HYPOGLYCAEMIC AGENTS. PART III

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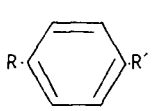
From the British Drug Houses Ltd., Graham Street, London, N.1

Received January 25, 1962

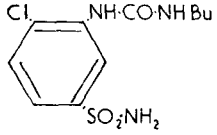
New variants of tolbutamide are described.

OUR work on hypoglycaemic agents is extended herein to some new variants of 1-butyl-3-*p*-toluenesulphonylurea (I; R = Me, R′ = SO_2·NH·CO·NHBu):

(*a*) 1-Cyclohexyl-3-*p*-fluorobenzenesulphonyl- and 3-*p*-fluorobenzenesulphonyl-1-phenyl-urea (I; R = F, R′ = SO_2·NH·CO·NH– cyclohexyl or Ph) have been prepared by reaction of the appropriate isocyanate with the sodium salt of *p*-fluorobenzenesulphonamide in aqueous acetone. The corresponding propyl and butyl analogues were previously described by Marshall and Sigal (1958).



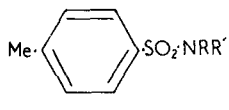
I



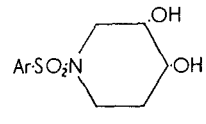
II

(*b*) 1-Butyl-3-*p*-methylsulphamoylphenylurea (I, R = SO_2·NHMe; R′ = NH·CO·NHBu) was prepared by reaction of *p*-aminobenzenesulphonmethylamide with butyl isocyanate in dioxan solution. 1-Butyl-3-(2-chloro-5-sulphamoylphenyl)urea (II) was similarly obtained from 3-amino-4-chlorobenzenesulphonamide (Petrow, Stephenson and Wild, 1960).

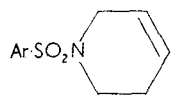
(*c*) Compounds containing a 3-arylsulphonylacetyl-1-butylurea group (I; R = F, Cl and Me; R′ = SO_2·CH_2·CO·NH·CO·NHBu) were prepared by reaction of 1-butyl-3-chloroacetylurea with the sodium salts of fluorobenzene-, chlorobenzene- and toluene-*p*-sulphinic acids.



III



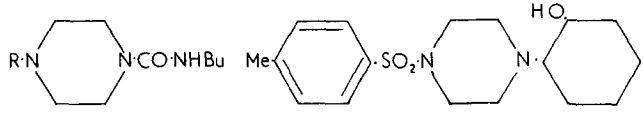
IV



V

(*d*) Budesinsky, Emr, Musil, Svab and Zikmund (1959) prepared a series of *p*-toluenesulphonamido-carboxylic acids. They reported that certain analogues of glycine (III, R = n-, iso- and t-butyl or t-pentyl; R′ = CH_2CO_2H) and of alanine (III, R = Pr; R′ = $CH(Me)CO_2H$) possessed up to 60 per cent of the hypoglycaemic activity of tolbutamide. We prepared the related *p*-fluoro- and *p*-chloro-benzenesulphonyl derivatives of α-alanine and α-amino-α-methylpropionic acid by reaction of the sodium salts of the acids with the appropriate sulphonyl chlorides in a two-phase 1,2-dichloroethane/water medium.

Work on amino-acid types was also extended to include the preparation of arylsulphonyl derivatives of di- and tri-hydroxy amines. Such compounds are relatively water-soluble and might be expected to metabolise *in vivo* to active amino-acids. Sulphonyl derivatives of the readily available 2-amino-2-methylpropane-1,3-diol and 2-amino-2-hydroxymethylpropane-1,3-diol were obtained by reaction with the appropriate arylsulphonyl chlorides in isopropanol or t-butanol in the presence of anhydrous sodium carbonate. 1-Arylsulphonyl derivatives of *cis*- and *trans*-piperidine-3,4-diol (IV) were prepared by hydroxylation of the 1-arylsulphonyl-1,2,3,6-tetrahydropyridine (V) under varied conditions. The *trans* diols (IV) were readily prepared by hydroxylation of the tetrahydropyridines with peracetic acid. The preparation of *cis*-cyclohexane-1,2-diol by hydroxylation of cyclohexene with sodium chlorate in aqueous solution using osmium tetroxide as catalyst was described by Böeseken and van Giffen (1920) and later by Clarke and Owen (1949). We found that the arylsulphonyltetrahydropyridines (V) were too insoluble in the aqueous medium to undergo hydroxylation by this method. The use of aqueous dioxan offered no advantages. However, high yields of *cis* diols were obtained using *ca* 65 per cent ethanol as hydroxylating medium at 50–60° progressive dilution of the mixture being carried out as the reaction proceeded.



VI VII

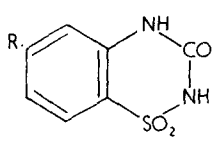
(*e*) Derivatives of butylcarbamoylpiperazine were prepared in which the 4-position was substituted by aroyl, furoyl, arylsulphonyl and diphenylcarbamoyl groups (cf. VI). Most of these were obtained by reaction of the appropriate acid chloride with 1-butylcarbamoylpiperazine (VI; R = H) but the *p*-methylbenzoyl derivative (VI, R = *p*-methylbenzoyl) was also obtained by reaction of 1-*p*-methylbenzoylpiperazine with butyl isocyanate.

Additionally, 1-formyl-4-*p*-toluenesulphonylpiperazine and 1-(*trans*-2-hydroxycyclohexyl)-4-*p*-toluenesulphonylpiperazine (VII) were synthesised.

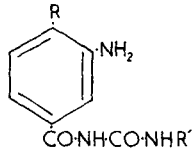
(*f*) The preparation of some 6-substituted 3,4-dihydro-3-oxobenzo-1,2,4-thiadiazine 1,1-dioxides (VIII) was undertaken as these compounds may be regarded as cyclised sulphonyl ureas.

