35. *Acyl Derivatives of* p-*Aminobenzenesulphonylguanidine.*

By P. R. Carter, D. H. Hey, and D. S. Morris.

Various acyl derivatives of *p*-amino- and *p*-nitro-benzenesulphonylguanidine are prepared. Acetylation of *p*-aminobenzenesulphonylguanidine gives *p*-acetamidobenzenesulphonylguanidine and p-*acetamidobenzenesulphonylacetylguanidine*, and the latter is also prepared from *p*-acetamidobenzenesulphonyl chloride and acetylguanidine and from p-*acetamidobenzenesulphonylacetylmethylisothiourea* and ammonia. The corresponding *mono-* and *di-propionyl* derivatives are also prepared. p-*Aminobenzenesulphonylacetylguanidine*, p-*aminobenzenesulphonylbenzoylguanidine*, and p-*aminobenzenesulphonyldibenzoylguanidine* are prepared by the reduction of the corresponding p-*nitro*-compounds. Condensation of *p*-acetamidobenzenesulphonylacetylguanidine with ethyl acetoacetate gives 6-*hydroxy*-2-p-*acetamidobenzenesulphonamido*-4-*methylpyrimidine*.

Of the various chemotherapeutic agents of the sulphonamide group, *p*-aminobenzenesulphonylguanidine (sulphaguanidine) is one of the most effective in the treatment of certain pathogenic infections of the intestinal tract. Divinskii and Vorob'eva (*Compt. rend. Acad. Sci. U.R.S.S.*, 1942, **36**, 203) observed that many sulphonamides are acetylated *in vivo* to give the less toxic acetyl derivatives, and showed that *p*-acetamidobenzenesulphonylguanidine is highly active physiologically and practically non-toxic. Northey (*Chem. Reviews*, 1940, **27**, 173) has also pointed out that some N^1-acylsulphanilamides are more active than sulphanilamide, and among these, N^1-acetylsulphanilamide (albucid, sulphacetamide), N^1-benzoylsulphanilamide (sulphabenzamide), and N^1-dimethylacrylylsulphanilamide (irgamide) have received considerable attention. Since the preparations described below were completed, Rose and Tuey (*J.*, 1946, 82) have reported that 2-(*p*-acetamidobenzenesulphonamido)-4 : 6-dimethoxypyrimidine, although devoid of *in vitro* activity, is almost as effective *in vivo* as the highly active free amine, 2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethoxypyrimidine, and have shown that this is due to rapid deacetylation in the body. There would thus appear to be a strong case for the examination of the *in vivo* activity of various acylated derivatives of *p*-aminobenzenesulphonylguanidine. *p*-Aminobenzenesulphonylguanidine possesses in all four basic centres which are capable of acylation. In the absence of conclusive evidence to the contrary the acyl groups in di- and tri-acylated *p*-aminobenzenesulphonylguanidines are regarded as being attached to different basic groups. The solubility of *p*-acetamidobenzenesulphonylacetylguanidine in cold aqueous sodium hydroxide may be taken as evidence of the presence of the group $\cdot SO_2 \cdot NH \cdot C\!:$.

Acetylation of *p*-aminobenzenesulphonylguanidine under mild conditions afforded *p*-acetamidobenzenesulphonylguanidine (I), identical with the product obtained from the condensation of *p*-acetamidobenzenesulphonyl chloride with guanidine as described by Marshall *et al.* (*Johns Hopkins Hosp. Bull.*, 1940, **67**, 163). Acetylation of *p*-aminobenzenesulphonylguanidine under more vigorous conditions afforded p-*acetamidobenzenesulphonylacetylguanidine* (III), the structure of which was confirmed by the preparation of identical compounds by (*a*) acetylation of *p*-acetamidobenzenesulphonylguanidine and (*b*) condensation of *p*-acetamidobenzenesulphonyl chloride with acetylguanidine. It has been found that *p*-acetamidobenzenesulphonylguanidine may also be prepared by heating urea with *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (II), which in turn may be formed by condensation of *p*-acetamidobenzenesulphonyl chloride with methyl*iso*thiourea sulphate or chloride in cold aqueous acetone with the gradual addition of alkali. After the completion of this work a similar method of preparation was described by Haworth, Rose, and Swain (B.P. 554,975 : see also Birtwell, Haworth, Rose, Swain, and Vasey, *J.*, 1946, 493). *p*-Acetamidobenzenesulphonylmethyl*iso*thiourea has also been mentioned by Winnek, Anderson, Marson, Faith, and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 1682) but no details were given.* Acetylation of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (II) gave p-*acetamidobenzenesulphonylacetylmethyl*iso*thiourea* (IV), which on treatment with ammonia gave methylthiol and *p*-acetamidobenzenesulphonylacetylguanidine (III). Partial hydrolysis of *p*-acetamidobenzenesulphonylacetylguanidine under acid or alkaline conditions afforded only *p*-acetamidobenzenesulphonylguanidine with no evidence of the formation of the isomeric p-*aminobenzenesulphonylacetylguanidine* (VII) : the latter compound was prepared by the catalytic reduction under neutral conditions of p-*nitrobenzenesulphonylacetylguanidine* (VI), prepared either by condensation of *p*-nitrobenzenesulphonyl chloride with acetylguanidine or by acetylation of *p*-nitrobenzenesulphonylguanidine (V). Acetylation of *p*-aminobenzenesulphonylacetylguanidine gave the expected *p*-acetamidobenzenesulphonylacetylguanidine referred to above. These reactions may be represented as shown on p. 145.

