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Hypoglycaemic agents*: variants of tolbutamide

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Further new variants of tolbutamide (and two new imidazolines) are described.

THE preparation of further new variants of the active compounds, 1-butyl-3-toluene-*p*-sulphonylurea (I; R=Me, R′=Bu), 1-perhydroazepin-1′-yl-3-toluene-*p*-sulphonylurea [I; R=Me, R′=$C_6H_{12}N$], (compare Dulin, Oster & McMahon, 1961), and 1-cyclohexyl-3-(*p*-vinylbenzenesulphonyl)-urea (I; R=CH:CH_2, R′=cyclohexyl) (Hayman, Petrow & Stephenson, 1964), is described herein.

Arylsulphonylureas containing a secondary or tertiary alkyl group R′, (I), were prepared by reaction of the sulphonylurethane (II; R=Cl or Me, R′=OEt) with the appropriate amine (Table 1). Additionally, two water-soluble derivatives [II; R=Cl or Me; R′=N(CH_2·CH_2OH)$_2$] were obtained by heating the urethanes with di(2-hydroxyethyl)amine.

p-Aminoacetophenone was converted into *p*-acetylbenzenesulphonyl chloride (III; R=CO·Me, R′=Cl) *via* the diazonium chloride (cf. Petrow, Stephenson & Wild, 1960), and thence to the sulphonylurea (I; R=CO·Me, R′=Bu) (Table 1). Whilst this work was in progress, the hypoglycaemic activity of this latter compound and of its *n*-propyl homologue, was reported by Blank, Farrina, Kerwin & Saunders (1961). Welles, Root & Anderson (1961) have discussed the metabolism of the cyclohexyl derivative (I; R=CO·Me, R′=cyclohexyl).

p-Acetylbenzenesulphonyl chloride was reacted with phosphorus pentachloride to yield *p*-(1-chlorovinyl)benzenesulphonyl chloride, smoothly converted to the sulphonamide (III; R=CCl:CH_2, R′=NH_2) with ammonia and thence to the sulphonylureas (I; R=CCl:CH_2, R′=Pr, Bu and cyclohexyl) by reaction with the appropriate isocyanates (Table 1).

Reaction of *p*-(2-chloroethyl)benzenesulphonamide (III; R=CH_2·CH_2·Cl, R′=NH_2) (Hayman, Petrow & Stephenson, 1964) with ethyl isocyanatoacetate yielded ethyl 5-[*p*-(2-chloroethyl)benzenesulphonyl] hydantoate (I; R=CH_2·CH_2·Cl, R′=CH_2·CO·OEt), which was converted by hot 6 N hydrochloric acid into the corresponding hydantoic acid (I; R=CH_2·CH_2·Cl, R′=CH_2·CO_2H). Dehydrohalogenation of the latter compound with aqueous ethanolic sodium hydroxide gave 5-(*p*-vinylbenzenesulphonyl)hydantoic acid (I; R=CH:CH_2, R′=CH_2·CO_2H). The ethyl ester of the latter compound was obtained directly by reaction of ethyl isocyanatoacetate with *p*-vinylbenzenesulphonamide.

Bromination of *p*-vinylbenzenesulphonamide (Hayman, Petrow & Stephenson, 1964) in acetic acid yielded the 1,2-dibromoethyl derivative (III; R=CHBr·CH_2Br, R′=NH_2), which on treatment with hot ethanolic

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* The fifth paper in this series.

potash gave *p*-ethynylbenzenesulphonamide (III; R=C:CH, R′=NH_2), and this was purified *via* its silver salt. The compound had the same melting-point as *p*-acetylbenzenesulphonamide, but analysis, mixed melting-point and infra-red spectrum confirmed its identity. The sulphonylureas (I; R=C:CH, R′=Pr, Bu and cyclohexyl) were obtained by normal means (Table 1).

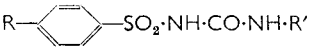
Stewart (1922) described *p*-sulphamoylcinnamic acid (III; R=CH:CH·CO_2H, R′=NH_2), obtained *via* chlorosulphonation of cinnamic acid, as a compound of m.p. 250–260°. Later, Burton & Hu (1949) obtained material of m.p. 276° by reaction of *p*-sulphamoylbenzaldehyde with malonic acid, whilst Müller (1949) obtained a compound of m.p. 285° by a Meerwein reaction between diazotised *p*-aminobenzenesulphonamide and acrylic acid. We have repeated Stewart's method of preparation, and obtained pure *p*-sulphamoylcinnamic acid, m.p. 275–277°, by alkaline hydrolysis of the readily purified methyl ester (III; R=CH:CH·CO·OMe, R′=NH_2). Preparation of the sulphonylbutylurea of the free acid (I; R=CH:CH·CO_2H, R′=Bu) was best accomplished by hydrolysis of the ethyl ester (I; R=CH:CH·CO·OEt, R′=Bu). The related diethylamide (I; R=CH:CH·CO·NEt_2, R′=Bu) was prepared by reaction of the di(acid chloride) (III; R=CH:CH·CO·Cl, R′=Cl) with diethylamine hydrochloride in refluxing chlorobenzene solution to yield the carboxyamide (III; R=CH:CH·CO·NEt_2, R′=Cl) (compare Jackman, Petrow, Stephenson & Wild, 1963). The latter compound was then converted *via* the sulphonamide (III; R=CH:CH·CO·NEt_2, R′=NH_2) into the sulphonylbutylurea by standard means (Table 1).

Acylated sulphonamides (III; R=Me or Cl, R′=NH·CO·Alk. or NH·CO·CH_2Ph) (Table 2) were obtained by refluxing the sulphonamide with the appropriate acid chloride in chlorobenzene solution.