They were readily obtained using the method first described by Parke and Williams (1950) whereby an amino-sulphonamide is heated with urea at 200–210°. Compounds were prepared in which the substituent R (VIII) was a methyl, methoxyl, trifluoromethyl group, or a fluorine, chlorine or bromine atom and the first of these was oxidised to the 6-carboxy derivative (VIII; R = CO_2H) using aqueous alkaline potassium permanganate.

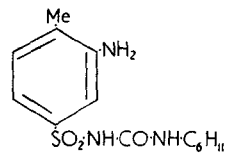
(*g*) Some 1-alkyl-(3-amino-4-methylbenzoyl)- and 1-alkyl-(3-amino-4-chlorobenzoyl)-ureas (IX, R = Me or Cl; R′ = Bu or C_6H_{11}) which bear a formal resemblance to the active hypoglycaemic agent, metahexanamide (X) (Haack, 1958), were obtained by reaction of the appropriate 4-methyl(or chloro)-3-nitrobenzoyl chloride with the alkylurea in benzene-pyridine followed by reduction of the nitro-compounds to the required amines.



VIII



IX



X

Biological study of the above compounds by Dr. A. David and his colleagues did not reveal significant hypoglycaemic activity.

Experimental

1-*Cyclohexyl*-3-p-*fluorobenzenesulphonylurea.* A solution of *p*-fluorobenzenesulphonamide (15·5 g.) in acetone (200 ml.) was cooled with stirring to 0° and treated successively with a solution of sodium hydroxide (3·6 g.) in water (10 ml.) and cyclohexyl isocyanate (12·1 g.). Stirring was continued at 0° for 30 min. then at 50–60° for 1 hr. when the mixture was cooled and poured into ice-water (600 ml.). After filtration to remove a small amount of insoluble material the filtrate was acidified to pH 6. The *product* (24·7 g.) had m.p. 144–145° after crystallisation from aqueous ethanol. Found: C, 52·1; H, 5·5; N, 9·7; S, 11·0. $C_{13}H_{17}FN_2O_3S$ requires C, 52·0; H, 5·7; N, 9·3; S, 10·7 per cent.

3-p-*Fluorobenzenesulphonyl*-1-*phenylurea,* had m.p. 154–156° after crystallisation from aqueous ethanol. Found: C, 53·1; H, 4·0; N, 9·5; S, 10·8. $C_{13}H_{11}FN_2O_3S$ requires C, 53·1; H, 3·8; N, 9·5; S, 10·9 per cent.

1-*Butyl*-3-p-*methylsulphamoylphenylurea.* To a solution of *p*-aminobenzenesulphonmethylamide (9·3 g.) in dioxan (50 ml.) was added butyl isocyanate (5·5 g.) and the mixture heated on the steam-bath for 4 hr. when excess of solvent was distilled off at reduced pressure. Crystallisation of the residue from aqueous ethanol yielded the *product* (7·3 g.), m.p. 165–167°. Found: C, 50·6; H, 6·7; N, 15·2; S, 11·2. $C_{12}H_{19}N_3O_3S$ requires C, 50·5; H, 6·7; N, 14·7; S, 11·2 per cent.

1-*Butyl*-3-(2-*chloro*-5-*sulphamoylphenyl*)*urea,* was prepared by reaction of 3-amino-4-chlorobenzenesulphonamide (11·36 g.) with butyl isocyanate (6 g.) in dioxan at 100° for 8 hr. The *product* (6·6 g.) had m.p. 188–190° (from aqueous ethanol). Found: C, 43·1; H, 5·3; Cl, 11·7; N, 13·8; S, 10·6. $C_{11}H_{16}ClN_3O_3S$ requires C, 43·2; H, 5·3; Cl, 11·6; N, 13·7; S, 10·5 per cent.

1-*Butyl*-3-(2-*methyl*-5-*sulphamoylphenyl*)*urea,* had m.p. 163–165° (from aqueous ethanol). Found: C, 50·1; H, 6·8; N, 14·3; S, 11·2. $C_{12}H_{19}N_3O_3S$ requires C, 50·4; H, 6·7; N, 14·7; S, 11·2 per cent.

1-*Butyl*-3-p-*toluenesulphonylacetylurea.* A solution of sodium toluene-*p*-sulphinate dihydrate (18·5 g.) and 1-butyl-3-chloroacetylurea (16·6 g.) in ethanol (200 ml.) was heated under reflux for 8 hr. The *product*, obtained on dilution, had m.p. 179–181° (from ethanol). Found: C, 53·6; H, 6·2; N, 8·9; S, 10·3. $C_{14}H_{20}N_2O_4S$ requires C, 53·8; H, 6·5; N, 9·0; S, 10·3 per cent.

1-*Butyl*-3-p-*fluorobenzenesulphonylacetylurea*, had m.p. 192–194° (from ethanol). Found: C, 49·5; H, 5·6; N, 8·4; S, 9·6. $C_{13}H_{17}FN_2O_4S$ requires C, 49·4; H, 5·4; N, 8·9; S, 10·1 per cent.

1-*Butyl*-3-p-*chlorobenzenesulphonylacetylurea*, had m.p. 212–214° (from ethanol). Found: C, 47·2; H, 5·2; Cl, 8·4; N, 11·0; S, 9·2. $C_{13}H_{17}ClN_2O_4S$ requires C, 46·9; H, 5·2; Cl, 8·4; N, 10·7; S, 9·6 per cent.