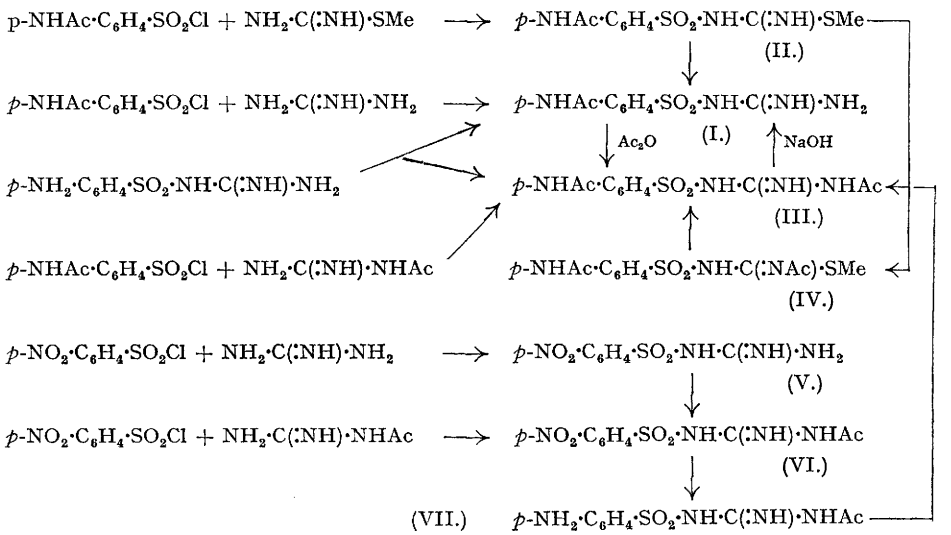
The corresponding *mono-* and *di-propionyl* derivatives of *p*-aminobenzenesulphonylguanidine were prepared in similar manner, and treatment of *p*-acetamidobenzenesulphonylguanidine with propionic anhydride gave p-*acetamidobenzenesulphonylpropionylguanidine*.

Benzoylation of *p*-nitrobenzenesulphonylguanidine with an excess of benzoic anhydride gave p-*nitrobenzenesulphonyldibenzoylguanidine*, but with a molecular proportion p-*nitrobenzenesulphonylbenzoylguanidine* was obtained. Both the mono- and the di-benzoyl derivative were reduced catalytically to p-*aminobenzenesulphonylbenzoylguanidine* and p-*aminobenzenesulphonyldibenzoylguanidine*, respectively.

Several methods have been reported by means of which sulphanilylaminopyrimidines may be

* Cox, (*J. Org. Chem.*, 1942, **7**, 307) had reported a similar method of preparation from arylsulphonylmethyl*iso*thioureas, but at the time of this work this paper was not available in Great Britain and was only seen in abstract (*Chem. Abstracts*, 1942, **36**, 6146). Acyl derivatives of *p*-aminobenzenesulphonylalkyl*iso*thioureas are also described by Kereszty and Wolf (Hungarian Patent, 127,731 ; *Chem. Abs.*, 1942, **36**, 2270) and by Bergmann, Israelashvili, and Weinberg, *J. Amer. Chem. Soc.*, 1946, **68**, 761).

