29. *Sulphanilamides of Some Aminopyrazoles, and a Note on the Application of* p-*Phthalimidobenzenesulphonyl Chloride to the Synthesis of Sulphanilamides.*

By M. J. S. Dewar and F. E. King.

By hydrolysis of their *p*-acetamidobenzenesulphonyl derivatives, sulphanilamides have been synthesised from 3-amino-, 4-amino-, 4-amino-3-methyl- and 5-amino-3-methyl-pyrazoles. p-*Phthalimidobenzenesulphonyl chloride* has been prepared in 95% yield and quantitatively converted into p-*phthalimidobenzenesulphonanilide*, but hydrolysis of the latter to the aminosulphonanilide occurs less readily than with the corresponding acetyl compound.

Biological tests of numerous sulphanilamides having established the superiority of those derived from nitrogenous heterocyclic compounds, several new aminosulphonamidopyrazoles have been prepared.

Each of the selected aminopyrazoles derives from ethyl 3-methylpyrazole-5-carboxylate (I), which has been synthesised by an improvement of Knorr's method (*Annalen*, 1894, **279**, 219) from ethyl acetylpyruvate and hydrazine. The methylpyrazole prepared from (I) by hydrolysis and decarboxylation was oxidised to pyrazole-3-carboxylic acid, and the aminopyrazole (Knorr, *Ber.*, 1904, **37**, 3520) obtained therefrom by the Curtius method was converted through the *p*-acetamidobenzenesulphonyl derivative into 3-*p*-aminobenzenesulphonamidopyrazole, described since this work was completed by Jensen (see *Chem. Abstr.*, 1942, 5793).

4-Aminopyrazole (Knorr, *loc. cit.*) was prepared from pyrazole—derived from the 3-carboxylic acid—by nitration and reduction of the 4-nitro-compound (Buchner and Fritzsch, *Annalen*, 1893, **273**, 265). Raney nickel hydrogenation has increased the yield of the base, which is 30—35% for chemical methods, to 88%. The recrystallised product of the action of *p*-acetamidobenzenesulphonyl chloride on the aminopyrazole was a *bisacetamidobenzenesulphonyl* derivative, but acid hydrolysis of the unpurified material gave a monosulphanilamide identical with the compound described by Raiziss, Clemence, and Freifelder (*J. Amer. Chem. Soc.*, 1941, **63**, 2739) as 4-*p*-aminobenzenesulphonamidopyrazole. The formation of a bisacetylsulphanilyl compound (cf. the corresponding disubstituted 3-aminopyrazole of Jensen, *loc. cit.*) suggests that the free sulphanilamide may be a derivative of the tautomeric imine, but the alkali-solubility of all our pyrazole sulphonamides excludes this possibility.

4-Nitro-3-methylpyrazole is also efficiently reduced over Raney nickel, the aminopyrazole being conveniently isolated as a *dihydrochloride*. The *p*-acetamidobenzenesulphonyl derivative was prepared in the usual way, and the p-*aminosulphonamide* liberated by acid hydrolysis.

5-Amino-3-methylpyrazole was prepared from the ester (I) by the Curtius reaction, and each intermediate in this degradation is described. Hydrolysis of the *p*-acetamidobenzenesulphonamide to 5-p-*aminobenzenesulphonamido*-3-*methylpyrazole* was effected in alkaline solution. The action of *p*-acetamidobenzenesulphonyl chloride on 3-methylpyrazole-5-carboxylic acid does not give a sulphanilamide but the *diketo-bis*-3'-*methylpyrazolopiperazine*.

The chlorosulphonation of phthalanil affords p-*phthalimidobenzenesulphonyl chloride* in nearly theoretical quantities. It is therefore more accessible than the corresponding acetyl compound, normally isolated in 60% yield, but in the phthalylsulphanilamides the protecting acyl group appears to be less easily removed. Thus, hydrolysis of the *phthalimidosulphonanilide* with sodium hydroxide is much slower than with the analogous acetyl compound, and the hydrazine method for the fission of phthalimido-groups (Ing and Manske, J., 1926, 2348) gave but little of the aminosulphonanilide. When the preparation of 1-*p*-aminobenzenesulphonamido-1 : 3 : 4-triazole was attempted from its *phthalyl* derivative, the more drastic conditions required totally destroyed the compound, whereas, the aminosulphonamide was obtained in 60% yield from the corresponding acetate. It is therefore concluded that the use of phthalimidobenzenesulphonyl chloride is unlikely to be advantageous except in the synthesis of sulphonamides of very stable amines. Four of the above sulphonamides were tested *in vitro* against *Streptococcus pyogenes*. Compared with sulphanilamide (equals 1), the 5-amino-3-methyl derivative has an activity of 3 : the index for 4-*p*-aminobenzenesulphonamidopyrazole is 1/3—1, and for 4-*p*-aminobenzenesulphonamido-3-methylpyrazole it is 1/9—1/3. The activity of 1-*p*-aminobenzenesulphonamido-1 : 3 : 4-triazole (sulphanilamide = 1) is 1/27—1/3.

Experimental.