N-p-*Fluorobenzenesulphonyl*-DL-α-*alanine.* A solution of fluorobenzene-*p*-sulphonyl chloride (21·4 g.) in 1,2-dichloroethane (100 ml.) was added dropwise with stirring to a solution of DL-α-alanine (8·9 g.) in 2N sodium hydroxide (55 ml.) and stirring was continued for 4 hr. after the addition was complete. The aqueous layer was separated, cooled in ice and acidified with hydrochloric acid. The *product* (10·0 g.) had m.p. 116–117° (from benzene). Found: C, 43·6; H, 4·2; N, 5·9; S, 12·7. $C_9H_{10}FNO_4S$ requires C, 43·7; H, 4·1; N, 5·7; S, 13·0 per cent.

N-p-*Chlorobenzenesulphonyl*-DL-α-*alanine* was similarly prepared. It had m.p. 155° (from water). Found: C, 40·9; H, 3·5; Cl, 13·5; N, 5·5; S, 11·9. $C_9H_{10}ClNO_4S$ requires C, 41·0; H, 3·8; Cl, 13·5; N, 5·3; S, 12·2 per cent.

α-p-*Chlorobenzenesulphonamido*-α-*methylpropionic acid*, was obtained in 20 per cent yield by reaction of a solution of chlorobenzene-*p*-sulphonyl chloride in 1,2-dichloroethane with α-amino-α-methylpropionic acid in 2N sodium hydroxide at 30–35°. It had m.p. 168–170° (from water). Found: C, 43·2; H, 4·5; Cl, 12·7; N, 4·8; S, 11·2. $C_{10}H_{12}ClNO_4S$ requires C, 43·2; H, 4·4; Cl, 12·8; N, 5·0; S, 11·5 per cent.

2-*Methyl*-2-p-*toluenesulphonamidopropane*-1,3-*diol.* To a hot solution of 2-amino-2-methylpropane-1,3-diol (21 g.) in isopropanol (300 ml.) containing anhydrous sodium carbonate (16 g.), toluene-*p*-sulphonyl chloride (38·1 g.) was added in portions with stirring. The mixture was then heated under reflux for 30 min. and filtered hot. The *product* (34·5 g.) separated on cooling, it had m.p. 124–126° after crystallisation from water or ethyl acetate-light petroleum (b.p. 60–80°). Found: C, 51·0; H, 6·6; N, 5·2; S, 12·0. $C_{11}H_{17}NO_4S$ requires C, 51·0; H, 6·6; N, 5·4; S, 12·4 per cent. A better yield of product (38 g.) was later obtained using t-butanol in place of isopropanol.

5-*Methyl*-5-*p-toluenesulphonamido*-1,3-*dioxol*-2-*one.* A solution of the foregoing diol (25·9 g.) in ethyl carbonate (100 ml.) containing anhydrous sodium carbonate (1 g.) as catalyst was heated under reflux for 10 hr. when the solvent was removed at reduced pressure. The residual solid was extracted with boiling ethyl acetate to yield the *product* (17·9 g.), m.p. 149–150° after crystallisation from ethyl acetate-light petroleum (b.p. 60–80°). Found: C, 50·4; H, 5·1; N, 5·0; S, 11·0. $C_{12}H_{15}NO_5S$ requires C, 50·5; H, 5·3; N, 4·9; S, 11·2 per cent.

2-p-*Chlorobenzenesulphonamido-2-methylpropane*-1,3-*diol* had m.p. 134–135° (from ethyl acetate). Found: C, 42·8; H, 4·7; Cl, 13·0; N, 5·1; S, 11·8. $C_{10}H_{14}ClNO_4S$ requires C, 42·9; H, 5·0; Cl, 12·7; N, 5·0; S, 11·5 per cent.

2-*Hydroxymethyl*-2-p-*toluenesulphonamidopropane*-1,3-*diol*. To a hot stirred solution of 2-amino-2-hydroxymethylpropane-1,3-diol (36·3 g.) in isopropanol (400 ml.) containing anhydrous potassium carbonate (31·1 g.), a solution of toluene-*p*-sulphonyl chloride (57 g.) in toluene (100 ml.) was added during 20 min. The mixture was then refluxed for 2 hr., filtered hot and the residue washed with hot toluene (50 ml.). The filtrate was evaporated to dryness at reduced pressure and the residual solid dissolved in boiling ethyl acetate (300 ml.). The solid (14 g.) which separated on cooling was collected and had m.p. 139–140° (from ethyl acetate-ethanol). It proved to be the toluene-*p*-sulphonic acid salt of 2-amino-2-hydroxymethylpropane-1,3-diol (m.p. not depressed on admixture with authentic material). Further concentration of the filtrate yielded the *product* (30 g.), m.p. 107–108° (from ethyl acetate). Found: C, 48·2; H, 6·2; N, 5·0; S, 11·7. $C_{11}H_{17}NO_5S$ requires C, 47·9; H, 6·3; N, 5·1; S, 11·6 per cent.

2-*Acetoxymethyl*-1,3-*diacetoxy*-2-p-*toluenesulphonamidopropane*. A solution of the foregoing triol (15 g.) in acetic anhydride (75 ml.) was heated under reflux for 4 hr. After removal of the solvent at reduced pressure, the *product* (16·4 g.) had m.p. 100–102° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 51·1; H, 6·0; N, 3·4. $C_{17}H_{23}NO_8S$ requires C, 50·9; H, 5·8; N, 3·5 per cent.

1,2,3,6-*Tetrahydro*-1-p-*toluenesulphonyl-pyridine*. A solution of toluene-*p*-sulphonyl chloride (1 mole.) in chloroform (500 ml.) was added with stirring during 20 min. to a solution of 1,2,3,6-tetrahydropyridine (2 mole.) in water (600 ml.). After 4 hr. the mixture was acidified with hydrochloric acid, the chloroform layer was separated, washed with water, concentrated to half-bulk and diluted with light-petroleum (b.p. 60–80°). The *product* (90 per cent yield) had m.p. 102–104° [from light petroleum (b.p. 80–100°)]. Found: C, 60·7; H, 6·3; N, 5·7. $C_{12}H_{15}NO_2S$ requires C, 60·7; H, 6·4; N, 5·9 per cent.

