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Hypoglycaemic agents*

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Various 3-substituted derivatives of 1-(*p*-vinylbenzenesulphonyl)urea, 1-[*p*-(2-chloroethyl)benzenesulphonyl]urea and 1-[*p*-(2-bromoethyl)benzenesulphonyl]urea are described. Several of the compounds possess noteworthy hypoglycaemic activity on oral administration in rabbits. In contrast, several related 5-substituted derivatives of 2-[*p*-(2-chloroethyl)benzenesulphonamido]-1,3,4-thiadiazoles and -1,3,4-oxadiazoles were virtually inactive.

REPLACEMENT of the methyl group of tolbutamide (I; R = Me, R′ = Bu) by one of the lower alkyl groups leads to sulphonylureas which still possess significant hypoglycaemic activity (Gryglewski, 1957; Gourley, 1958). A new structural type in which the methyl group is replaced by an alkenyl group, and specifically by a vinyl group (I; R = $CH:CH_2$, R′ = Bu), is reported herein. As this compound showed significant biological activity the work was extended to the preparation of the *p*-vinylbenzenesulphonylureas listed in Table 2. The most potent compounds in the series proved to be the n-butyl, cyclopentyl, cyclohexyl and cycloheptyl derivatives (I; R = $CH:CH_2$, R′ = Bu^n, cyclopentyl, cyclohexyl or cycloheptyl).

New intermediate isocyanates were prepared by standard methods, viz—reaction of the amine hydrochloride with excess of phosgene in an appropriate solvent at or near the boiling-point. Several of the isocyanates (Table 1) were characterised by conversion into the phenylureas. *p*-Vinylbenzenesulphonamide, used in early preparative work, was obtained from 4-(2-bromoethyl)benzenesulphonamide (II; X = Br, Y = NH_2) by an improved process based upon the earlier work of Inskeep & Deanin (1947) and of Wiley & Ketterer (1953). It was later found to be more convenient to prepare the *p*-vinylbenzene derivatives by the action of aqueous ethanolic alkali hydroxide upon the appropriate l-substituted 3-[*p*-(2-bromo- or chloro-ethyl)benzenesulphonyl]ureas (Table 3). Later biological data revealed that several of these compounds themselves (I; R = $CH_2{\cdot}CH_2{\cdot}Br$ or $CH_2{\cdot}CH_2{\cdot}Cl$, R′ = Bu^n, cyclohexyl or, cycloheptyl) were at least equal to the derived *p*-vinylbenzene compounds in hypoglycaemic activity.

p-(2-Chloroethyl)benzenesulphonyl chloride (II; X = Y, Y = Cl), a compound not previously described in the literature, was obtained by direct chlorosulphonation of phenethyl chloride at 15–20°, and converted into the required sulphonamide (II; X = Cl, Y = NH_2) by reaction with ammonia in a two-phase chloroform–water medium.

Three sulphonylthioureas (III; R = $CH:CH_2$, R′ = Pr^n, Bu^n or allyl), were prepared by reaction of *p*-vinylbenzenesulphonamide with the appropriate isothiocyanate. Reaction of *p*-(2-chloroethyl)benzenesulphonamide with butyl isothiocyanate yielded the sulphonylthiourea (III; R =

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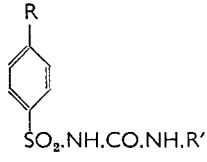
* The fourth paper in this series.

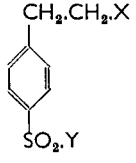
$CH_2{\cdot}CH_2{\cdot}Cl$, R′ = Bu^n), which was smoothly oxidised to the sulphonylurea (I; R = $CH_2{\cdot}CH_2{\cdot}Cl$, R′ = Bu^n) by the action of hydrogen peroxide in alkaline solution (compare Shah, Mhasalkar, Patki & Deliwala, 1959). Some of the 2-chloroethyl and 2-bromoethyl compounds (Table 3) were also prepared by routes other than that involving reaction of the sulphonamide with an isocyanate in aqueous alkaline acetone (see Experimental), but these routes invariably gave inferior yields of products.

Finally, a series of 2-[*p*-(2-chloroethyl)benzenesulphonamido]-1,3,4-thiadiazoles (IV; R = $CH_2{\cdot}CH_2{\cdot}Cl$, R′ = alkyl, X = S) [compare Janbon, Chaptal, Vedel & Schaap (1942) and Loubatierès (1944, 1955)], and of 2-[*p*-(2-chloroethyl)benzenesulphonamide]-1,3,4-oxadiazoles (IV; R = $CH_2{\cdot}CH_2{\cdot}Cl$, R′ = alkyl, X = O) [compare O'Neal, Rosen, Russell & Blumenthal (1962)] were synthesised. Two of the thiadiazoles were converted into the corresponding 2-(*p*-vinylbenzenesulphonamido)-1,3,4-thiadiazoles (IV; R = $CH{:}CH_2$, R′ = Pr^i or Bu^i, X = S) by treatment with ethanolic alkaline hydroxide solution. Surprisingly, these latter heterocyclic derivatives were all less active than the aromatic types (I).

We are indebted to Dr. A. David and his colleagues for biological data.



