazone analogues with their oral absorption in man.[19]

(*a*) *pK_a study.* The pK_a values and the hypoglycemic activities of a number of 1-aryl-3-arylsulphonylureas are listed in Table III. Within each series, the most acidic compounds are

Table III. Relationship between hypoglycemic activity and pK_a

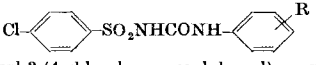
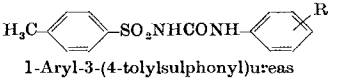
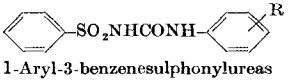
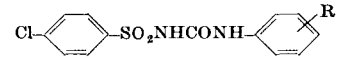
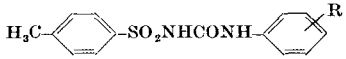
R	pK_a	Activity 2 h	Activity 4 h	R	pK_a	Activity 2 h	Activity 4 h
							
		1-Aryl-3-(4-chlorobenzenesulphonyl)ureas					
4-Cl	5·2	++	++	3,4-$(CH_3O)_2$	5·6	−	
4-Br	5·3	+	+	2,5-$(CH_3O)_2$	5·6	−	
4-F	5·4	++	−	4-CH_3	5·7	+	−
3-CH_3O	5·5	+ to ++	−	4-$(CH_3)_2N$	6·1	++++	++++
							
		1-Aryl-3-(4-tolylsulphonyl)ureas					
4-F	5·9	++ to +++	−	4-CH_3O	6·5	++	−
4-Br	5·9	+	+	4-$(CH_3)_2N$	6·5	+	−
4-Cl	5·9	+	−	2-CH_3O	6·5	−	
3-CH_3O	6·1	−		4-CH_3O-2-CH_3	6·6	−	
4-CH_3	6·2	+	−	2,4-$(CH_3O)_2$	6·7	−	
5-Cl-2,4-$(CH_3O)_2$	6·4	−					
							
		1-Aryl-3-benzenesulphonylureas					
4-Br	5·7	+ to ++	+				
4-F	5·7	++	++				
4-CH_3O	6·0	+ to ++	−				
2-CH_3O	6·3	−					
4-$(CH_3)_2N$	6·4	++++	+ to ++				

Table IV. Relationship between hypoglycemic activity and solubility

R	Solubility, mg/ml at pH 7·0 and 25°	Activity 2 h	Activity 4 h	R	Solubility, mg/ml at pH 7·0 and 25°	Activity 2 h	Activity 4 h
							
		1-Aryl-3-(4-chlorobenzenesulphonyl)ureas					
3,4-$(CH_3O)_2$	6·6	−		4-$(CH_3)_2N$	1·5	++++	++++
4-H	3·8	++	+	2-CH_3O	1·4	−	
2,5-$(CH_3O)_2$	3·4	−		4-CH_3	1·1	+	
3-CH_3O	3·1	+ to ++	−	2-CH_3O-5-Cl	0·6	−	
4-CH_3O	2·9	+	−	4-I	0·5	−	
4-F	2·7	++	−	2,4-$(CH_3O)_2$	0·4	−	
4-Cl	2·0	++	++	3,4-$(CH_3)_2$	0·3	−	
4-Br	2·0	+	+	3,4-$(Cl)_2$	0·2	−	
							
		1-Aryl-3-(4-tolylsulphonyl)ureas					
4-H	4·7	++	+	4-Br	0·75	+	+
4-F	4·6	++ to +++	−	2,5-$(CH_3O)_2$	0·64	−	
4-CH_3	3·1	+	−	2-CH_3O	0·60	−	
3,4-$(CH_3O)_2$	2·6	−		4-I	0·28	−	
4-CH_3O	2·1	++	−	3,4-$(CH_3)_2$	0·20	−	
4-Cl	1·8	+	−	2,4-$(CH_3O)_2$	0·18	−	
2-CH_3O-5-CH_3	1·2	−		3,4-$(Cl)_2$	0·16	−	
4-$(CH_3)_2N$	1·1	+	−	2,4-$(CH_3O)_2$-5-Cl	0·12	−	
3-CH_3O	0·9	−		2-CH_3O-5-Cl	0·07	−	
							
		1-Aryl-3-benzenesulphonylureas					
4-F	>11	++	++				
2-CH_3O	6·9	−					
4-Br	2·7	+ to ++	+				
4-$(CH_3)_2N$	2·6	++++	+ to ++				

usually the most active, and they are also the analogues monosubstituted in the *para*-position. Sulphonylureas containing the *p*-dimethylaminophenyl group are the exception; they are very active, and, as expected, are less acidic than the other active compounds.

(*b*) *Solubility study.* The solubilities of a number of sulphonylureas are listed in Table IV. The active 1-aryl-3-arylsulphonylureas, almost without exception, have solubilities greater than 1·0 mg/ml in aqueous buffer at pH 7·0 and 25°. The lower biological activity of the insoluble compounds, after oral administration, may be due to their poor absorption from the gut.[19] A few compounds, 1-(4-chlorobenzenesulphonyl)-3-(3,4-dimethoxyphenyl)urea, 1-(4-chlorobenzenesulphonyl)-3-(2,5-dimethoxyphenyl)urea, 1-(3,4-dimethoxyphenyl)-3-(4-tolylsulphonyl)urea and 1-benzenesulphonyl-3-(2-methoxyphenyl)urea, have a solubility greater than 1·0 mg/ml, but they are inactive. Although aqueous solubility is one physical property which can be related to the hypoglycemic activity of these sulphonylureas, other physical or chemical properties could be of more importance.