3,4-*Dibromo*-1-p-*toluenesulphonylpiperidine* was prepared by reaction of the foregoing compound with bromine in acetic acid, had m.p. 116–117° (from aqueous ethanol). Found: C, 36·3; H, 3·4; N, 3·6; S, 8·3. $C_{12}H_{15}Br_2NO_2S$ requires C, 36·3; H, 3·8; N, 3·5; S, 8·1 per cent.

Trans-1-p-*Toluenesulphonylpiperidine*-3,4-*diol*. A solution of 1,2,3,6-tetrahydro-1-*p*-toluenesulphonylpyridine (47·4 g.) in acetic acid (50 ml.) at 80° was added to a solution of peracetic acid [prepared from acetic acid (150 ml.) and 30 per cent hydrogen peroxide (46 ml.)] at the same temperature and heating was continued for 4 hr. The solution was concentrated to one third bulk at reduced pressure, diluted with saturated salt solution and the oil isolated with chloroform. The chloroform extract was washed free from acid and peroxide and the solvent removed at reduced pressure. The residual product was boiled with 80 per cent ethanol (60 ml.) containing sodium carbonate (20 g.) for 30 min. when it

was diluted with water and extracted with chloroform. Concentration of the extract yielded the *product* (28·5 g.) m.p. 126–127° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 53·2; H, 6·1; N, 5·2; S, 11·5. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·3; N, 5·2; S, 11·8 per cent.

trans-3,4-*Diacetoxy*-1-p-*toluenesulphonylpiperidine*. A solution of the foregoing diol (8·8 g.) in acetic anhydride (50 ml.) was heated under reflux for 3 hr. when excess of anhydride was distilled at reduced pressure. The *product* (11 g.) had m.p. 106–107° from ethyl acetate-light petroleum (b.p. 60–80°). Found: C, 54·0; H, 6·1; N, 4·0; S, 8·7. $C_{16}H_{21}NO_6S$ requires C, 54·1; H, 6·0; N, 3·9; S, 9·0 per cent. It was reconverted into the original *trans*-diol by short warming with 0·5N ethanolic hydrochloric acid.

cis-1-p-*Toluenesulphonylpiperidine*-3,4-*diol*. A solution of 1,2,3,6-tetrahydro-1-*p*-toluenesulphonylpyridine (59·3 g.) in warm ethanol (600 ml.) was stirred, treated with a solution of sodium chlorate (35·5 g.) in water (200 ml.), heated to 60° and a solution of osmium tetroxide (0·25 g.) in water (125 ml.) added. Water (450 ml.) was added in portions to the mixture at intervals as the hydroxylation proceeded care being taken not to precipitate the starting material. Heating was continued for 4 hr. when the solution was filtered from osmic oxide and concentrated at reduced pressure until separation of solids occurred when the *product* (53·2 g.) was collected. Saturation of the filtrate with sodium chloride followed by extraction with chloroform yielded a further quantity (10·8 g.) of material. It had m.p. 138–139° (from ethyl acetate). Found: C, 52·9; H, 6·3; N, 5·3; S, 11·7. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·3; N, 5·2; S, 11·8 per cent. The *diacetyl* derivative had m.p. 131–133° (from ethanol). Found: C, 54·4; H, 5·8; N, 4·0; S, 8·6. $C_{16}H_{21}NO_6S$ requires C, 54·1; H, 6·0; N, 3·9; S, 9·0 per cent. It was reconverted into the *cis*-diol by heating at reflux temperature with N ethanolic hydrochloric acid.

1-p-*Chlorobenzenesulphonyl*-1,2,3,6-*tetrahydropyridine*, had m.p. 67–68° [from light petroleum (b.p. 60–80°)]. Found: C, 51·0; H, 4·8; Cl, 13·7; N, 5·2; S, 12·3. $C_{11}H_{12}ClNO_2S$ requires C, 51·3; H, 4·7; Cl, 13·8; N, 5·4; S, 12·5 per cent.

trans-1-p-*Chlorobenzenesulphonylpiperidine*-3,4-*diol* was prepared by hydroxylation of the foregoing compound with peracetic acid. It had m.p. 157–158° (from ethyl acetate). Found: C, 45·0; H, 5·0; N, 4·8; S, 11·1. $C_{11}H_{14}ClNO_4S$ requires C, 45·3; H, 4·8; N, 4·8; S, 11·0 per cent. In one reaction 4-*acetoxy*-3-*hydroxy*-1-p-*toluenesulphonylpiperidine* was isolated along with the required diol after hydrolysis of the crude reaction product with dilute ethanolic hydrochloric acid. It had m.p. 166–168° (from ethanol). Found: C, 47·0; H, 4·7; N, 4·5; S, 9·5. $C_{13}H_{16}ClNO_5S$ requires C, 46·8; H, 4·8; N, 4·2; S, 9·6 per cent. Infra-red spectra confirmed the presence of hydroxyl and acetoxy groups.

trans-3,4-*Diacetoxy*-1-p-*chlorobenzenesulphonylpiperidine* was obtained by heating the foregoing diol or its monoacetate with acetic anhydride. It had m.p. 152–154° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 47·7; H, 4·9; Cl, 9·8; N, 4·0; S, 8·4. $C_{15}H_{18}ClNO_6S$ requires C, 47·9; H, 4·8; Cl, 9·4; N, 3·7; S, 8·5 per cent.

cis-1-p-*Chlorobenzenesulphonylpiperidine*-3,4-*diol* was prepared by hydroxylation of 1-*p*-chlorobenzenesulphonyl-1,2,3,6-tetrahydropyridine with sodium chlorate-osmium tetroxide in aqueous ethanol. It (90 per cent yield) had m.p. 167–168° (from ethyl acetate). Found: C, 45·2; H, 4·6; N, 5·0. $C_{11}H_{14}ClNO_4S$ requires C, 45·3; H, 4·8; N, 4·8 per cent. The *diacetyl* derivative had m.p. 131–133° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 48·2; H, 4·9; N, 3·8; S, 8·2. $C_{15}H_{18}ClNO_6S$ requires C, 47·9; H, 4·8; N, 3·7; S, 8·5 per cent.