(I)



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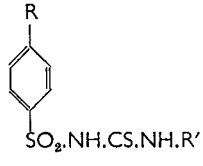

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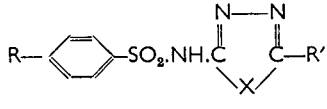


(IV)

Experimental

Most of the examples given typify the methods used for the preparation of the compounds listed in Tables 1 to 3, which contain relevant analytical data.

trans-4-*Methylcyclohexyl isocyanate.* A suspension of *trans*-4-methylcyclohexylamine hydrochloride in chloronaphthalene (200 ml, "mixed isomers") was heated to 140° and treated with a fairly rapid stream of phosgene gas for 3 hr. The phosgene was stopped and nitrogen passed into the mixture whilst the temperature was raised to 180–200° for 3 hr. The residual oil was distilled at 5 mm to yield crude material (50·8 g), b.p. 60–100° at 5 mm. This was refractionated to give the pure *product* (35·5 g), b.p. 60 to 60·5° at 6 mm.

1-(trans-4-*Methylcyclohexyl*)-3-*phenylurea.* The foregoing isocyanate

TABLE 1. ISOCYANATES (R.NCO) AND DERIVED PHENYLUREAS (R.NH.CO.NH.Ph)

R	Reaction solvent for R.NCO	b.p. °C	mm	n_D	°C	m.p. °C of phenylurea	Formula	Found C	Found H	Found N	Required C	Required H	Required N
t-Pentyl	c	110–114	A.P.	1·4320	28		$C_6H_{11}NO$						
t-Pentyl						127–129	$C_{12}H_{18}N_2O$	70·1	8·4	13·8	69·85	8·8	13·6
Heptyl	e	184	A.P.	1·4295	26		$C_8H_{15}NO$	68·4	11·1	9·6	68·1	10·7	9·9
Heptyl						65–66	$C_{14}H_{22}N_2O$	71·3	9·2	11·9	71·7	9·5	12·0
Octyl	e	196	A.P.	1·4460	22		$C_9H_{17}NO$	70·2	10·7	8·8	69·6	11·0	9·0
Octyl						72–73	$C_{15}H_{24}N_2O$	72·6	9·9	11·0	72·5	9·7	11·3
Cyclopentyl	d	145–146	A.P.	1·4470	26		C_6H_9NO	64·5	8·3	12·7	64·9	8·2	12·6
Cyclopentyl						204–206	$C_{12}H_{16}N_2O$	70·8	8·0	13·6	70·55	7·9	13·7
trans-2-Methylcyclohexyl	e	58–60	6	1·4550	23		$C_8H_{13}NO$	69·6	9·4	9·9	69·0	9·4	10·1
trans-2-Methylcyclohexyl						157–159*	$C_{14}H_{20}N_2O$						
trans-3-Methylcyclohexyl	e	66	10	1·4522	22		$C_8H_{13}NO$	69·7	9·6	10·0	69·0	9·4	10·1
trans-3-Methylcyclohexyl						165–167*	$C_{14}H_{20}N_2O$						
trans-4-Methylcyclohexyl	e	60	6	1·4500	23		$C_8H_{13}NO$	68·6	9·2	10·2	69·0	9·4	10·1
trans-4-Methylcyclohexyl						214–216*	$C_8H_{13}NO$						
Cycloheptyl	e	69–70	16	1·4670	27	185–187	$C_{14}H_{20}N_2O$	72·4	8·7	11·8	72·4	8·7	12·1
Cycloheptyl							$C_9H_{15}NO$						
Cyclo-octyl	d	85–87	7	1·4814	25	154–156	$C_{15}H_{22}N_2O$	73·3	8·9	11·3	73·2	9·0	11·4
Cyclo-octyl							$C_9H_{13}NO$			10·1			10·1
Cyclohexylmethyl	e	194–196	A.P.	1·4751	22	128–130	$C_{14}H_{20}N_2O$	72·9	8·4	11·9	72·4	8·7	12·1
Cyclohexylmethyl							$C_9H_{15}NO$						
2-Cyclohexylethyl	e	215–217	A.P.			106–108	$C_{15}H_{22}N_2O$	73·2	8·7	11·4	73·2	9·0	11·4
2-Cyclohexylethyl							$C_9H_9NO_2$	66·5	5·6	8·4	66·2	5·6	8·6
2-Phenoxyethyl	b	122	7·5			134–136	$C_{15}H_{16}N_2O_2$	70·0	6·4	10·9	70·35	6·3	10·9
2-Phenoxyethyl							C_9H_9NOS			12·5			12·5
2-Ethylthioethyl	a	188–190	A.P.			75–76	$C_{11}H_{16}N_2OS$	59·2	6·9	14·0′	58·9	7·2	14·3′
2-Ethylthioethyl													

(*a*) toluene.
(*b*) chlorobenzene.
(*c*) nitrobenzene.
(*d*) *o*-dichlorobenzene.
(*e*) α-chloronaphthalene (usually mixed isomers).

′ = sulphur.
* = identical with compounds synthesised from amine, $R.NH_2$ and phenyl isocyanate.

(1 g) was added to a solution of aniline (1 ml) in dry benzene (10 ml) and the mixture was heated on a steam-bath for 10 min and then diluted with light petroleum (b.p. 60–80°). The *product* had m.p. 214–216° (from ethanol) and was identical with the material obtained by reaction of phenyl isocyanate with *trans*-4-methylcyclohexylamine.