prepared by the condensation of *p*-nitro-, *p*-amino-, or *p*-acetamido-benzenesulphonylguanidine with 1 : 3-diketones and similar compounds. The condensation of *p*-acetamidobenzenesul-



phonylacetylguanidine with ethyl acetoacetate could give rise to either the ethyl ester of 2-*p*-acetamidobenzenesulphonamido-4 : 6-dimethylpyrimidine-5-carboxylic acid with elimination of water, or 2-*p*-acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine with elimination of water and ethyl acetate; but it was found that when the above two reagents were heated together at 150° in presence of zinc chloride the latter product was in fact formed. This compound was subsequently described by Rose and Swain (*J.*, 1945, 691), who prepared it by heating *p*-acetamidobenzenesulphonylguanidine with ethyl acetoacetate (cf. Ganapathi, Deliwala, and Shirsat, *Proc. Indian Acad. Sci.*, 1942, **16***A*, 115).

Experimental.

p-Acetamidobenzenesulphonylguanidine was prepared from *p*-acetamidobenzenesulphonyl chloride (Smiles and Stewart, *Org. Synth.*, Coll. Vol. I, Second Ed., 8) and guanidine nitrate as described by Marshall *et al.* (*loc. cit.*). Crystallisation from 50% acetic acid gave the monohydrate in colourless plates, m. p. 264°. The *p*-acetamidobenzenesulphonyl chloride was purified by the method of Pence and Winter (*J. Amer. Chem. Soc.*, 1939, **61**, 2977). Hydrolysis with 6N-hydrochloric acid as described by Marshall *et al.* (*loc. cit.*) gave *p*-aminobenzenesulphonylguanidine, which separated from 95% alcohol in fine colourless needles, which softened at 168—178°, and melted at 189°.

Action of Acetic Anhydride on p-*Aminobenzenesulphonylguanidine.*—(a) Acetic anhydride (50 c.c.) was added slowly with shaking to a solution of *p*-aminobenzenesulphonylguanidine (21·4 g.) in warm dry pyridine (60 c.c.). Heat was developed, and a crystalline deposit separated. The mixture was cooled and filtered. Crude *p*-acetamidobenzenesulphonylguanidine (12·3 g., m. p. 262°) was collected; after crystallisation from 50% acetic acid it melted at 264°, both alone and on admixture with the compound prepared as above from *p*-acetamidobenzenesulphonyl chloride and guanidine nitrate.

(b) Acetic anhydride (50 c.c.) was added to *p*-aminobenzenesulphonylguanidine (21·4 g.) in warm dry pyridine (60 c.c.) as described above. The mixture was then boiled under reflux for 3 hours, during which the solid dissolved to give a clear brown solution. After removal of pyridine and excess of acetic anhydride under reduced pressure, the glassy residue was crystallised from 50% acetic acid (200 c.c.). A second crystallisation from the same solvent (or from ethyl alcohol) gave p-*acetamidobenzenesulphonylacetylguanidine* (21·2 g.) in colourless needles (or prisms from alcohol), m. p. 261° (Found: C, 44·6; H, 4·8. $C_{11}H_{14}O_4N_4S$ requires C, 44·3; H, 4·7%). The same compound (13·9 g.) was obtained when *p*-acetamidobenzenesulphonylguanidine (25·6 g.) was boiled under reflux for two hours with dry pyridine (60 c.c.) and acetic anhydride (40 c.c.). The same compound was also obtained when a mixture of *p*-acetamidobenzenesulphonyl chloride (1·86 g.) and acetylguanidine (0·81 g.), prepared from free guanidine and ethyl acetate as described by Traube (*Ber.*, 1910, **43**, 3588), in dry pyridine (10 c.c.) was boiled gently under reflux for 20 minutes and then kept at 100° for 2 hours. The cold mixture was filtered and the filtrate was evaporated to dryness in a vacuum. Trituration of the oily residue with ice-water (50 c.c.) gave a solid product which was recrystallised first from 50% acetic acid (charcoal) and then from ethyl alcohol. *p*-Acetamidobenzenesulphonylacetylguanidine was obtained, as above, in colourless prisms, m. p. 261°.

When *p*-acetamidobenzenesulphonylacetylguanidine (2·98 g.) was added to a cold solution of sodium hydroxide (1·2 g.) in water (10 c.c.), the solid dissolved, and after standing for 6 hours *p*-acetamidobenzenesulphonylguanidine, m. p. and mixed m. p. 264°, separated. Hydrolysis with boiling N/10-hydrochloric acid for ½ hour was very incomplete, but boiling under reflux for 2 hours, followed by neutralisation and

concentration, gave *p*-aminobenzenesulphonylguanidine, m. p. and mixed m. p. 189° after crystallisation from alcohol.