Compounds bearing some formal resemblance to the active perhydroazepinyl compound [I; R=Me, R′=$C_6H_{12}N$] were prepared by reaction of the sulphonylurethanes (II; R=Me or Cl, R′=OEt) with diamines of type NH_2·[CH_2]$_n$·R′ [where n=2, 3 or 4 and R′=NEt_2, perhydro-azepin-1-yl ($C_6H_{12}N$) or NH·Ph] (Table 3). The intermediate diamines were obtained by methods analogous to those described by Pozhil'tsova-Arbuzov (1953), Welvart (1955) and Mull & others (1958).

In connection with another research project, we had found that 4-chloro-3-nitrobenzenesulphonamide (IV; R=H) reacted with excess of hydrazine in boiling ethanol to yield 1-hydroxy-6-sulphamoyl-benztriazole (V; R=H) (cf. Müller; Müller & Zimmerman; Müller & Hoffmann, 1925). Reaction of this compound with 1 or 2 moles of butyl isocyanate in aqueous alkaline acetone yielded mixed products which contained none of the required sulphonylurea (V; R=CO·NH·Bu). The latter compound was, however, readily obtained by reaction of 1-butyl-3-(4-chloro-3-nitrobenzenesulphonyl)urea (IV; R=CO·NH·Bu) with excess of hydrazine in boiling ethanol. The corresponding carbonyl derivative (VI) was similarly obtained *via* 1-butyl-3-(4-chloro-3-nitrobenzoyl)urea. Reaction of the sulphonamide (IV; R=H) with phenylhydrazine gave the required sulphamoylbenztriazole (VII; R=H). The same compound was

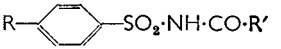
TABLE 1.



R	R′	m.p. (° C)	Formula	Found					Required				
				C	H	Cl	N	S	C	H	Cl	N	S
Me	$(C_3H_7)_2CH$	151–152	$C_{15}H_{24}N_2O_3S$	58·0	7·9		9·0	10·7	57·7	7·7		9·0	10·3
Me	$EtMe_2C$	128–130	$C_{13}H_{20}N_2O_3S$	55·1	7·0		9·9	11·4	54·9	7·1		9·9	11·3
Cl	$EtMe_2C$	140–142	$C_{12}H_{17}ClN_2O_3S$	47·5	5·3	12·0	9·0	10·5	47·3	5·6	11·6	9·2	10·5
Me	Et_3C	154–156	$C_{15}H_{24}N_2O_3S$	57·9	7·7		8·8	10·2	57·7	7·7		9·0	10·3
Me·CO	C_4H_9	156–157	$C_{13}H_{18}N_2O_4S$	52·5	6·1		9·4	10·6	52·3	6·1		9·4	10·7
$CH_2:C(Cl)$	C_3H_7	134–136	$C_{12}H_{15}ClN_2O_3S$	47·7	4·9	11·4	9·2	10·4	47·6	5·0	11·7	9·3	10·6
$CH_2:C(Cl)$	C_4H_9	136–138	$C_{13}H_{17}ClN_2O_3S$			11·0	8·7	10·3			11·2	8·8	10·1
$CH_2:C(Cl)$	Cyclohexyl	180–182	$C_{15}H_{19}ClN_2O_3S$	52·8	5·5	10·5	8·4	9·7	52·7	5·3	10·4	8·2	9·4
CH:C	C_3H_7	183–184	$C_{12}H_{14}N_2O_3S$	54·0	4·9		10·5	12·3	54·1	5·3		10·5	12·0
CH:C	C_4H_9	177–178	$C_{13}H_{16}N_2O_3S$				10·1	11·5				10·0	11·4
CH:C	Cyclohexyl	177–179	$C_{15}H_{18}N_2O_3S$	59·2	6·0		8·9	10·5	58·8	5·9		9·1	10·5
$HO_2C·CH:CH$	C_4H_9	217 (d.)	$C_{14}H_{18}N_2O_5S$	51·6	5·6		8·5		51·5	5·6		8·6	
MeO·O·C·CH:CH	Cyclohexyl	202–204	$C_{17}H_{22}N_2O_5S$	55·6	6·0		7·6	8·9	55·7	6·1		7·6	8·8
EtO·O·C·CH:CH	C_4H_9	129–131	$C_{16}H_{22}N_2O_5S$	54·5	6·4		8·2	9·0	54·2	6·3		7·9	9·1
$Et_2N·CO·CH:CH$	C_4H_9	188–190	$C_{18}H_{27}N_3O_4S$	56·8	7·0		10·8	8·4	56·7	7·1		11·0	8·4
H	4-Methylcyclohexyl*	178–180	$C_{14}H_{20}N_2O_3S$	57·0	6·7		9·6	10·8	56·7	6·8		9·5	10·8
Me	2-Methylcyclohexyl*	172–174	$C_{15}H_{22}N_2O_3S$	58·3	6·9		8·7	9·9	58·05	7·1		9·0	10·3
Cl	2-Methylcyclohexyl*	193–194	$C_{14}H_{19}ClN_2O_3S$	50·8	5·7	11·1	8·3	10·0	50·8	5·8	10·7	8·5	9·7

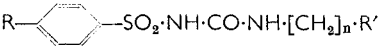
* *trans* isomer

TABLE 2.