Styrene-4-sulphonamide (i) A solution of *p*-(2-bromoethyl)benzenesulphonamide (80 g) [compare Inskeep & Deanin (1947) and Wiley & Ketterer (1953)] in ethanol (800 ml) was treated with a solution of potassium hydroxide (60 g) in ethanol (800 ml) and the mixture heated under reflux for 8 hr after which time the bulk of the ethanol was boiled off. The residual solid was dissolved in water (550 ml), and the solution was heated to 90° and filtered after the addition of decolorising charcoal. The cooled filtrate was acidified with hydrochloric acid to yield the *product* (52·5 g), m.p. 138–139°. This material was pure enough for use. A sample crystallised from water had m.p. 140–141°. Found: C, 52·3; H, 4·8; N, 7·3; S, 17·0. Calc. for $C_8H_9NO_2S$: C, 52·4; H, 5·0; N, 7·6; S, 17·5%.

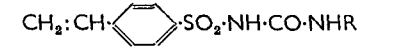
(ii) (*a*) p-(2-*Chloroethyl*)*benzenesulphonyl chloride.* 2-Phenethyl chloride (216 g) was added dropwise with stirring to chlorosulphonic acid (537 g) at 15–20°, and the mixture was stirred for a further hr and then poured onto crushed ice (5 litres). The oil was extracted with chloroform and the extract washed successively with water, 5% sodium bicarbonate solution and water. The chloroform was boiled off from the extract and the residual oil distilled at 0·6 mm to give the *product* (55% yield), b.p. 125–130°, m.p. 54–56° [from ether–light petroleum (b.p. 40–60°)]. Found: C, 40·6; H, 3·4; S, 13·6. $C_8H_8Cl_2O_2S$ requires C, 40·2; H, 3·4; S, 13·4%. A small quantity of a lower-boiling fraction (110–125° at 0·6 mm) presumably contained the *ortho*-sulphonyl chloride.

(*b*) p-(2-*Chloroethyl*)*benzenesulphonamide.* A solution of the foregoing sulphonyl chloride (131 g) in chloroform (400 ml) was added slowly with stirring to aqueous ammonia (800 ml, d = 0·880). After 1 hr the *product* (92·6 g) was collected; it had m.p. 179–181° (from water). Found: C, 43·7; H, 4·6; Cl, 16·1; N, 6·4; S, 14·7. $C_8H_{10}ClNO_2S$ requires C, 43·7; H, 4·6; Cl, 16·1; N, 6·4; S, 14·6%.

(*c*) A solution of the foregoing compound (11·0 g) in ethanol (50 ml) was treated with a solution of potassium hydroxide (8·4 g) in ethanol (75 ml) and the mixture heated under reflux for 3 hr. The solvent was distilled off at reduced pressure, and water (200 ml) added to dissolve the residual solid. The solution was filtered and the filtrate acidified with 5N hydrochloric acid to yield the *product* (7·8 g), m.p. 141–143° (from water containing a little hydroquinone).

1-*Phenyl*-3-(p-*vinylbenzenesulphonyl*)*urea.* A solution of styrene-4-sulphonamide (7·3 g) in acetone (90 ml) was treated with a solution of sodium hydroxide (1·8 g) in a minimum volume of water. The mixture was cooled to 0° and treated with phenyl isocyanate (3·13 g). Stirring was continued for 1 hr at 0°, then for 3 hr at 25°; the mixture was then poured onto crushed ice (800 ml) and filtered. The filtrate was acidified with dilute hydrochloric acid to yield the *product* (11·4 g), m.p. 162–164°.