1-*Formyl*-4-p-*toluenesulphonylpiperazine*. A solution of 1-formylpiperazine (25 g.) (cf. Horrom, Freifelder and Stone, 1955), in benzene (100 ml.) was treated with a solution of toluene-*p*-sulphonyl chloride (20·75 g.) in benzene (50 ml.), when the mixture was heated under reflux for 1 hr. and filtered hot to remove formylpiperazine hydrochloride (15·5 g.). The product (22·9 g.) separated on cooling and had m.p. 144–145° (from benzene). Found: C, 54·0; H, 5·7; N, 10·4; S, 12·3. $C_{12}H_{16}N_2O_3S$ requires C, 53·7; H, 6·0; N, 10·4; S, 12·0 per cent.

1-*Butylcarbamoylpiperazine hydrochloride*. To a stirred solution of anhydrous piperazine (86 g.) in ethanol (900 ml.) was added concentrated hydrochloric acid (87·5 ml.). The solution was heated to 60° and treated with butyl isocyanate (100 g.) added during 20 min. The mixture was allowed to stand overnight and filtered to remove piperazine dihydrochloride [26 g., m.p. 345° (decomp.)]. The filtrate was concentrated to about 200 ml. and the *product* (136 g.) separated on cooling. It had m.p. 242–244° (from ethanol). Found: C, 48·7; H, 9·2; Cl, 15·8; N, 18·7. $C_9H_{20}ClN_3O$ requires C, 48·8; H, 9·1; Cl, 16·0; N, 19·0 per cent.

1-*Butylcarbamoyl*-4-p-*chlorobenzenesulphonylpiperazine*. A solution of the foregoing hydrochloride (22·15 g.) in pyridine (60 ml.) at about 60° was treated with chlorobenzene-*p*-sulphonyl chloride (21·1 g.) added during 15 min. When the addition was complete the mixture was allowed to cool and was diluted with water (500 ml.). The *product* (27 g.) which separated had m.p. 175–176° (from aqueous methanol). Found: C, 50·3; H, 6·3; Cl, 10·2; N, 12·1; S, 9·2. $C_{15}H_{22}ClN_3O_3S$ requires C, 50·0; H, 6·2; Cl, 9·9; N, 11·7; S, 8·9 per cent.

1-*Butylcarbamoyl*-4-p-*toluenesulphonylpiperazine* was obtained in 80 per cent yield using the foregoing method. It had m.p. 133–135° (from aqueous methanol. Found: C, 56·2; H, 7·2; N, 12·5; S, 9·8. $C_{16}H_{25}N_3O_3S$ requires C, 56·6; H, 7·4; N, 12·4; S, 9·4 per cent.

1-p-*Methylbenzoylpiperazine hydrochloride*. A solution of piperazine monohydrochloride, prepared from piperazine hexahydrate (77·6 g.) and concentrated hydrochloric acid (35 ml.), in ethanol (150 ml.) was stirred at 20° and treated with *p*-toluoyl chloride (30·9 g.) added during 20 min. The mixture was stirred for a further hour at room temperature and then for 30 min. at 70° when solvent was removed at reduced pressure. Water (2 vol.) was added to the residue to dissolve piperazine dihydrochloride and the insoluble *product* purified by crystallisation from methanol-acetone. It had m.p. 283–285° (decomp.). Found: C, 59·7; H, 7·2; Cl, 14·9; N, 11·6. $C_{12}H_{17}ClN_2O$ requires C, 59·9; H, 7·1; Cl, 14·7; N, 11·6 per cent.

1-*Butylcarbamoyl*-4-p-*methylbenzoylpiperazine.* (*a*) A solution of the foregoing hydrochloride (12·0 g.) in acetone (100 ml.) and water (40 ml.) was treated with sodium carbonate (2·7 g.) and butyl isocyanate (5 g.) and the mixture heated under reflux for 30 min. The acetone was boiled off and the residual solid crystallised from aqueous ethanol to yield the *product* (14 g.), m.p. 137–138°. Found: C, 67·2; H, 8·3; N, 13·0. $C_{17}H_{25}N_3O_2$ requires C, 67·3; H, 8·3; N, 13·8 per cent. (*b*) A suspension of 1-butylcarbamoylpiperazine (22·15 g.) in pyridine (50 ml.) was stirred and treated with *p*-toluoyl chloride (15·45 g.) added during 15 min. Reaction was completed by heating on the steam bath for 10 min. The mixture was cooled, diluted with ice-water (150 ml.) and acidified with 2N hydrochloric acid (about 180 ml.). The *product* (20 g.) had m.p. 137–138° when crystallised from aqueous methanol or ethyl acetate.

1-*Butylcarbamoyl*-4-*furoylpiperazine* was obtained in 63 per cent yield using the foregoing method. It has m.p. 135–137° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 60·4; H, 7·6; N, 15·0. $C_{14}H_{21}N_3O_3$ requires C, 60·2; H, 7·6; N, 15·0 per cent.

1-*Butylcarbamoyl*-4-*diphenylcarbamoylpiperazine*, had m.p. 168–169° (from ethyl acetate). Found: C, 69·6; H, 7·5; N, 14·7. $C_{22}H_{28}N_4O_2$ requires C, 69·4; H, 7·4; N, 14·7 per cent.