R	R′	m.p. (° C)	Formula	Found					Required				
				C	H	Cl	N	S	C	H	Cl	N	S
Cl	Et	122–124	$C_9H_{10}ClNO_3S$	44·1	4·1	14·4	5·5	12·7	43·6	4·1	14·3	5·7	12·9
Cl	C_3H_7	99–101	$C_{10}H_{12}ClNO_3S$	46·0	4·3	13·6	5·5	12·2	45·9	4·6	13·6	5·4	12·3
Me	C_5H_{11}	79–81	$C_{13}H_{19}NO_3S$	58·1	6·9		5·3	11·7	57·9	7·1		5·2	11·9
Cl	C_5H_{11}	100–102	$C_{12}H_{16}ClNO_3S$	50·0	5·6		4·6		49·7	5·6		4·8	
Me	Et_2CH	96–98	$C_{13}H_{19}NO_3S$	58·4	7·0		4·9	12·0	57·9	7·1		5·2	11·9
Cl	Et_2CH	117–118	$C_{12}H_{16}ClNO_3S$	49·7	5·4	12·4	4·8	11·1	49·7	5·6	12·2	4·8	11·1
Me	$Ph{\cdot}CH_2$	149–151	$C_{15}H_{15}NO_3S$	62·0	5·3		5·0	11·4	62·3	5·2		4·8	11·1
Cl	$Ph{\cdot}CH_2$	152–153	$C_{14}H_{12}ClNO_3S$	54·5	4·0	11·9	4·7	10·7	54·3	3·9	11·4	4·5	10·4

TABLE 3.



R	R′	n	m.p. (° C)	Formula	Found					Required				
					C	H	Cl	N	S	C	H	Cl	N	S
Me	$C_6H_{12}N$	2	178–180	$C_{16}H_{25}N_3O_3S$	56·7	7·7		12·4	9·8	56·6	7·4		12·4	9·4
Cl	Et_2N	2	170–171	$C_{13}H_{20}ClN_3O_3S$	46·6	6·2	10·8	12·5	9·8	46·8	6·0	10·6	12·6	9·6
Cl	$C_6H_{12}N$	2	202–204	$C_{15}H_{22}ClN_3O_3S$	49·8	6·2	9·8	11·8	8·9	50·1	6·2	9·9	11·7	8·9
Cl	$C_6H_{12}N$	3	202–204	$C_{16}H_{24}ClN_3O_3S$	51·5	6·2	9·6	11·1	8·7	51·4	6·5	9·5	11·2	8·6
Cl	Ph·NH	3	144–145	$C_{16}H_{18}ClN_3O_3S$	52·7	5·2	9·8	11·3	8·6	52·2	4·9	9·6	11·4	8·7
Cl	$C_6H_{12}N$	4	184–185	$C_{17}H_{26}ClN_3O_3S$	52·1	6·5	9·2	11·0	8·2	52·6	6·8	9·1	10·8	8·3

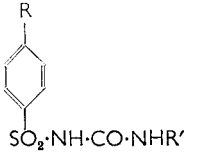
obtained from phenylhydrazine and the sulphonylurea (IV; R=CO·NH·Bu) due to fission of the urea group. Treatment of the sulphamoylbenztriazole (VII; R=H) with butyl isocyanate furnished the required butylsulphonylurea (VII; R=CO·NH·Bu). Both derivatives (VII; R=H or CO·NH·Bu) undoubtedly belong to the group of "meso-ionic" compounds (compare Goldstein & Voegeli, 1943 and Deorha & Joshi, 1961).

Further related benztriazoles, substituted in the 1-position by butyl, cyclohexyl or phenyl groups were obtained by reaction of the sulphonylurea (IV; R=CO·NH·Bu) with the appropriate amine to yield the nitro-amines (VIII; R=Bu, Ph or cyclohexyl, R′=NO_2). Reduction with sodium dithionite in aqueous ethanol gave the derived *o*-phenylenediamines (VIII; R=Bu, Ph or cyclohexyl, R′=NH_2), which were smoothly converted to the benztriazoles (IX; R=Bu, Ph or cyclohexyl) with nitrous acid. Additionally, 3-amino-4-butylaminobenzenesulphonamide was converted into the benzimidazole (X; R=H) by heating with formic acid, and this in turn yielded the required sulphonylurea (X; R=CO·NH·Bu).

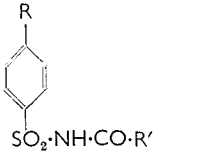
p-Vinylbenzoic acid, prepared by an improved procedure (cf. Jäger & Waight, 1963), was converted *via* its acid chloride into 1-butyl-3-(*p*-vinylbenzoyl)urea (XII; X=O) by reaction with butylurea. The corresponding thiourea (XII; X=S) was also prepared.

Following the report on the hypoglycaemic activity of salicylic acid derivatives by Luthra & Tayal (1962) and the testing of benzimidazole derivatives for such activity (Tiwari & Swaroop, 1962) we prepared three imidazolines (XIII; R=H, OH or Me) compounds which contain features common to both salicylates and benzimidazoles.

Of the compounds described, only the sulphonylureas of type (I; R=C:CH or CCl:CH_2, R′=butyl or cyclohexyl) possessed significant hypoglycaemic activity (Dr. A. David, private communication).



I



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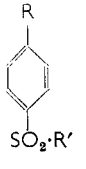

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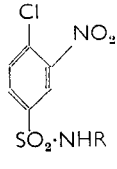

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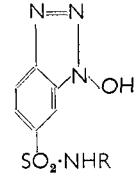

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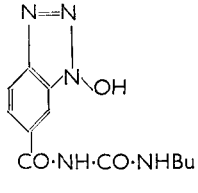

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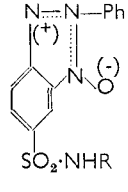

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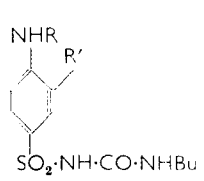
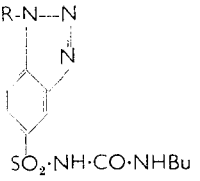


VIII



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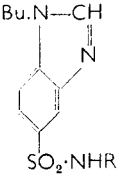

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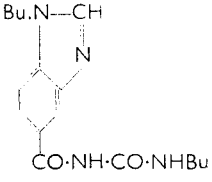

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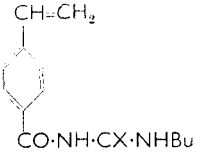
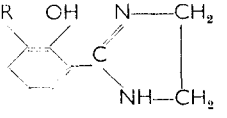


XII



XIII

Experimental

Melting-points are uncorrected.