TABLE 2. 3-SUBSTITUTED 1-*p*-VINYLBENZENESULPHONYL-UREAS AND -THIOUREAS



R	m.p. °C	Formula	Found C	Found H	Found N	Found S	Required C	Required H	Required N	Required S
Ethyl	100–102	$C_{13}H_{14}N_2O_3S$	51·7	5·5	10·8	12·5	52·0	5·5	11·0	12·6
Propyl	105–106	$C_{12}H_{16}N_2O_3S$	53·4	6·0	10·6	12·0	53·7	6·0	10·4	12·0
Butyl	116–117	$C_{13}H_{18}N_2O_3S$	55·3	6·0	10·0	11·3	55·3	6·4	9·9	11·4
Pentyl	86–88	$C_{14}H_{20}N_2O_3S$	56·5	6·9	9·5	10·7	56·7	6·8	9·5	10·8
Hexyl	139–140	$C_{15}H_{22}N_2O_3S$	58·0	7·2	9·0	10·4	58·0	7·1	9·0	10·3
Heptyl	118–119	$C_{16}H_{24}N_2O_3S$	59·3	7·4	8·8	10·0	59·3	7·5	8·6	9·9
Octyl	92–94	$C_{17}H_{26}N_2O_3S$	60·5	7·5	8·2	9·8	60·3	7·7	8·3	9·5
Isopropyl	112–113	$C_{12}H_{16}N_2O_3S$	53·7	5·8	10·3	11·7	53·7	6·0	10·4	12·0
Isobutyl	150–151	$C_{13}H_{18}N_2O_3S$	55·6	6·3	10·0	11·5	55·3	6·4	9·9	11·4
s-Butyl	133–134	$C_{13}H_{18}N_2O_3S$	54·9	6·3	9·7	11·2	55·3	6·4	9·9	11·4
t-Butyl	134–135	$C_{13}H_{18}N_2O_3S$	44·4	6·6	9·7	11·3	55·3	6·4	9·9	11·4
Isopentyl	113–114	$C_{14}H_{20}N_2O_3S$	56·8	6·8	9·4	10·8	56·7	6·8	9·5	10·8
t-Pentyl	118–119	$C_{14}H_{20}N_2O_3S$	56·5	6·9	9·4	10·7	56·7	6·8	9·5	10·8
1-Ethylpropyl	134–135	$C_{14}H_{20}N_2O_3S$	56·7	6·6	9·7	11·0	56·7	6·8	9·5	10·8
Isohexyl	113–114	$C_{15}H_{22}N_2O_3S$	58·2	6·7	9·0	10·5	58·0	7·1	9·0	10·3
1-Propylbutyl	158	$C_{16}H_{24}N_2O_3S$	59·4	7·6	8·5	9·5	59·3	7·5	8·6	9·9
Allyl	131–132	$C_{13}H_{14}N_2O_3S$	54·0	5·3	10·7	12·1	54·1	5·3	10·5	12·0
3-Propoxypropyl	120–122	$C_{15}H_{22}N_2O_4S$	55·6	6·8	8·6	9·9	55·2	6·8	8·6	9·8
3-Butoxypropyl	70–72	$C_{16}H_{24}N_2O_4S$	56·1	6·9	8·5	9·4	56·4	7·1	8·2	9·4
3-Isobutoxypropyl	96–97	$C_{16}H_{24}N_2O_4S$	56·3	7·0	8·1	9·2	56·4	7·1	8·2	9·4
3-Cyclohexyloxypropyl	97–99	$C_{18}H_{26}N_2O_4S$	59·0	7·2	7·7	8·7	59·0	7·2	7·6	8·7
Cyclopentyl	161·5–162*	$C_{14}H_{18}N_2O_3S$	57·0	6·0	9·5	10·8	57·1	6·2	9·5	10·9
Cyclohexyl	169·5–170*	$C_{15}H_{20}N_2O_3S$	58·7	6·6	9·0	10·2	58·4	6·5	9·1	10·4
Cycloheptyl	146·5–147*	$C_{16}H_{22}N_2O_3S$	59·3	6·6	8·7	9·8	59·6	6·9	8·7	9·9
Cyclo-octyl	140–142	$C_{17}H_{24}N_2O_3S$	60·3	7·1	8·2	9·9	60·7	7·2	8·3	9·5
trans-2-Methylcyclohexyl	157	$C_{16}H_{22}N_2O_3S$	59·6	6·9	8·7	9·9	59·6	6·9	8·7	9·9
trans-3-Methylcyclohexyl	155–156	$C_{16}H_{22}N_2O_3S$	59·5	6·8	8·5	9·6	59·6	6·9	8·7	9·9
trans-4-Methylcylohexyl	183–184	$C_{16}H_{22}N_2O_3S$	59·7	6·9	8·7	10·1	59·6	6·9	8·7	9·9
Cyclohexylmethyl	170	$C_{16}H_{22}N_2O_3S$	59·2	7·0	8·4	9·8	59·6	6·9	8·7	9·9
2-Cyclohexylethyl	101–102	$C_{17}H_{24}N_2O_3S$	60·5	7·2	8·5	9·6	60·7	7·2	8·3	9·5
Benzyl	158	$C_{16}H_{16}N_2O_3S$	61·0	5·2	8·9	10·0	60·7	5·1	8·9	10·1
Phenethyl	137–138	$C_{17}H_{18}N_2O_3S$	62·1	5·7	8·6	9·4	61·8	5·5	8·5	9·7
2-Phenoxyethyl	168–169	$C_{17}H_{18}N_2O_4S$	59·0	5·4	8·3	9·0	58·9	5·2	8·1	9·3
Phenyl	168–169	$C_{15}H_{14}N_2O_3S$	59·6	4·9	9·2	10·5	59·6	4·7	9·3	10·6
p-Tolyl	169–170	$C_{16}H_{16}N_2O_3S$	61·1	5·3	8·8	10·3	60·7	5·1	8·9	10·1
p-Methoxyphenyl	138–139	$C_{16}H_{16}N_2O_4S$	57·9	4·8	8·3	9·6	57·8	4·9	8·4	9·6
p-Ethoxyphenyl	166–167	$C_{17}H_{18}N_2O_4S$	59·1	5·4	7·9	9·1	58·9	5·2	8·1	9·3
p-Chlorophenyl	178	$C_{15}H_{13}ClN_2O_3S$	53·3	3·8	8·1	9·1 10·1′	53·5	3·9	8·3	9·5 10·5′

TABLE 2—*continued*

R	m.p. °C	Formula	Found C	Found H	Found N	Found S	Required C	Required H	Required N	Required S
p-Bromophenyl	178–180	$C_{16}H_{13}BrN_2O_3S$	47·5	3·6	7·3	8·1 20·8+	47·3	3·4	7·4	8·4 21·0+
1-Naphthyl	161	$C_{19}H_{16}N_2O_3S$	65·0	4·7	7·9	9·1	64·8	4·6	8·0	9·1
2-Ethylthioethyl	109–110	$C_{13}H_{18}N_2O_3S_2$	49·6	5·7	8·8	20·0	49·70	5·8	8·9	20·4
		$CH_2{:}CH\cdot C_6H_4\cdot SO_2\cdot NH\cdot CS\cdot NHR$								
Propyl	90–91	$C_{13}H_{18}N_2O_3S_2$	50·9	5·3	9·7	22·5	50·7	5·7	9·8	22·6
Butyl	94–95	$C_{13}H_{16}N_2O_3S_2$	52·5	6·1	9·8	21·2	52·3	6·1	9·4	21·5
Allyl	89–91	$C_{12}H_{14}N_2O_3S_2$	50·5	4·6	9·5	—	51·0	5.0	9·9	—

* Corrected m.p. ′ = chlorine. + = bromine.