1-(2-*Hydroxycyclohexyl*)*piperazine dihydrochloride* (cf. Mousseron, 1932). A solution of 2-chlorocyclohexanol (67·3 g.) and piperazine hexahydrate (194 g.) in ethanol (400 ml.) was treated with a solution of potassium hydroxide (28 g.) in methanol (80 ml.) and the mixture heated under reflux for 4 hr. It was then concentrated to half bulk when 1,4-di(2-hydroxycyclohexyl)piperazine (15 g., m.p. 203–205°) separated on cooling and was removed. The filtrate was treated with carbon disulphide (25 ml.) and the resultant *dithiocarbamate* collected and washed with ethanol. This was suspended in ethanol (400 ml.), concentrated hydrochloric acid (60 ml.) added and the mixture heated under reflux for 1 hr. It was then concentrated at reduced pressure to yield the *product* (56·7 g.) m.p. 264–266° (from methanol). Found: C, 46·9; H, 8·5; Cl, 27·6; N, 11·2. $C_{10}H_{22}Cl_2N_2O$ requires C, 46·7; H, 8·6; Cl, 27·6; N, 10·9 per cent.

1-(2-*Hydroxycyclohexyl*)-4-p-*toluenesulphonylpiperazine.* A suspension of the foregoing dihydrochloride (21·5 g.) in pyridine (100 ml.) was stirred and treated with toluene-*p*-sulphonyl chloride (15·9 g.) and heated on the steam-bath for 15 min. The solution was cooled and poured into ice-water (500 ml.). The *product* (23 g.) was collected and washed with water. It had m.p. 169–171° (from aqueous ethanol). Found: C, 60·5; H, 7·7; N, 7·9; S, 9·3. $C_{17}H_{26}N_2O_3S$ requires C, 60·3; H, 7·7; N, 8·3; S, 9·5 per cent.

4-*Chlorosulphonyl*-3-*nitrotoluene* (compare Zincke and Rose, 1914). A solution of 4-amino-3-nitrotoluene (60·8 g.) in 24 per cent hydrochloric acid (480 ml.) was diazotised at 0° with a solution of sodium nitrite (30·8 g.) in water (72 ml.). The filtered solution was added with stirring to a saturated solution of sulphur dioxide in acetic acid (640 ml.) containing cupric chloride dihydrate (28 g.) at 15°. After 20 min. the mixture was diluted with ice-water and the *product* (90 g.) collected and washed with

ice water. It had m.p. 99–101° [from 1,2-dichloroethane-light petroleum (b.p. 60–80·)]. Found: C, 36·0; H, 2·5; Cl, 15·2; N, 6·0; S, 13·4. Calc. for $C_7H_6ClNO_4S$: C, 35·7; H, 2·6; Cl, 15·1; N, 5·9; S, 13·6 per cent.

3-*Nitrotoluene*-4-*sulphonamide*. The foregoing sulphonyl chloride was added with stirring during 20 min. to a mixture of ammonia solution (700 ml., d = 0·880) and chloroform (300 ml.) at 15–20°. After 1 hr. excess of ammonia and chloroform were boiled off and the residual liquid acidified. The *product* (68 g.) had m.p. 170–172° (from 40 per cent ethanol). Found: 39·5; H, 3·8; N, 13·0; S, 14·5. Calc. for $C_7H_8N_2O_4S$: C, 38·9; H, 3·7; N, 13·0; S, 14·9 per cent.

3-*Aminotoluene*-4-*sulphonamide*. A mixture of the foregoing nitro-compound (32·4 g.), iron powder (30 g.), water (200 ml.) 20 per cent acetic acid (9 ml.) and n-octanol (1 ml.) was heated under reflux for 3 hr. and filtered hot. The filtrate was boiled with charcoal, filtered and the solution cooled to 0°. The product (22 g.), had m.p. 126–127° (from water). Found: C, 45·6; H, 5·3; N, 15·1; S, 17·4. $C_7H_{10}N_2O_2S$ requires C, 45·2; H, 5·4; N, 15·1; S, 17·2 per cent.

3,4-*Dihydro*-6-*methyl*-3-*oxobenzo*-1,2,4-*thiadiazine* 1,1-*dioxide*. A mixture of the foregoing amine (18·6 g.) and urea (6·6 g.) was heated at 200° for 30 min. The residual solid was dissolved in hot water (150 ml.), cooled, and acidified to Congo red with concentrated hydrochloric acid. The *product* (18·5 g.), had m.p. 291–293° (from ethanol). Found: C, 45·4; H, 3·4; N, 13·4; S, 15·0. $C_8H_8N_2O_3S$ requires C, 45·3; H, 3·8; N, 13·2; S, 15·1 per cent.

6-*Carboxy*-3,4-*dihydro*-3-*oxobenzo*-1,2,4-*thiadiazine* 1,1-*dioxide*. A stirred solution of the foregoing compound (9·9 g.) in N/2 sodium hydroxide (150 ml.) was warmed to 60–70° and treated during 2 hr. with powdered potassium permanganate (14·7 g.). The mixture was filtered hot and the insoluble sludge washed with hot water. The combined filtrate and washings were cooled and acidified to pH 2 with concentrated hydrochloric acid. The *product* (9·75 g.) which separated, had m.p. 304–305° (decomp.) after crystallisation from water. Found: C, 39·9; H, 2·7; N, 11·6; S, 13·5. $C_8H_6N_2O_5S$ requires C, 39·7; H, 2·5; N, 11·6; S, 13·2 per cent.