The first seven examples illustrate the methods used for the compounds listed in Tables 1 to 3, which also include analytical data.

1-(1-*Propylbutyl*)-3-*toluene-p-sulphonylurea.* A mixture of 4-aminoheptane (11·5 g) and methyl toluene-*p*-sulphonylcarbamate (11·4 g) was heated on the steam-bath for 8 hr. It was then cooled, diluted with water (500 ml) and acidified with concentrated hydrochloric acid (20 ml). The resultant viscous material was extracted with 5% sodium carbonate solution and filtered to remove unchanged sulphonamide. Acidification of the filtrate yielded the *product* (5·8 g), which had m.p. 151 to 152° after crystallisation from aqueous ethanol.

1,1-Di(2-*hydroxyethyl*)-3-*toluene*-p-*sulphonylurea.* A mixture of ethyl toluene-*p*-sulphonylcarbamate (18·2 g) and di(2-hydroxyethyl)amine (21 g) in chlorobenzene (100 ml) was heated at 110–120° for 4 to 5 hr. The mixture was then cooled, poured into water (200 ml) containing ammonia solution (50 ml, d=0·880), and extracted twice with ether. The aqueous layer was cooled and acidified with hydrochloric acid to yield the *product* (16·0 g), m.p. 107–108° (decomp.) [from acetone-light petroleum (b.p. 60–80°)]. Found: C, 47·3; H, 5·9; N, 9·3; S, 10·2. $C_{12}H_{18}N_2O_5S$ requires C, 47·7; H, 6·0; N, 9·3; S, 10·6%.

1-(p-*Chlorobenzenesulphonyl*)-3,3-di(2-*hydroxyethyl*)*urea* had m.p. 105–107° (decomp.) [from acetone-light petroleum (b.p. 60–80°)]. Found: C, 41·3; H, 4·6; Cl, 10·9; N, 8·8; S, 10·1. $C_{11}H_{15}ClN_2O_5S$ requires C, 40·9; H, 4·7; Cl, 11·0; N, 8·7; S, 9·9%.

1-*Butyl*-3-(p-*acetylbenzenesulphonyl*)*urea.* (*a*) A solution of *p*-aminoacetophenone (36·8 g) in concentrated hydrochloric acid (95 ml) and water (45 ml) was diazotised at 0° to 5° with a solution of sodium nitrite (20·7 g) in water (35 ml). The resultant solution was added to a stirred saturated

solution of sulphur dioxide in acetic acid (220 ml) containing cupric chloride dihydrate (11·8 g). When the vigorous reaction was complete the mixture was diluted with ice-water. The *product* was collected and washed with cold water. A portion, crystallised from toluene-light petroleum (b.p. 60–80°), had m.p. 86–88°. Found: C, 44·4; H, 3·1; Cl, 16·4; S, 14·9. p-*Acetylbenzenesulphonyl chloride*, $C_8H_7ClO_3S$ requires C, 43·9; H, 3·2; Cl, 16·2; S, 14·7%. (*b*) A solution of the foregoing sulphonyl chloride in chloroform (300 ml) was added with stirring to ammonia solution (300 ml, d=0·880) at room temperature to yield p-*acetylbenzenesulphonamide*, m.p. 180–181° (aqueous ethanol). Found: C, 48·3; H, 4·7; N, 7·0; S, 16·0. $C_8H_9NO_3S$ requires C, 48·2; H, 4·6; N, 7·0; S, 16·1%. (Yield 62% for the two stages). (*c*) To a solution of the sulphonamide (19·9 g) in acetone (250 ml) was added a solution of sodium hydroxide (4·0 g) in a minimum of water. The mixture was stirred, cooled to 0° and treated with butyl isocyanate (10·9 g) added during 10 min. Water (125 ml) was added after a short while to dissolve separated solids. After 1 hr the mixture was filtered, the filtrate diluted with ice-water (300 ml) and acidified to pH 6 with acetic acid. The *product* (77%) was collected, and washed with cold water. It had m.p. 156 to 157° after crystallisation from aqueous ethanol.

1-*Butyl*-3-[p-(1-*chlorovinyl*)*benzenesulphonyl*]*urea*. A solution of *p*-acetylbenzenesulphonyl chloride (40 g) in toluene (100 ml) was added with stirring during 20 min to a slurry of phosphorus pentachloride (50 g) in toluene (100 ml), and the mixture was heated on a steam-bath for 30 min. It was then cooled and added slowly with stirring to ammonia solution (800 ml, d=0·880). Stirring was continued for 30 min, after which time the solids (16·4 g) were collected and washed with water. The sulphonamide had m.p. 143–144° (decomp.) after crystallisation from aqueous ethanol. Found: C, 44·1; H, 3·4; Cl, 16·4; N, 6·6; S, 14·8. p-(1-*Chlorovinyl*)*benzenesulphonamide*, $C_8H_8ClNO_2S$, requires C, 44·1; H, 3·7; Cl, 16·3; N, 6·4; S, 14·7%. Reaction of the sulphonamide with butyl isocyanate in aqueous alkaline acetone, as described earlier, furnished the *product* (91% yield), m.p. 136–138° (from aqueous methanol).

Ethyl 5-[p-(2-*chloroethyl*)*benzenesulphonyl*]*hydantoate*. Ethyl isocyanatoacetate (27·1 g) was added during 15 min to a stirred mixture of *p*-(2-chloroethyl)benzenesulphonamide (44 g) in acetone (400 ml) and sodium hydroxide (8·0 g) in water (30 ml) at 0°–5°. When the addition was complete, stirring was continued for 4 hr at 25°, and then the mixture was poured into ice-cold water (3 litres) and filtered. Acidification of the filtrate with dilute hydrochloric acid yielded the *product* (63·2 g), m.p. 127–129° [from acetone-light petroleum (b.p. 60–80°)]. Found: C, 45·1; H, 5·0; Cl, 10·3; N, 7·9; S, 9·3. $C_{13}H_{17}ClN_2O_5S$ requires C, 44·75; H, 4·9; Cl, 10·2; N, 8·0; S, 9·2%.