TABLE 3. 3-SUBSTITUTED 1-(*p*-2-HALOGENOETHYL)BENZENESULPHONYLUREAS

$X\cdot CH_2\cdot CH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot NHR$

R	X	m.p. °C	Formula	Found C	Found H	Found Hal	Found N	Found S	Required C	Required H	Required Hal	Required N	Required S
Propyl	Cl	142–144	$C_{12}H_{17}ClN_2O_3S$	47·4	5·8	11·7	9·1	10·2	47·3	5·6	11·6	9·2	10·5
Butyl	Cl	122–123	$C_{13}H_{19}ClN_2O_3S$	49·2	6·2	10·9	8·9	10·0	49·0	6·0	11·1	8·8	10·1
t-Butyl	Cl	142–143	$C_{13}H_{19}ClN_2O_3S$	49·4	6·1	10·8	8·8	9·8	49·0	6·0	11·1	8·8	10·1
Cyclopentyl	Cl	111–112	$C_{14}H_{19}ClN_2O_3S$	51·2	5·9	10·5	8·2	9·6	50·8	5·8	10·7	8·4	9·7
Cyclohexyl	Cl	129–130	$C_{15}H_{21}ClN_2O_3S$	52·3	6·0	10·4	7·9	8·9	52·2	6·1	10·3	8·1	9·3
Cycloheptyl	Cl	127–129	$C_{16}H_{23}ClN_2O_3S$	53·4	6·2	10·2	8·0	9·3	53·5	6·5	9·9	7·8	8·9
Butyl	Br	132–134	$C_{13}H_{19}BrN_2O_3S$	43·2	5·1	22·2	8·1	8·9	43·0	5·3	22·0	7·7	8·8
t-Butyl	Br	145–146	$C_{13}H_{19}BrN_2O_3S$	42·7	5·5	22·2	7·5	9·2	43·0	5·3	22·0	7·7	8·8
Cyclopentyl	Br	150–151	$C_{14}H_{19}BrN_2O_3S$	44·6	5·0	21·3	7·2	8·2	44·8	5·1	21·3	7·5	8·6
Cyclohexyl	Br	165–166	$C_{15}H_{21}BrN_2O_3S$	46·4	5·3	21·0	7·4	8·4	46·3	5·4	20·5	7·2	8·2
Cycloheptyl	Br	152–155	$C_{16}H_{23}BrN_2O_3S$	48·0	5·5	19·6	6·9	8·2	47·6	5·7	19·8	6·9	7·9

Crystallisation from acetone–light petroleum (b.p. 60–80°) raised the m.p. to 168–169°.

1-[p-(2-*Bromoethyl*)*benzenesulphonyl*]-3-*cyclohexylurea*. Cyclohexyl isocyanate (68·8 g) was added with stirring to a mixture of *p*-(2-bromoethyl)benzenesulphonamide (132 g) in acetone (1200 ml) with a solution of sodium hydroxide (20 g) in water (20 ml) at 8–12° during 20 min. Stirring was continued at room temperature for 1 hr and then at 35–45° for 2 hr. The mixture was cooled and poured onto crushed ice (*ca* 4 litres). The resultant solution was filtered and the filtrate acidified with dilute hydrochloric acid to yield the *product* (187 g), m.p. 165–166° (from aqueous ethanol).

1-*Cyclohexyl*-3-(p-*vinylbenzenesulphonyl*)*urea*. A refluxing suspension of the foregoing compound (38·9 g) in ethanol (150 ml) was treated with a solution of sodium hydroxide (8·8 g) in water (10 ml) and heating continued for 3 hr. It was then evaporated to dryness at reduced pressure and the residue dissolved in water (500 ml), heated to 80° with decolorising charcoal and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid to yield the *product* (18·2 g), m.p. 169·5–170° (decomp.) (corr.) after crystallisation from aqueous ethanol.

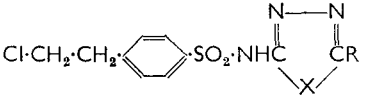
3-[p-(2-*Chloroethyl*)*benzenesulphonyl*]-1-*t-butylurea* was prepared in 80% yield by reaction of t-butyl isocyanate with *p*-(2-chloroethyl)benzenesulphonamide in aqueous acetone containing an equivalent of sodium hydroxide as described earlier. It had m.p. 142–143° (from aqueous ethanol). 3-(p-*Vinylbenzenesulphonyl*)-1-*t-butylurea* was obtained in 80% yield when a solution of the foregoing compound (8 g) in ethanol (75 ml) was treated with a solution of sodium hydroxide (2·5 g) in water (4 ml) and the mixture refluxed for 3 hr. It had m.p. 134–135° (from aqueous ethanol). 1-*Propyl*-3-(p-*vinylbenzenesulphonyl*)*thiourea*. Propyl isothiocyanate (2·4 g) was added with stirring to a solution of styrene-4-sulphonamide (3·7 g) in acetone (45 ml) containing 10N sodium hydroxide solution (2 ml) at 0–5°. The mixture was stirred at 20–25° for 4 hr, and then poured onto crushed ice. After filtration the filtrate was acidified to yield the *product* (4·4 g), m.p. 90–91° [from benzene-light petroleum b.p. 60–80°)].