Experimental

*Chemical**

1,1-Diphenyl-3-(4-fluorophenyl)urea. 4-Fluoroaniline (40 g, 0·36 mole) and diphenylcarbamoyl chloride (36·2 g, 0·156 mole) were added to 100 ml of absolute ethanol. This mixture was heated to reflux for 16 h, concentrated *in vacuo*, and the residue extracted with chloroform and water. The chloroform layer was separated, washed with N hydrochloric acid and water, and dried (Na_2SO_4 anhyd.). Chloroform was removed *in vacuo* and the resulting product was crystallized from 95 per cent ethanol; the yield was 41·6 g (88 per cent), m.p. 154–155°.

Anal. Calcd. for $C_{19}H_{15}FN_2O$: C, 74·49; H, 4·94; N, 9·15. Found: C, 74·65; H, 5·25; N, 9·19.

All of the triarylureas (VI) were prepared by the above procedure with the exception of 1,1-diphenyl-3-(4-dimethylaminophenyl)urea, in which case the acid wash was omitted.

* Melting points are uncorrected.

Preparation of Sulphonylureas

Method A. 1-Benzenesulphonyl-3-(4-chlorophenyl)urea. To a mixture of triethylamine (30 ml) and dimethylformamide (15 ml) was added benzenesulphonamide (10 g, 0·064 mole) and 4-chlorophenylisocyanate (10 g, 0·064 mole). After being stirred overnight, the mixture was diluted with water (100 ml) and extracted twice with ether. The aqueous layer was collected and acidified in the cold with N hydrochloric acid. The product was collected by suction filtration and dried; yield, 12·5 g (63 per cent), m.p. 222–223°.

The same procedure was used for all compounds prepared by Method A.

Method B. 1-(4-Chlorobenzenesulphonyl)-3-(4-fluorophenyl)urea. A mixture of 1,1-diphenyl-3-(4-fluorophenyl)urea (10·5 g, 0·0343 mole) and the sodium salt of 4-chlorobenzenesulphonamide (7·3 g, 0·0343 mole) was heated in dimethylformamide (40 ml) at 100° for 16 h. After being cooled, the dimethylformamide mixture was diluted with 2 per cent sodium carbonate solution (100 ml) and extracted twice with ether. The aqueous layer was cooled and acidified with N hydrochloric acid. The white crystalline product that separated was collected by suction filtration and dried; yield, 7·5 g (67 per cent), m.p. 183–184°.

All of the Method B preparations followed essentially this procedure, except that in the preparation of compounds containing a basic function the alkaline aqueous layer was carefully acidified in the cold to pH 4, and the product that separated was collected and dried.

Pharmacology

Male rats (Wistar strain) weighing 150–175 g were fasted for 18 h before the oral administration of the compound. The compounds were administered, via a stomach tube, in dosages of 100 mg/kg, as a 1 per cent solution in carboxymethyl cellulose. Blood glucose values were determined with an Auto Analyzer,* using a micromethod which is a modification of the procedure described by Hoffman.[20] Glucose determinations were made prior to, and 2 and 4 h following, administration of the sulphonyl-

* Technicon Instruments Corporation, Chauncey, New York.

ureas. Six rats were used for each compound. Tolbutamide or chlorpropamide was employed as a standard in each experiment.

Physical Measurements

pK_a. The potentiometric titrations, using a Beckman Model G pH meter, of the arylsulphonylureas (approximately 70 mg) were carried out in dioxan–water (50 per cent, v/v) medium with standard 0·5 N sodium hydroxide. A blank titration was also run on the solvent medium. The pK_a values correspond to the pH at the 50 per cent neutralization point in these titration curves.

Solubility. Each solubility tube was charged with 20 ml of pH 7·0 MacIlvaine buffer,[21] with an appropriate excess of the arylsulphonylurea. These suspensions were mechanically agitated at 25° for 4 h and the resulting filtrates analyzed for arylsulphonylurea content by ultraviolet spectrophotometry. All determinations were conducted in duplicate.

Summary. A series of 1-aryl-3-arylsulphonylureas have been prepared, either by the reaction of an arylisocyanate with a sulphonamide or by the reaction of the salt of a sulphonamide with the appropriate 1-aryl-3,3-diphenylureas. The hypoglycemic activities of the active compounds are indicated in Table II. The most active compound was 1-(4-chlorobenzenesulphonyl)-3-(4-dimethylaminophenyl)urea, which was comparable in hypoglycemic activity to chlorpropamide. A study of the pK_a's and aqueous solubilities of a number of 1-aryl-3-arylsulphonylureas was made. Generally, the more acidic compounds were the most active, with the exception of the sulphonylureas containing the *p*-dimethylaminophenyl group. Moreover, the active sulphonylureas generally showed a solubility greater than 1·0 mg/ml at pH 7·0 and 25°.

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