N-(p-*Acetamidobenzenesulphonyl*)-S-*methylisothiourea*.—Aqueous sodium hydroxide (10 g. in 20 c.c.) was added slowly with stirring to a solution of *p*-acetamidobenzenesulphonyl chloride (23·3 g.) and methyl*iso*thiourea sulphate (14 g.) in acetone (100 c.c.) kept below 0°. (In place of methyl*iso*thiourea sulphate the corresponding quantity of the chloride may be used.) After standing overnight the reaction mixture was acidified with glacial acetic acid. *p*-Acetamidobenzenesulphonylmethyl*iso*thiourea (11 g.) separated; it crystallised from alcohol or aqueous alcohol in small needles, m. p. 235° (Found: C, 42·4; H, 4·8; N, 14·75. Calc. for $C_{10}H_{13}O_3N_3S_2$: C, 41·9; H, 4·5; N, 14·6%). Cox (*loc. cit.*) reported m. p. 230—232°, and B.P. 554,975 m. p. 236° for this compound. An intimate mixture of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (1 g.) and urea (1 g.) was heated at 150° for about 2 hours. When liberation of methylthiol had ceased, the melt was allowed to cool, treated with boiling water (25 c.c.) and charcoal, and filtered hot. On cooling, *p*-acetamidobenzenesulphonylguanidine (0·5 g.) separated in white needles, m. p. 264° both alone and on admixture with an authentic specimen.

p-*Acetamidobenzenesulphonylacetylmethylisothiourea*.—A mixture of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (1·7 g.), anhydrous sodium acetate (0·5 g.), and acetic anhydride (10 c.c.) was boiled under reflux for 3 hours. The product was isolated by pouring on ice, and after standing, the white precipitate (1·5 g.) was collected. Recrystallisation from aqueous alcohol gave p-*acetamidobenzenesulphonylacetylmethylisothiourea* in needles, m. p. 92° (Found: N, 11·4. $C_{12}H_{15}O_4N_3S_2$ requires N, 11·4%). A stream of dry ammonia was passed through this compound (1 g.), heated at 210°, until evolution of methylthiol had ceased. When cold, the melt was dissolved in hot water (20 c.c.), boiled with charcoal, and filtered. On cooling, *p*-acetamidobenzenesulphonylacetylguanidine (0·7 g.) separated, which after crystallisation from alcohol had m. p. 261°, both alone and on admixture with the compound prepared as described above by direct acetylation of sulphanilylguanidine.

p-*Nitrobenzenesulphonylacetylguanidine*.—(a) Dry pyridine (10 c.c.) was added to a mixture of acetylguanidine (0·85 g.), prepared by the method of Traube (*loc. cit.*), and *p*-nitrobenzenesulphonyl chloride (1·88 g.), prepared as described by Bell (*J.*, 1928, 2776) and purified by the procedure used by Pence and Winter (*loc. cit.*) for *p*-acetamidobenzenesulphonyl chloride. Heat was developed, and a clear solution obtained. After standing for 2 hours, the mixture was filtered from a highly water-soluble crystalline deposit, and the filtrate evaporated to dryness on the water-bath under reduced pressure. Trituration of the residue with water gave p-*nitrobenzenesulphonylacetylguanidine* in low yield; after several crystallisations from alcohol, this was obtained in colourless prisms, m. p. 230—231° (Found: C, 37·9; H, 3·4. $C_9H_{10}O_5N_4S$ requires C, 37·8; H, 3·5%).

(b) *p*-Nitrobenzenesulphonyl chloride (2·21 g.) was added gradually with shaking to a solution of acetylguanidine acetate (1·61 g.), prepared by the method of Korndörfer (*Arch. Pharm.*, 1903, **241**, 467), in dry pyridine (20 c.c.). The brown solution was heated at 100° for 15 minutes, after which the solvent was removed under reduced pressure and the residue triturated with ice-water. Crystallisation several times from alcohol gave *p*-nitrobenzenesulphonylacetylguanidine in low yield, m. p. 230—231°, both alone and on admixture with the compound prepared above by method (a).