The following examples illustrate other methods used for the preparation of some of the compounds listed in the Tables:

1-[p-(2-*Chloroethyl*)*benzenesulphonyl*]-3-*cyclohexylurea*. (*a*) *Ethyl* p-(2-*chloroethyl*)*benzenesulphonylcarbamate* (see Marshall & Segal, 1958). A mixture of *p*-(2-chloroethyl)benzenesulphonamide (11 g) and anhydrous potassium carbonate (20 g) in acetone (100 ml) was heated under reflux with stirring, and ethyl chloroformate (6 g) added during 1 hr. Heating was continued for a further 3 hr and the solid collected after cooling. This was dissolved in water (80 ml) and acidified with hydrochloric acid to yield the *product* (10·1 g), m.p. 107–109° (from dilute ethanol). Found: C, 45·5; H, 5·0; Cl, 12·2; N, 5·1; S, 10·9. $C_{11}H_{14}ClNO_4S$ requires C, 45·3; H, 4·8; Cl, 12·2; N, 4·8; S, 11·0%.

(*b*) A solution of the foregoing carbamate (2·9 g) in boiling toluene (25 ml) was treated with cyclohexylamine (1 g) and the mixture heated

TABLE 4. 5-SUBSTITUTED 2-[*p*-(2-CHLOROETHYL)BENZENESULPHONAMIDO]-1,3,4-THIADIAZOLES AND -1,3,4-OXADIAZOLES



R	X	m.p. °C	Formula	Found					Required				
				C	H	Cl	N	S	C	H	Cl	N	S
Propyl	S	126–127	$C_{13}H_{16}ClN_3O_2S_2$	45·1	4·8	10·4	12·0	18·7	45·1	4·7	10·25	12·1	18·55
Isopropyl	S	133–134	$C_{13}H_{16}ClN_3O_2S_2$	45·3	4·5	10·3	12·2	18·6	45·1	4·7	10·25	12·1	18·55
Cyclopropyl	S	166–168	$C_{13}H_{14}ClN_3O_2S_2$	45·5	3·7	10·4	12·1	18·5	45·4	4·1	10·3	12·2	18·65
Isobutyl	S	134–135	$C_{14}H_{18}ClN_3O_2S_2$	46·5	4·8	9·9	11·6	17·9	46·7	5·0	9·85	11·7	17·8
s-Butyl	S	121–122	$C_{14}H_{18}ClN_3O_2S_2$	47·0	5·1	10·1	11·4	18·2	46·7	5·0	9·85	11·7	17·8
t-Butyl	S	204–206	$C_{14}H_{18}ClN_3O_2S_2$	46·7	5·0	9·9	11·6	17·8	46·7	5·0	9·85	11·7	17·8
Cyclopentyl	S	151–153	$C_{15}H_{18}ClN_3O_2S_2$	48·9	5·2	9·6	11·0	17·3	48·5	4·9	9·5	11·3	17·25
Cyclohexyl	S	180–183	$C_{16}H_{20}ClN_3O_2S_2$	49·5	5·1	9·4	10·8	16·7	49·8	5·2	9·2	10·9	16·6
2-Cyclopentylethyl	S	204–206	$C_{17}H_{22}ClN_3O_2S_2$	51·1	5·9	9·2	10·5	16·4	51·0	5·5	8·9	10·5	16·6
Ethyl	O	139–141	$C_{12}H_{14}ClN_3O_3S$	45·9	4·4	11·1	13·2	10·0	45·6	4·5	11·2	13·3	10·15
Propyl	O	110–112	$C_{13}H_{16}ClN_3O_3S$	47·7	4·7	11·0	12·9	9·9	47·3	4·9	10·75	12·7	9·7
Isopropyl	O	118–120	$C_{13}H_{16}ClN_3O_3S$	47·6	5·0	11·0	12·6	10·0	47·3	4·9	10·75	12·7	9·7
Isobutyl	O	100–102	$C_{14}H_{18}ClN_3O_3S$	49·0	5·0	10·7	12·4	9·6	48·9	5·3	10·3	12·2	9·3
t-Butyl	O	161–163	$C_{14}H_{18}ClN_3O_3S$	48·6	5·5	10·3	12·2	8·9	48·9	5·3	10·3	12·2	9·3
Cyclohexyl	O	102–103	$C_{16}H_{20}ClN_3O_3S$	52·1	5·4	10·0	11·7	9·1	51·95	5·45	9·6	11·4	8·7

under reflux for 4 hr, after which time volatile material was distilled off at reduced pressure. The residue was extracted with 1% aqueous ammonia solution, filtered, and the filtrate acidified with dilute hydrochloric acid. The *product* (1·2 g) had m.p. 129–130° (from aqueous ethanol).

1-*Butyl*-3-[p-(2-*chloroethyl*)*benzenesulphonyl*]*urea* [see Georgiev (1960) and Das Gupta (1961)]. (*a*) p-(2-*Chloroethyl*)*benzenesulphonylurea*. A mixture of p-(2-chloroethyl)benzenesulphonamide (22 g) and potassium cyanate (10·1 g) in ethanol (200 ml) and heated under reflux for 2 hr, and then ethanol (100 ml) was distilled off. The potassium salt was collected, dissolved in water, filtered, and the filtrate acidified with dilute hydrochloric acid to yield the *product* (18 g), m.p. 178–180° (from ethanol). Found: C, 41·2; H, 4·3; Cl, 13·2; N, 10·7; S, 11·9. $C_9H_{11}ClN_2O_3S$ requires C, 41·2; H, 4·2; Cl, 13·5; N, 10·7; S, 12·2%.