5-[p-(2-*Chloroethyl*)*benzenesulphonyl*]*hydantoic acid*. The foregoing hydantoate (53·8 g) was heated on the steam-bath with 6 N hydrochloric acid (270 ml) for 1 hr. After cooling, the solids were collected, washed with water, and dissolved in 2% ammonia solution. The solution was filtered and the filtrate acidified with hydrochloric acid to yield the

product (45·4 g), m.p. 179–180° (decomp.) (from dilute ethanol). Found: C, 41·5; H, 4·0; Cl, 11·2; N, 9·0; S, 10·2. $C_{11}H_{13}ClN_2O_5S$ requires C, 41·2; H, 4·1; Cl, 11·1; N, 8·7; S, 10·0%.

5-(p-*Vinylbenzenesulphonyl*)*hydantoic acid.* A solution of the foregoing hydantoic acid (21·2 g) in ethanol (250 ml) was heated on the steam-bath and treated portionwise with a solution of sodium hydroxide (8·0 g) in water (30 ml). The reaction was completed by heating for 1 hr, and then the solvent was distilled off at reduced pressure. The residue was dissolved in hot water (200 ml) and filtered after the addition of charcoal. After cooling, the filtrate was acidified with dilute hydrochloric acid to yield the *product*, m.p. about 200° (decomp.) (from aqueous ethanol). Found: C, 46·7; H, 4·3; N, 9·5; S, 11·3. $C_{11}H_{12}N_2O_5S$ requires C, 46·5; H, 4·3; N, 9·9; S, 11·3%.

Ethyl 5-(p-*Vinylbenzenesulphonyl*)*hydantoate* was prepared by reaction of ethyl isocyanatoacetate (7·1 g) with *p*-vinylbenzenesulphonamide (9·15 g) in acetone (120 ml) containing sodium hydroxide (2·0 g) dissolved in water (5 ml). It had m.p. 173–4° (decomp.) (from ethanol). Found: C, 49·6; H, 5·2; N, 9·0; S, 10·2. $C_{13}H_{16}N_2O_5S$ requires C, 50·0; H, 5·2; N, 9·0; S, 10·3%.

1-*Cyclohexyl*-3-(p-*ethynylbenzenesulphonyl*)*urea.* (*a*) p-(1,2-*Dibromoethyl*)*benzenesulphonamide.* A solution of styrene-*p*-sulphonamide (89 g) in acetic acid (890 ml) was treated with stirring with a solution of bromine (80 g) in acetic acid (100 ml). The *product* (106 g), isolated by dilution with water (1,500 ml), had m.p. 177–179° (from methanol). Found: C, 27·7; H, 2·7; Br, 46·1; N, 3·9; S, 9·0. $C_8H_9Br_2NO_2S$ requires C, 28·0; H, 2·6; Br, 46·6; N, 4·1; S, 9·3%.

(*b*) p-*Ethynylbenzenesulphonamide.* A solution of the foregoing dibromo-derivative (21 g) in ethanol (250 ml) was treated with a solution of potassium hydroxide (16 g) in a minimum of water, and the mixture heated under reflux for 90 min. Water (250 ml) and acetic acid (25 ml) were then added, the excess of ethanol was boiled off and the mixture was filtered hot after the addition of charcoal. The solids (9·4 g) were dissolved in methanol (200 ml), stirred and treated with a solution of silver nitrate (10 g) in water (50 ml). The acetylide was collected, washed with methanol and added to a stirred solution of potassium cyanide (20 g) in water (200 ml). The pH of the mixture was adjusted to 9 with dilute nitric acid. The *product* (4·8 g) had m.p. 180–182° after crystallisation from water. Found: C, 52·7; H, 3·5; N, 8·0; S, 18·0. $C_8H_7NO_2S$ requires C, 53·0; H, 3·9; N, 7·7; S, 17·7%.

(*c*) 1-Cyclohexyl-3-(*p*-ethynylbenzenesulphonyl)urea was obtained by reaction of the foregoing sulphonamide with cyclohexyl isocyanate in aqueous alkaline acetone. It had m.p. 177–179° after crystallisation from aqueous ethanol.

Methyl p-*sulphamoylcinnamate* was obtained by esterification of crude *p*-sulphamoylcinnamic acid (Stewart, 1922). It had m.p. 188–190° (from aqueous methanol). Found: C, 49·6; H, 4·6; N, 5·4. $C_{10}H_{11}NO_4S$ requires C, 49·8; H, 4·6; N, 5·8%. Hydrolysis of the ester (4·84 g) with a solution of sodium hydroxide (4·8 g) in water (30 ml) on the steam bath

for 1 hr yielded, after acidification, pure *p*-sulphamoylcinnamic acid, m.p. 275–277° after crystallisation from acetic acid (compare Burton & Hu, 1949 and Müller, 1949)

Ethyl p-*sulphamoylcinnamate* had m.p. 133–135° (from aqueous ethanol). Found: C, 51·6; H, 5·1; N, 5·4; S, 12·4. $C_{11}H_{13}NO_4S$ requires, C, 51·8; H, 5·1; N, 5·5; S, 12·6%.

p-*Chlorosulphonylcinnamoyl chloride.* A solution of *p*-chlorosulphonylcinnamic acid (49·4 g) in 1,2-dichloroethane (300 ml) containing formdimethylamide (2 ml) was heated to boiling and treated with thionyl chloride (36 g), added during 30 min. The mixture was heated under reflux for 4 hr and then the volatile material was distilled off. The residual *product* had m.p. 116–118° after crystallisation from 1,2-dichloroethane—light petroleum (b.p. 60–80°). Found: C, 41·2; H, 2·4; Cl, 26·8; S, 11·7. $C_9H_6Cl_2O_3S$ requires C, 40·7; H, 2·3; Cl, 26·7; S, 12·1%.