(c) *p*-Nitrobenzenesulphonylguanidine (14·6 g.), prepared from *p*-nitrobenzenesulphonyl chloride and guanidine nitrate in the same manner as was used by Marshall *et al.* (*loc. cit.*) for the preparation of *p*-acetamidobenzenesulphonylguanidine, was heated under reflux with an excess of acetic anhydride (50 c.c.) for 2 hours. The crystalline deposit which separated on cooling was collected and washed with alcohol and ether. Recrystallisation from alcohol gave *p*-nitrobenzenesulphonylacetylguanidine (7·5 g.) in colourless prisms, m. p. 230—231°, both alone and on admixture with the sample prepared by methods (a) and (b) above.

p-Nitrobenzenesulphonylacetylguanidine is sparingly soluble in cold water, but dissolves in cold dilute sodium hydroxide to give a colourless solution which turns yellow and deposits *p*-nitrobenzenesulphonylguanidine, m. p. 224°, on standing.

p-*Aminobenzenesulphonylacetylguanidine*.—Finely powdered *p*-nitrobenzenesulphonylacetylguanidine (1 g.) was suspended in absolute alcohol (250 c.c.) and shaken with Raney nickel (1 g.) in an atmosphere of hydrogen at room temperature and pressure. The theoretical volume of hydrogen was absorbed in 6 hours. The mixture was warmed and filtered, and the filtrate concentrated to 50 c.c. by heating under reduced pressure at 40°. On cooling to 0° p-*aminobenzenesulphonylacetylguanidine* (0·6 g.) separated in very pale yellow prisms, m. p. 210°, after recrystallisation from alcohol (Found: C, 42·4; H, 4·9. $C_9H_{12}O_3N_4S$ requires C, 42·2; H, 4·7%). This compound is readily hydrolysed in alkaline media but is stable when suspended in a buffer solution at pH 2·4 at 41°. On being boiled with an excess of acetic anhydride for 2 hours and poured into water, *p*-acetamidobenzenesulphonylacetylguanidine was obtained, m. p. and mixed m. p. 261° after crystallisation from alcohol. Reduction of *p*-nitrobenzenesulphonylacetylguanidine by boiling with iron filings and calcium chloride in aqueous alcohol afforded *p*-aminobenzenesulphonylguanidine.

Action of Propionic Anhydride on p-*Aminobenzenesulphonylguanidine*.—(a) Propionic anhydride (2·6 g.) was added to a hot solution of the guanidine (4·28 g.) in dry pyridine (25 c.c.). After standing overnight at room temperature, the mixture was evaporated to dryness under reduced pressure and the white solid residue was crystallised twice from boiling water (100 c.c.). p-*Propionamidobenzenesulphonylguanidine* (3·6 g.) was obtained in colourless plates, m. p. 195—196° (Found: C, 41·8; H, 5·7. $C_{10}H_{14}O_3N_4S,H_2O$ requires C, 41·7; H, 5·55%).

(b) *p*-Aminobenzenesulphonylguanidine (4·28 g.) was boiled under reflux for 3 hours with dry pyridine (25 c.c.) and propionic anhydride (7·8 g.). The clear brown solution was evaporated to dryness under reduced pressure. Crystallisation of the residual glass from 50% acetic acid (50 c.c.) (charcoal) gave p-*propionamidobenzenesulphonylpropionylguanidine* (2·7 g.) in colourless needles, which softened at 240° and melted at 247° (Found: C, 47·9; H, 5·5. $C_{13}H_{18}O_4N_4S$ requires C, 47·85; H, 5·5%). The same compound was obtained when *p*-propionamidobenzenesulphonylguanidine was heated under reflux for 2 hours with excess of propionic anhydride, followed by evaporation on the water-bath under reduced pressure and crystallisation of the residue as before.

p-*Acetamidobenzenesulphonylpropionylguanidine.*—*p*-Acetamidobenzenesulphonylguanidine (2·56 g., 0·01 mol.) was boiled under reflux overnight with dry pyridine (15 c.c.) and propionic anhydride (2·6 g., 0·02 mol.). On cooling, the unchanged guanidine which separated (m. p. and mixed m. p. 264°), was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure on the water-bath. The residual oil was taken up in warm absolute alcohol. Addition of water precipitated p-*acetamidobenzenesulphonylpropionylguanidine*, which crystallised from dilute acetic acid in colourless needles, m. p. 203° (Found : C, 45·75; H, 5·3. $C_{12}H_{16}O_4N_4S$ requires C, 46·15; H, 5·1%).