(*b*) A mixture of the foregoing sulphonylurea (6·6 g), isobutyl methyl ketone (20 ml) and acetone (2 ml) was treated with butylamine (2 g), added during 20 min with occasional shaking. It was then heated under reflux for 2 hr, cooled, treated with 4% aqueous sodium hydroxide solution (25 ml), and the organic layer separated and washed with water. The combined aqueous extracts were acidified with dilute sulphuric acid and the *product* (6·55 g) collected. It had m.p. 122–123° (from aqueous ethanol).

2 (*a*) 1-*Butyl*-3-[p-(2-*chloroethyl*)*benzenesulphonyl*]*thiourea*. Butyl isothiocyanate (12·7 g) was added with stirring to a mixture of p-(2-chloroethyl)benzenesulphonamide (22·0 g) in acetone (225 ml) containing sodium hydroxide (4 g) in water (4 ml) at 0–5°. It was then warmed to 50° for 3 hr, cooled and poured onto crushed ice (2 litres). The solution was filtered and the filtrate acidified with hydrochloric acid to yield the *product* (26·5 g), m.p. 110–112° (from aqueous ethanol). Found: C, 46·9; H, 5·7; Cl, 10·5; N, 8·6; S, 18·7. $C_{13}H_{19}ClN_2O_2S$ requires C, 46·6; H, 5·7; Cl, 10·6; N, 8·4; S, 19·2%.

(*b*) Hydrogen peroxide (10 ml of 10% solution) was added to a stirred solution of the foregoing sulphonylthiourea (4 g) in water (60 ml) containing sodium hydroxide (2·0 g) and the mixture was warmed to 40° for 1 hr. The solution was cooled, acidified with dilute hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water and the chloroform distilled off to yield the *product* (1·6 g), m.p. 122–123° (from aqueous ethanol).

1-[p-(2-*Bromoethyl*)*benzenesulphonyl*]-3-*cyclohexylurea* [see Nantka-Namirski & Betzecki (1959)]. (*a*) O-*Methylcyclohexylurea*. A mixture of cyclohexylurea (25·6 g) and dimethyl sulphate (25·2 g) was heated carefully to 100°, kept at that temperature for 10 min, then it was cooled, poured onto crushed ice and basified with 30% aqueous sodium hydroxide solution. The mixture was extracted with benzene, the benzene was distilled off and the residual oil distilled at 8 mm to yield the *product*, b.p. 115–118°. Found: N, 17·8. $C_8H_{16}N_2O$ requires N, 17·9%.

(*b*) Solutions of the foregoing urea (3·9 g) in acetone (10 ml) and of p-(2-bromoethyl)benzenesulphonyl chloride (7·1 g) in acetone (10 ml) were added simultaneously to a stirred mixture of potassium carbonate

(3·4 g) in acetone (15 ml) and water (10 ml) at 10° and stirring was continued for 1 hr further. The mixture was poured onto crushed ice (150 ml), extracted with benzene and the extract washed once with water and concentrated. The residual material was hydrolysed by heating with concentrated hydrochloric acid on the steam-bath for 10 min. The crude material (7 g) was collected, washed with water, dissolved in 2% aqueous ammonia solution and filtered to remove insoluble material. Acidification of the filtrate with dilute hydrochloric acid yielded the *product* (3·3 g), m.p. 165–166° (from aqueous ethanol).

2-*Amino*-5-*cyclopentyl*-1,3,4-*thiadiazole*. Cyclopentylcarbonyl chloride (48·5 g) was added to a mixture of thiosemicarbazide (30·5 g) and phosphorus trichloride (40 ml), which was then heated at 60–70° for 5 hr. The mixture was then cooled, diluted with water (300 ml) and the solution basified with 20% aqueous sodium hydroxide solution. The solids were collected, washed with cold water, dissolved in warm dilute hydrochloric acid, filtered and the filtrate basified with aqueous sodium hydroxide solution. The *product* (26·2 g) had m.p. 234–236° (decomp) (from aqueous ethanol). Found: C, 49·6; H, 6·3; N, 24·9; S, 19·0. Calc. for $C_7H_{11}N_3S$: C, 49·7; H, 6·55; N, 24·8; S, 18·9%.

2-*Amino*-5-(2-*cyclopentylethyl*)-1,3,4-*thiadiazole* had m.p. 234–236° (from ethanol). Found: C, 54·7; H, 7·7; N, 21·1; S, 16·6. $C_9H_{15}N_3S$ requires C, 54·8; H, 7·7; N, 21·3; S, 16·25%.

2-[p-(2-*Chloroethyl*)*benzenesulphonamido*]-5-(2-*cyclopentylethyl*)-1,3,4-*thiadiazole*. A solution of the foregoing thiadiazole (9·85 g) in pyridine (35 ml) was cooled slightly and treated with a solution of *p*-(2-chloroethyl)-benzenesulphonyl chloride (12 g) in pyridine (35 ml) and the mixture allowed to stand at room temperature overnight. It was then poured into water (250 ml) and the solution acidified with hydrochloric acid. The solids (15·8 g) were collected, washed with water, dissolved in 2% aqueous ammonia solution and the solution heated to 60° and filtered after the addition of decolorising charcoal. The filtrate was acidified with dilute hydrochloric acid to yield the *product*, m.p. 204–206° (from ethanol).