p-Chlorosulphonylcinnamdiethylamide. A solution of the foregoing di(acid chloride) (5·32 g) in chlorobenzene (30 ml) was treated with diethylamine hydrochloride (2·2 g) and the mixture heated under reflux for 6 hr. Most of the solvent was distilled off at reduced pressure, and then dilution with light petroleum (b.p. 60–80°) furnished the *product* (5·5 g), m.p. 103–104°. Found: C, 51·6; H, 5·2; Cl, 12·0; N, 4·7; S, 10·6. $C_{13}H_{16}ClNO_3S$ requires C, 51·7; H, 5·3; Cl, 11·7; N, 4·6; S, 10·6%.

p-*Sulphamoylcinnamdiethylamide*, obtained in 88% yield by reaction of the foregoing sulphonyl chloride with liquid ammonia, had m.p. 193–195° (from aqueous methanol). Found: C, 55·6; H, 6·2; N, 10·2; S, 11·4. $C_{13}H_{18}N_2O_3S$ requires C, 55·3; H, 6·4; N, 9·9; S, 11·4%.

p-(*Butylcarbamoylsulphamoyl*)*cinnamdiethylamide*, obtained by reaction of the foregoing sulphonamide with butyl isocyanate in aqueous alkaline acetone, had m.p. 188–190° (from ethanol).

N-p-*Chlorobenzenesulphonylbutyramide.* A mixture of *p*-chlorobenzenesulphonamide (38·3 g), butyryl chloride (23·3 g) and chlorobenzene (100 ml) was heated under reflux for 1 hr. Dilution with light petroleum (b.p. 60–80°) furnished the *product* (45 g), m.p. 99–101° [from benzene—light petroleum (b.p. 60–80°)].

1-(p-*Chlorobenzenesulphonyl*)-3-(2-*perhydroazepin*-1′-*ylethyl*)*urea.* A solution of methyl *p*-chlorobenzenesulphonylcarbamate (12 g) in toluene (120 ml) was treated with 2-perhydroazepin-1′-ylethylamine (9 g) (Welvart, 1955), and the mixture heated at 100° for 3 hr. The toluene was distilled off at reduced pressure and the solid residue crystallised from water to yield the *product* (50%), m.p. 202–204°.

3-*Perhydroazepin*-1′-*ylbutyronitrile.* 3-Chlorobutyronitrile (52·0 g) was added during 30 min to a solution of hexamethyleneimine (99 g) in a mixture of benzene (100 ml) and chloroform (20 ml), and the mixture was heated under reflux for 3 hr. The mixture was cooled and water added to dissolve the imine hydrochloride. The organic layer was washed with water, and the solvent distilled off. The residual oil was distilled at 0·01 mm to yield the *product* (64 g), b.p. 80–82°; n_D^{24}, 1·4710. Found: C, 72·1; H, 10·7; N, 16·9. $C_{10}H_{18}N_2$ requires C, 72·2; H, 10·9; N, 16·9%.

1-(4-*Aminobutyl*)*perhydroazepine*. A solution of the foregoing nitrile (64 g) in ethanol (300 ml) was reduced at 100°–110° and 50 atmos. pressure with hydrogen, using Raney nickel as catalyst. The *product* (49 g) had b.p. 85–90° at 0·1 mm and n_D^{20}, 1,481. Found: C, 70·4; H, 12·9; N, 16·9. $C_{10}H_{22}N_2$ requires C, 70·5; H, 13·0; N, 16·5%.

1-*Butyl*-3-(4-*chloro*-3-*nitrobenzenesulphonyl*)*urea* was obtained in 98% yield by reaction of 4-chloro-3-nitrobenzenesulphonamide (47·4 g) in acetone (450 ml) containing sodium hydroxide (8 g) in water (20 ml) with butyl isocyanate (24 g), using the method described earlier. The *product* had m.p. 169–170° (from methanol). Found: C, 39·5; H, 4·1, N, 12·3. $C_{11}H_{14}ClN_3O_5S$ requires C, 39·4; H, 4·20; N, 12·5%.

1-*Butyl*-3-(1-*hydroxybenztriazole*-6-*sulphonyl*)*urea*. A solution of the foregoing sulphonylbutylurea (20·1 g) in ethanol (100 ml) was heated with hydrazine hydrate (18 g) under reflux for 3 hr with removal of ethanol over the last hour. The straw-coloured residue was dissolved in water (250 ml) and the solution acidified with hydrochloric acid. The *product* was collected and washed with water. It (16·2 g) had m.p. 169° (decomp.) after crystallisation from aqueous ethanol. Found: C, 41·8; H, 5·0; N, 22·2; S, 10·4. $C_{11}H_{15}N_5O_4S$ requires C, 42·2; H, 4·8; N, 22·4; S, 10·2%.

1-*Butyl*-3-(4-*chloro*-3-*nitrobenzoyl*)*urea*. Butylurea (28 g) was added to a solution of 4-chloro-3-nitrobenzoyl chloride (48 g) in toluene (400 ml) containing pyridine (5 drops), and the mixture was heated under reflux for 6 hr. The *product* (53·5 g) separated on cooling. It had m.p. 143–145° after crystallisation from ethanol. Found: C, 48·5; H, 4·9; Cl, 11·7; N, 13·9. $C_{12}H_{14}ClN_3O_4$ requires C, 48·1; H, 4·7; Cl, 11·8; N, 14·0%.

1-*Butyl*-3-(1-*hydroxybenztriazole*-6-*carbonyl*)*urea* was obtained in 65% yield when a solution of the foregoing compound (25 g) in ethanol (250 ml) was heated with hydrazine hydrate (25 g) under reflux for 8 hr. It had m.p. 220° (decomp.) (from aqueous ethanol).