4-*Methoxy*-2-*nitrobenzenesulphonamide*. A solution of 4-amino-3-nitroanisole (50·4 g.) in 24 per cent hydrochloric acid (360 ml.) was diazotised at 0–5° with a solution of sodium nitrite (23·2 g.) in water (54 ml.). The filtered solution was added to a stirred solution of acetic acid saturated with sulphur dioxide containing cupric chloride dihydrate (21·0 g., dissolved in a minimum of water) at 15°. Reaction was completed by warming to 25° for 20 min. when the mixture was diluted with ice water (1 litre). The *sulphonyl chloride* (82 g. moist) was used for the next stage of the reaction. A sample crystallised from 1,2-dichloroethane-light petroleum (b.p. 60–80°) had m.p. 80–82°. Found: C, 33·6; H, 2·5; Cl, 14·1; N, 5·4; S, 12·5. $C_7H_6ClNO_5S$ requires C, 33·4; H, 2·4; Cl, 14·1; N, 5·6; S, 12·8 per cent. Reaction with ammonia solution (d = 0·880)-chloroform as described earlier, furnished the *sulphonamide* (32 g.) m.p. 143–145° (from aqueous ethanol). Found: C, 36·4; H, 3·6;

N, 12·1; S, 13·7. $C_7H_8N_2O_5S$ requires C, 36·2; H, 3·5; N, 12·1; S, 13·8 per cent.

2-*Amino*-4-*methoxybenzenesulphonamide*. Reduction of the foregoing nitro-sulphonamide with iron powder in acidulated water as described earlier furnished the *product*, m.p. 141–142° after crystallisation from water. Found: C, 41·2; H, 5·1; N, 14·1; S, 16·0. $C_7H_{10}N_2O_3S$ requires C, 41·6; H, 5·0; N, 13·9; S, 15·9 per cent.

3,4-*Dihydro*-6-*methoxy*-3-*oxobenzo*-1,2,4-*thiadiazine* 1,1-*dioxide* was obtained in 82 per cent yield when the foregoing amino-sulphonamide (12·0 g.) was heated with urea (3·9 g.) at 210° for 30 min. It had m.p. 290–291° (decomp.) after crystallisation from ethanol. Found: C, 42·3; H, 3·3; N, 12·4; S, 14·2. $C_8H_8N_2O_4S$ requires C, 42·1; H, 3·5; N, 12·3; S, 14·1 per cent.

4-*Fluoro*-2-*nitrobenzenesulphonamide*. A solution of 4-fluoro-2-nitroaniline [cf. Swarts (1915)] in 24 per cent hydrochloric acid was diazotised and converted into the *sulphonyl chloride* as described earlier. This did not crystallise readily and was therefore dissolved in 1,2-dichloroethane, washed acid-free and added with stirring to aqueous ammonia (d = 0·880) to yield the *product*, m.p. 155–156° (from water). Found: C, 32·6; H, 2·2; N, 12·7. $C_6H_5FN_2O_4S$ requires C, 32·4; H, 2·3; N, 12·7 per cent.

2-*Amino*-4-*fluorobenzenesulphonamide*. A solution of the foregoing nitro-sulphonamide (4·47 g.) in ethanol (50 ml.) was hydrogenated in the presence of 5 per cent palladised charcoal (0·5 g.). The *product* (3·4 g.) had m.p. 126–128° (from water). Found: C, 37·8; H, 3·6; N, 14·8; S, 16·9. $C_6H_7FN_2O_2S$ requires C, 37·9; H, 3·7; N, 14·7; S, 16·9 per cent.

6-*Fluoro*-3,4-*dihydro*-3-*oxobenzo*-1,2,4-*thiadiazine*-1,1-*dioxide* was obtained by reaction of the foregoing amino-sulphonamide with urea at 200° for 30 min. It had m.p. 272–274° after crystallisation from water. Found: C, 38·8; H, 2·4; N, 12·8; S, 14·7. $C_7H_5FN_2O_3S$ requires C, 38·9; H, 2·3; N, 13·0; S, 14·8 per cent.

2-*Amino*-4-*chlorobenzenesulphonamide* was obtained in 80 per cent yield by reduction of 2-nitro-4-chlorobenzenesulphonamide [Meerwein *et al.* (1957)] with iron powder in 70 per cent ethanol containing 1 per cent of acetic acid. It had m.p. 139–141° after crystallisation from dilute ethanol. Found: C, 35·2; H, 3·2; Cl, 17·0; N, 13·5; S, 15·4. $C_6H_7ClN_2O_2S$ requires C, 34·9: H, 3·4; Cl, 17·2; N, 13·6; S, 15·5 per cent.

6-*Chloro*-3,4-*dihydro*-3-*oxobenzo*-1,2,4-*thiadiazine* 1,1-*dioxide* was prepared by heating the foregoing amino-sulphonamide with urea at 200° for 45 min. It had m.p. 304° (decomp.) (from ethanol). Found: C, 36·5; H, 2·1; Cl, 15·0; N, 12·3; S, 14·0. $C_7H_5ClN_2O_3S$ requires C, 36·1; H, 2·2; Cl, 15·2; N, 12·0; S, 13·8 per cent.

4-*Bromo*-2-*nitrobenzenesulphonamide* was obtained by the diazo-route already described from 4-bromo-2-nitroaniline [Hartley (1928)]. The intermediate 4-*bromo*-2-*nitrobenzenesulphonyl chloride* had m.p. 100–102° [from 1,2-dichloroethane-light petroleum (b.p. 60–80°)]. Found: C, 23·9; H, 1·2; Total halogen, 38·5; N, 4·9; S, 10·7. $C_6H_3BrClNO_4S$ requires C, 24·0; H, 1·0; Total halogen, 38·4; N, 4·7; S, 10·7 per cent. The *sulphonamide*, obtained by reaction of the sulphonyl chloride in

aqueous ammonia (d = 0·880)-chloroform medium, had m.p. 176–178° (from aqueous ethanol). Found: C, 25·6; H, 1·9; Br, 28·4; N, 10·1. $C_6H_5BrN_2O_4S$ requires C, 25·6; H, 1·8; Br, 28·4; N, 10·0 per cent.