Action of Benzoic Anhydride on p-*Nitrobenzenesulphonylguanidine.*—(a) A mixture of *p*-nitrobenzenesulphonylguanidine (4·88 g.) and benzoic anhydride (18 g.), prepared as described by Kaufmann and Luterbacher (*Ber.*, 1909, **42**, 3483), was heated at 150—160° for 4 hours. When cold, the melt set to a solid mass, which was powdered and boiled under reflux with dry ether (500 c.c.). The insoluble material was collected, boiled with alcohol, cooled, and filtered. The insoluble p-*nitrobenzenesulphonyldibenzoylguanidine* (4·5 g.) separated from absolute alcohol (*ca.* 3000 c.c.) in colourless needles, m. p. 197° (Found : C, 56·1; H, 3·4. $C_{21}H_{16}O_6N_4S$ requires C, 55·8; H, 3·5%).

(b) A mixture of *p*-nitrobenzenesulphonylguanidine (19·5 g.) and benzoic anhydride (22·0 g.) was heated at 150° for 3 hours and then at 200° for 1 hour. The melt, which solidified on cooling, was powdered and extracted with boiling dry ether, and the insoluble residue was crystallised from absolute alcohol (7500 c.c.). p-*Nitrobenzenesulphonylbenzoylguanidine* (17·0 g.) separated in colourless plates, m. p. 227° (Found : C, 48·4; H, 3·4. $C_{14}H_{12}O_5N_4S$ requires C, 48·3; H, 3·45%). The same compound was obtained in small yield from *p*-nitrobenzenesulphonylguanidine and benzoyl chloride by boiling under reflux for 6 hours in pyridine solution, followed by evaporation of the solvent and repeated crystallisation of the residue from absolute alcohol.

p-*Aminobenzenesulphonylbenzoylguanidine.*—A suspension of finely powdered *p*-nitrobenzenesulphonylbenzoylguanidine (1 g.) and Raney nickel (1 g.) in absolute alcohol (300 c.c.) was shaken with hydrogen at room pressure and temperature. When the theoretical volume of hydrogen had been absorbed the solution was warmed and filtered (charcoal). Concentration of the filtrate afforded needles of p-*aminobenzenesulphonylbenzoylguanidine*, which after further crystallisation from alcohol melted at 249° (Found : C, 53·2; H, 4·4. $C_{14}H_{14}O_3N_4S$ requires C, 52·8; H, 4·4%); it is stable at 41° when suspended in a buffer solution at pH 2·4.

p-*Aminobenzenesulphonyldibenzoylguanidine.*—*p*-Nitrobenzenesulphonyldibenzoylguanidine was catalytically reduced as described above for the corresponding monobenzoyl derivative. Recrystallisation of the product from absolute alcohol gave p-*aminobenzenesulphonyldibenzoylguanidine* in very pale yellow needles, m. p. 225° (Found : C, 59·6; H, 4·2. $C_{21}H_{18}O_4N_4S$ requires C, 59·7; H, 4·3%). Hydrolysis with 2N-sodium hydroxide for 2 hours at 100° gave *p*-aminobenzenesulphonylguanidine.

2-p-*Acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine.*—A mixture of *p*-acetamidobenzenesulphonylacetylguanidine (3 g.), freshly fused powdered zinc chloride (7 g.), and ethyl acetoacetate (15 c.c.) was heated in an oil-bath at 150° for 3 hours in a flask fitted with an air condenser and a calcium chloride guard-tube. When cold, the mass was extracted with water and then with ether. The insoluble residue (2·4 g.) was crystallised from 50% acetic acid and finally from aqueous alcohol. The pyrimidine was obtained in prisms, m. p. 277° (Found : C, 48·2; H, 4·5; N, 17·1. Calc. for $C_{13}H_{14}O_4N_4S$: C, 48·45; H, 4·35; N, 17·4%). A specimen of the same compound was prepared by heating *p*-acetamidobenzenesulphonylguanidine with excess of ethyl acetoacetate at 160° for 2 hours according to the method of Rose and Swain (*loc. cit.*). No depression in m. p. was obtained when the products prepared by the two methods were mixed.

The thanks of the authors are due to Dr. J. H. Beynon for assistance with some of the preliminary experimental work.

British Schering Research Institute,
Alderley Edge, Cheshire.

[*Received, February 24th*, 1947.