4-*Butylamino*-3-*nitrobenzenesulphonamide*. A mixture of 4-chloro-3-nitrobenzenesulphonamide (23·7 g) and butylamine (25 ml) in ethanol (50 ml) was heated under reflux for 2·5 hr. The *product* (26·8 g) was collected and washed with cold ethanol. It had m.p. 184°–185° (from ethanol). Found: C, 43·8; H, 5·3; N, 15·4; S, 11·8. $C_{10}H_{15}N_3O_4S$ requires C, 43·9; H, 5·5; N, 15·4; S, 11·7%.

3-*Amino*-4-*butylaminobenzenesulphonamide*. A hot solution of the foregoing nitroamine (13·65 g) in water (130 ml) and ethanol (75 ml) was treated portionwise with a slurry of sodium dithionite (28 g) in water (40 ml) (compare Ashton & Suschitzky, 1957). The mixture was heated on the steam-bath for 1 hr and then diluted with water. The *product* (10·4 g), which crystallised, had m.p. 127–129° (from water). Found: C, 49·3; H, 7·1; N, 17·3; S, 13·2. $C_{10}H_{17}N_3O_2S$ requires C, 49·4; H, 7·0; N, 17·3; S, 13·2%.

1-*Butyl*-5-*sulphamoylbenztriazole*. A suspension of the foregoing diamine (8·4 g) in water (150 ml), ethanol (20 ml) and concentrated hydrochloric acid (4 ml) was stirred vigorously and treated during 15 min with a solution of sodium nitrite (3 g) in water (20 ml), and then the

reaction was completed by warming the mixture to 60° for 1 hr. The *product* (6 g) was collected and washed with water. It was crystallised from water after the addition of charcoal and had m.p. 134–136°. Found: C, 47·1; H, 5·5; N, 21·8; S, 12·6. $C_{10}H_{14}N_4O_2S$ requires C, 47·2; H, 5·5; N, 22·1; S, 12·6%.

1-*Butyl*-3-(1-*butylbenztriazole*-5-*sulphonyl*)*urea*, obtained in 90% yield by reaction of the foregoing compound with butyl isocyanate in aqueous alkaline acetone, had m.p. 140–141° (aqueous methanol). Found: C, 51·3; H, 6·9; N, 20·1; S, 8·9. $C_{15}H_{23}N_5O_3S$ requires C, 51·0; H, 6·6; N, 19·8; S, 9·1%.

1-*Butyl*-5-*sulphamoylbenzimidazole*. A mixture of 3-amino-4-butylaminobenzenesulphonamide (9·7 g) and formic acid (10 ml) was heated on the steam-bath for 3 hr, and then the excess of formic acid was distilled off at reduced pressure. Crystallisation of the residual solid from aqueous ethanol furnished the *product* (9·4 g), m.p. 160–162°. Found: C, 52·1; H, 5·8; N, 17·2. $C_{11}H_{15}N_3O_2S$ requires C, 52·2; H, 6·0; N, 16·6%.

1-*Butyl*-3-(1-*butylbenzimidazole*-5-*sulphonyl*)*urea* was obtained in 83% yield by reaction of the foregoing sulphonamide with butyl isocyanate under standard conditions. It had m.p. 189–190° (from ethanol). Found: N, 15·9; S, 8·8. $C_{16}H_{24}N_4O_3S$ requires N, 15·9; S, 9·1%.

1-*Butyl*-5-*sulphamoylbenzimidazol*-2-*one*. An intimate mixture of 3-amino-4-butylaminobenzenesulphonamide (5 g) and urea (5 g) was heated at 150° for 3 hr and the residue stirred with water (40 ml) during cooling. The *product* (4·8 g) had m.p. 199–201° (from ethanol). Found: C, 49·0; H, 5·5; N, 15·2. $C_{11}H_{15}N_3O_3S$ requires C, 49·1; H, 5·6; N, 15·6%.

4-*Cyclohexylamino*-3-*nitrobenzenesulphonamide*, obtained in 82% yield from 4-chloro-3-nitrobenzenesulphonamide, had m.p. 165–167° (from ethanol). Found: C, 48·5, H, 5·8; N, 14·2; S, 10·6. $C_{12}H_{17}N_3O_4S$ requires C, 48·2; H, 5·7; N, 14·0; S, 10·7%.

3-*Amino*-4-*cyclohexylaminobenzenesulphonamide* was obtained in 67% yield by reduction of the foregoing nitro-compound with sodium dithionite in aqueous ethanol. It had m.p. 138–139° (aqueous ethanol). Found: C, 53·5; H, 7·1; N, 15·6; S, 11·9. $C_{12}H_{19}N_3O_2S$ requires C, 53·2; H, 7·6; N, 15·9; S, 11·7%.

1-*Cyclohexyl*-5-*sulphamoylbenztriazole*, obtained in 96% yield by diazotisation of the foregoing amine, had m.p. 219–220° (from aqueous ethanol). Found: C, 51·2; H, 5·6; N, 20·1; S, 11·5. $C_{12}H_{16}N_4O_2S$ requires C, 51·4; H, 5·8; N, 20·0; S, 11·4%.

1-*Butyl*-3-(1-*cyclohexylbenztriazole*-5-*sulphonyl*)*urea* had m.p. 164–166° (aqueous ethanol). Found: C, 53·9; H, 6·6; N, 18·4; S, 8·4. $C_{17}H_{25}N_5O_3S$ requires C, 53·8; H, 6·6; N, 18·5; S, 8·5%.

2-*Nitro*-4-*sulphamoyldiphenylamine* (compare Fischer, 1891) had m.p. 181–183° (from aqueous methanol). Found: C, 49·6; H, 3·9; N, 14·4, S, 11·0. Calc. for $C_{12}H_{11}N_3O_4S$: C, 49·1; H, 3·8; N, 14·3; S, 10·9%.