2-*Amino*-4-*bromobenzenesulphonamide*, obtained by reduction of the foregoing nitro-sulphonamide in 70 per cent ethanol containing 0·5 per cent acetic acid, had m.p. 146–148° (from water). Found: C, 28·7; H, 2·6; N, 11·2; S, 12·6. $C_6H_7BrN_2O_2S$ requires C, 28·7; H, 2·8; N, 11·2; S, 12·8 per cent.

6-*Bromo*-3,4-*dihydro*-3-*oxobenzo*-1,2,4-*thiadiazine* 1,1-*dioxide*, obtained by heating the foregoing amino-sulphonamide with urea at 200° for 45 min., had m.p. 313–315° (decomp.) (from aqueous ethanol). Found: C, 30·4; H, 1·9; N, 10·3; S, 11·8. $C_7H_5BrN_2O_3S$ requires C, 30·3; H, 1·8; N, 10·1; S, 11·6 per cent.

3,4-*Dihydro*-3-*oxo*-6-*trifluoromethylbenzo*-1,2,4-*thiadiazine* 1,1-*dioxide* was obtained by heating 2-amino-4-trifluoromethylbenzenesulphonamide (Holdrege, Babel and Cheney, 1959), with urea at 200° for 30 min. It had m.p. 233–235° (from aqueous ethanol). Found: C, 36·2; H, 2·3; N, 10·5. $C_8H_5F_3N_2O_3S$ requires C, 36·1; H, 1·9; N, 10·5 per cent.

1-*Butyl*-3-(4-*methyl*-3-*nitrobenzoyl*)*urea*. A solution of 4-methyl-3-nitrobenzoyl chloride (61·4 g.) (King and Murch, 1925) in benzene (120 ml.) was added dropwise to a stirred solution of butylurea (38·3 g.) in pyridine (23·7 g.) and benzene (300 ml.) during 30 min. The mixture was warmed to 60° for 1 hr., cooled to below 5° and the solids collected and washed with water. The *product* (32·2 g.) had m.p. 119–120° (from ethanol). Found: C, 56·0; H, 6·3; N, 14·8. $C_{13}H_{17}N_3O_4$ requires C, 55·9; H, 6·1; N, 15·0 per cent.

3-(3-*Amino*-4-*methylbenzoyl*)-1-*butylurea* was prepared by hydrogenation of the foregoing nitro-compound (20·6 g.) with 5 per cent palladium-charcoal catalyst (4 g.) in ethanol (500 ml.). It (13·6 g.) had m.p. 134–136° (from ethanol). Found: C, 62·4; H, 7·7; N, 16·7. $C_{13}H_{19}N_3O_2$ requires C, 62·6; H, 7·7; N, 16·9 per cent.

1-*Cyclohexyl*-3-(4-*methyl*-3-*nitrobenzoyl*)*urea* was obtained in 52 per cent yield by reaction of 4-methyl-3-nitrobenzoyl chloride with cyclohexylurea in pyridine-benzene. It had m.p. 210–212° (from ethanol or benzene). Found: C, 58·8; H, 6·3; N, 14·0. $C_{15}H_{19}N_3O_4$ requires C, 59·0; H, 6·3; N, 13·8 per cent.

3-(3-*Amino*-4-*methylbenzoyl*)-1-*cyclohexylurea* was obtained in 47 per cent yield by reduction of the foregoing nitro-compound with iron powder-ferrous sulphate in 60 per cent ethanol. It had m.p. 203–205° (from ethanol). Found: C, 65·2; H, 7·4; N, 14·9. $C_{15}H_{21}N_3O_2$ requires C, 65·4; H, 7·7; N, 15·3 per cent.

1-*Butyl*-3-(4-*chloro*-3-*nitrobenzoyl*)*urea* was obtained in 75 per cent yield by reaction of 4-chloro-3-nitrobenzoyl chloride (Montagne, 1900) with butylurea in benzene-pyridine. It had m.p. 143–145° (from ethanol). Found: C, 48·1; H, 4·8; Cl, 11·8; N, 14·1. $C_{12}H_{14}ClN_3O_4$ requires C, 48·1; H, 4·7; Cl, 11·8; N, 14·0 per cent.

3-(3-*Amino*-4-*chlorobenzoyl*)-1-*butylurea*, obtained in 80 per cent yield by reduction of the foregoing nitrocompound with iron powder-ferrous

sulphate in 80 per cent ethanol, had m.p. 157–158° (from ethanol). Found: C, 53·5; H, 5·9; Cl, 13·0; N, 15·6. $C_{12}H_{16}ClN_3O_2$ requires C, 53·4; H, 6·0; Cl, 13·2; N, 15·6 per cent.

3-(4-*Chloro*-3-*nitrobenzoyl*)-1-*cyclohexylurea*, obtained in 73 per cent yield, had m.p. 205–206° (from ethanol). Found: C, 51·8; H, 4·9; Cl, 10·9; N, 12·8. $C_{14}H_{16}ClN_3O_4$ requires C, 51·6; H, 5·0; Cl, 10·9; N, 12·9 per cent.

3-(3-*Amino*-4-*chlorobenzoyl*-1-*cyclohexylurea*, obtained in 71 per cent yield by iron powder-ferrous sulphate reduction of the foregoing nitro-compound in 80 per cent ethanol, had m.p. 204–206° (from aqueous ethanol). Found: C, 57·3; H, 6·1; Cl, 12·3; N, 14·5. $C_{14}H_{18}ClN_3O_2$ requires C, 56·9; H, 6·1; Cl, 12·0; N, 14·2 per cent.

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