5-*Isobutyl*-2-(p-*vinylbenzenesulphonamido*)-1,3,4-*thiadiazole*. A solution of 2-[*p*-(2-chloroethyl)benzenesulphonamido]-5-isobutyl-1,3,4-thiadiazole (18·05 g) in ethanol (200 ml) was treated with a solution of sodium hydroxide (5 g) in water (5 ml) and the mixture was heated under reflux for 4 hr. Solvent was distilled off at reduced pressure, the residual solid was dissolved in water (200 ml) and the solution was acidified with hydrochloric acid. The *product* (12·2 g) had m.p. 135–136° (from aqueous ethanol). Found: C, 51·6; H, 5·7; N, 12·8; S, 19·6. $C_{14}H_{17}N_3O_2S_2$ requires C, 52·0; H, 5·3; N, 13·0; S, 19·8%.

5-*Isopropyl*-2-(*p-vinylbenzenesulphonamido*)-1,3,4-*thiadiazole*, prepared by the foregoing method, had m.p. 122–123° (from aqueous ethanol). Found: C, 50·5; H, 5·1; N, 13·4; S, 20·5. $C_{13}H_{15}N_3O_2S_2$ requires C, 50·4; H, 4·9; N, 13·6; S, 20·7%.

2-*Amino*-5-*isopropyl*-1,3,4-*oxadiazole* (compare Swain, U.S. Patent 2,883,391). A solution of isobutyrohydrazide (36·8 g) in methanol

(70 ml) was added dropwise with stirring to a solution of cyanogen bromide (38·6) in methanol (70 ml), with cooling to 20–25°. After the addition was complete the mixture was refluxed for 2 hr, and then concentrated to remove most of the methanol. The residual oil was dissolved in boiling water (70 ml) and the solution brought to pH 8–9 by the addition of ammonia solution. The solids (17·8 g) were dissolved in acetone and the solution was filtered to remove insoluble material. Dilution of the filtrate with light petroleum (b.p. 60–80°) furnished the *product*, m.p. 180–182° (from acetone). Found: C, 47·5; H, 7·5; N, 33·4. $C_5H_9N_3O$ requires C, 47·2; H, 7·1; N, 33·05%.

2-*Amino*-5-*isobutyl*-1,3,4-*oxadiazole* had m.p. 167–169° after crystallisation from acetone-light petroleum (b.p. 40–60°). Found: C, 51·4; H, 8·3; N, 29·7. $C_6H_{11}N_3O$ requires C, 51·0; H, 7·85; N, 29·8%.

2-*Amino*-5-*t-butyl*-1,3,4-*oxadiazole* had m.p. 222–224° (from aqueous ethanol). Found: C, 50·9; H, 7·8; N, 30·2. $C_6H_{11}N_3O$ requires C, 51·0; H, 7·85; N, 29·8%.

2-[p-(2-*Chloroethyl*)*benzenesulphonamido*]-5-*propyl*-1,3,4-*oxadiazole*. A solution of 2-amino-5-propyl-1,3,4-oxadiazole (12·7 g) in pyridine (60 ml) was cooled below 20° and treated with a solution of *p*-(2-chloroethyl)-benzenesulphonyl chloride (23·9 g) in pyridine (60 ml). The mixture was allowed to stand overnight and then diluted with water (250 ml) and acidified with concentrated hydrochloric acid with cooling. The solids were collected, washed with water and dissolved in dilute ammonia solution. The solution was heated to 50° and filtered after the addition of decolorising charcoal. Acidification of the filtrate with dilute hydrochloric acid furnished the *product* (13·1 g), m.p. 110–112° (from aqueous ethanol).

References

Das Gupta, S. J. (1961). *J. Indian chem. Soc.*, **38**, 417–418.
Georgiev, A. (1960). *Compt. rend. acad. Bulgare sci.*, **13**, 315–318.
Gourley, D. R. H. (1958). *Proc. Soc. exp. Biol., N.Y.*, **99**, 68–71.
Gryglewski, R. (1958). *Dissertationes Pharm.*, **10**, 151–168.
Inskeep, G. E. & Deanin, R. (1947). *J. Amer. chem. Soc.*, **69**, 2237–2238.
Janbon, M., Chaptal, P., Vedel, A. & Schaap, J. (1942). *Montpellier méd.*, 441.
Loubatières, A. (1944). *Compt. rend. Soc. Biol., Paris*, **138**, 766.
Loubatières, A. (1955). *Therapie*, **10**, 907.
Marshall, J. & Sigal, M. V. (1958). *J. org. Chem.*, **23**, 923 and 927.
Nantka-Namirski, P. & Betzecki, C. (1959). *Acta Polon. Pharm.*, **16**, 475–478.
O'Neal, J. B., Rosen, H., Russell, P. B., Adams, A. C. & Blumenthal, A. (1962). *J. med. pharm. Chem.*, **5**, 617.
Shah, M. H., Mhasalkar, M. Y., Patki, V. M. & Deliwala, C. V. (1959). *J. Sci. Ind. Res. (India)*, **18B**, 202.
Swain, A. P. (1959). U.S. Patent 2,883,391.
Wiley, R. H. & Ketterer, C. C. (1953). *J. Amer. chem. Soc.*, **75**, 4519–4521.