2-*Amino*-4-*sulphamoyldiphenylamine* had m.p. 156–158° (aqueous methanol). Found: C, 54·6; H, 5·1; N, 16·3; S, 12·1. $C_{12}H_{13}N_3O_2S$ requires C, 54·7; H, 5·0; N, 16·0; S, 12·2%.

1-*Phenyl*-5-*sulphamoylbenztriazole* had m.p. 257–259° after precipitation from alkaline solution with hydrochloric acid. Found: C, 52·7; H, 3·5; N, 20·8. $C_{12}H_{10}N_4O_2S$ requires C, 52·5; H, 3·7; N, 20·4%.

1-*Butyl*-3-(1-*phenylbenztriazole*-5-*sulphonyl*)*urea*, m.p. 165–167° (from ethanol). Found: C, 54·3; H, 4·9; N, 19·2. $C_{13}H_{19}N_5O_3S$ requires C, 54·7; H, 5·1; N, 18·8%.

1-*Oxy*-2-*phenyl*-6-*sulphamoylbenztriazole* was obtained by heating a mixture of 4-chloro-3-nitrobenzenesulphonamide (23·7 g) and phenylhydrazine (32·4 g) in ethanol (100 ml) for 7 hr. It had m.p. 252° (decomp.) after washing with dilute hydrochloric acid and then with ethanol. Found: C, 49·7; H, 3·6; N, 18·9; S, 11·0. $C_{12}H_{10}N_4O_3S$ requires C, 49·7; H, 3·5; N, 19·3; S, 11·0%.

1-*Butyl*-3-(1-*oxy*-2-*phenylbenztriazole*-6-*sulphonyl*)*urea*, m.p. 182–184° (from ethanol). Found: C, 52·7; H, 4·7; N, 18·3; S, 7·9. $C_{17}H_{19}N_5O_4S$ requires C, 52·4; H, 4·9; N, 18·0; S, 8·2%.

p-*Vinylbenzoyl chloride*. A solution of *p*-vinylbenzoic acid (29·6 g) in dry benzene (70 ml) was treated with thionyl chloride (36 ml), the mixture heated under reflux for 1 hr, and then the excess of volatile material was distilled off on a steam-bath at *ca* 30 mm. The residual oil was treated with hydroquinone (0·5 g) and distilled at 0·5 mm to yield the *product* (21·4 g), b.p. 91–92°. Found: C, 65·0; H, 4·3; Cl, 20·7. C_9H_7ClO requires C, 64·9; H, 4·3; Cl, 21·3%.

1-*Butyl*-3-(p-*vinylbenzoyl*)*urea*. A solution of *p*-vinylbenzoyl chloride (8·2 g) in benzene (25 ml) was added during 10 min to a stirred solution of butylurea (6·4 g) and pyridine (4 ml) in benzene (75 ml) at 10°. Stirring was continued for 1 hr and the mixture was then heated to 60° for 1 hr further. It was then cooled, the precipitate of pyridine hydrochloride was filtered off and the filtrate was concentrated to about 25 ml at reduced pressure. The *product* (7 g) separated on dilution with light petroleum (b.p. 60–80°). It had m.p. 116–118° (from ethanol). Found: C, 68·2; H, 7·4; N, 11·3. $C_{14}H_{18}N_2O_2$ requires C, 68·3; H, 7·4; N, 11·4%.

1-*Butyl*-3-(p-*vinylbenzoyl*)*thiourea*. *p*-Vinylbenzoyl chloride (11·0 g) was added during 5 min to a stirred solution of ammonium thiocyanate (5·7 g) in acetone (40 ml) and the mixture heated under reflux for 5 min. It was then cooled and treated during 10 min with a solution of butylamine (4 g) in acetone (15 ml) and finally heated under reflux for 15 min. Most of the acetone was boiled off and the residue was then stirred with water (200 ml). The water was decanted off and the residual solid triturated with methanol to yield the *product* (3·7 g), m.p. 77–79° [from light petroleum (b.p. 60–80°)]. Found: C, 64·1; H, 7·2; N, 10·5; S, 12·2. $C_{14}H_{18}N_2OS$ requires C, 64·0; H, 6·9; N, 10·7; S, 12·2%.

2-(*o-Hydroxyphenyl*)*imidazoline*. Phenyl salicylate (42·8 g) was added carefully to 1,2-diaminoethane (13·2 g) and the mixture heated at 180° (internal temperature) for 1 hr. Phenol and some water were then distilled off under reduced pressure. The residue was dissolved in 2 N hydrochloric acid (400 ml) and filtered to remove about 3 g of 1,2-di(*o*-hydroxybenzamido)ethane. The filtrate was evaporated to dryness at reduced pressure, and the residue dissolved in water and neutralised with

ammonia solution to yield the *product* (21·8 g), m.p. 207–209° (from methanol). Found: C, 66·5; H, 6·2; N, 17·5. Calc. for $C_9H_{10}N_2O$, C, 66·6; H, 6·2; N, 17·3%.

2-(2,3-*Dihydroxyphenyl*)*imidazoline hydrochloride* was obtained in 53% yield by reaction of methyl catechuate with 1,2-diaminoethane at 160–170° for 1 hr at about 100 mm pressure. It had m.p. 272–274° (decomp.) (from ethanol-ether). Found: C, 50·5; H, 5·2; Cl, 16·1; N, 13·0. $C_9H_{11}ClN_2O_2$ requires C, 50·4; H, 5·2; Cl, 16·5; N, 13·05%.

2-(2-*Hydroxy*-m-*tolyl*)*imidazoline*, obtained in 52% yield by reaction of phenyl 2-hydroxy-*m*-toluate with 1,2-diaminoethane, had m.p. 260–262° (from 2-ethoxyethanol). Found: C, 68·0; H, 6·6; N, 16·2. $C_{10}H_{12}N_2O$ requires C, 68·2; H, 6·9; N, 15·9%.

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