Ethyl 3-*Methylpyrazole*-5-*carboxylate*.—Hydrazine hydrate (10 g., 0·2 mol.) in alcohol (25 c.c.) was added slowly with shaking and cooling to a solution of ethyl $\alpha\gamma$-diketo-*n*-valerate (31·6 g., 0·2 mol.) in alcohol (75 c.c.). After refluxing for 1 hour, the alcohol was distilled; the pyrazole (30·5 g., 99%) crystallised from aqueous alcohol in long acicular plates, m. p. 82° (Found : C, 54·7; H, 6·5. Calc. for $C_7H_{10}O_2N_2$: C, 54·5; H, 6·5%).

3-p-*Aminobenzenesulphonamidopyrazole*.—3-Aminopyrazole (5·8 g.) (Knorr, *loc. cit.*) and *p*-acetamidobenzenesulphonyl chloride (16·3 g.) in dry acetone (20 c.c.) and pyridine (8 c.c.) were left overnight at room temperature, and water then added. The gum which separated slowly solidified but could not be purified. Hydrolysis with acid proved unsatisfactory : the crude amide (5·6 g.) was therefore heated for 5 hours on a steam-bath with potassium hydroxide (3·4 g.) in water (10 c.c.); much tarry material was then removed by charcoal treatment, and the aminobenzenesulphonamide precipitated by acetic acid. Several crystallisations from water gave rhombic needles, m. p. 227—228°, easily soluble in alkali (Found : N, 23·7; S, 13·6. Calc. for $C_9H_{10}O_2N_4S$: N, 23·5; S, 13·4%). Jensen (*loc. cit.*) gives m. p. 235°.

4-p-*Aminobenzenesulphonamidopyrazole* (cf. Raiziss *et al.*, *loc. cit.*).—Catalytic reduction of 4-nitropyrazole (Buchner and Fritsch, *loc. cit.*) with Raney nickel gave the aminopyrazole, isolated as dihydrochloride, in 88% yield. Condensation of the hydrochloride (2·9 g.) with *p*-acetamidobenzenesulphonyl chloride (4·5 g.) in acetone (15 c.c.) and pyridine (5 c.c.) at room temperature gave, on pouring into water, a product from which, by repeated crystallisation from 50%

acetic acid, a *bisacetamidobenzenesulphonamide* was isolated in microscopic rhombs, m. p. 190—192° (Found: N, 14·2; S, 13·6. $C_{19}H_{19}O_6N_5S_2$ requires N, 14·7; S, 13·4%).

The crude acetyl compound (2·5 g.) was heated at 100° with hydrochloric acid (5 c.c., 20%) for 30 minutes, and the solution cooled, filtered from sulphanilic acid, and basified with ammonia. Crystallisation of the precipitated sulphonamide from water gave microscopic rhombs (1·07 g., 50%), m. p. 185° (Found: N, 23·5; S, 13·8. Calc. for $C_9H_{10}O_2N_4S$: N, 23·5; S, 13·4%).

4-Amino-3-methylpyrazole.—4-Nitro-3-methylpyrazole (6·7 g.), hydrogenated at 3 atms. in cold alcoholic solution (50 c.c.) with Raney nickel (2 g.), was reduced in 5 hours. The oily residue obtained by evaporation was dissolved in ether and precipitated by hydrogen chloride as the *dihydrochloride*, which crystallised from alcohol–ether in short hexagonal prisms (6·35 g., 89%), m. p. 195—200° (decomp.) (Found: N, 24·9; Cl, 40·9. $C_4H_9N_3,2HCl$ requires N, 24·7; Cl, 41·7%).

4-p-Aminobenzenesulphonamido-3-methylpyrazole.—The amine hydrochloride (3·18 g.) and *p*-acetamidobenzenesulphonyl chloride (4·6 g.) were left overnight with pyridine (5 c.c.) and acetone (15 c.c.). Addition of water gave the acetamidosulphonamide (4·17 g., 76%), which was heated at 100° for 30 minutes with hydrochloric acid (6 c.c., 20%). The *aminobenzenesulphonamide* precipitated from the cold filtered solution with ammonia crystallised from water in minute silvery plates (1·64 g., 61%), m. p. 176° (Found: N, 21·3; S, 12·4. $C_{10}H_{12}O_2N_4S$ requires N, 22·2; S, 12·7%).

3-Methylpyrazole-5-carbohydrazide.—Ethyl 3-methylpyrazole-5-carboxylate (58·4 g.) and hydrazine hydrate (25 g.), heated under reflux for 8 hours, gave a product which crystallised from water in stout hexagonal prisms containing water of crystallisation. After drying at 100°, the *hydrazide* (46·8 g., 90%) had m. p. 153—154° (Found: C, 42·9; H, 5·7. $C_5H_8ON_4$ requires C, 42·9; H, 5·7%).

3-Methylpyrazole-5-carbazide.—To a solution of the hydrazide (46·8 g.) in 2N-nitric acid (250 c.c.), stirred and cooled below 5°, a solution of sodium nitrite (25 g.) in water (50 c.c.) was slowly added. After 1 hour, the *azide* was collected, washed with ice-water, and dried over calcium chloride in a vacuum (Found: N, 45·0. $C_5H_5ON_5$ requires N, 46·3%).

Ethyl 3-Methyl-5-pyrazylcarbamate.—The dry azide (41·9 g.) was refluxed in boiling alcohol (200 c.c.) for 5 hours; the solvent was then evaporated, and the residue dissolved in hot water. The *urethane* (25·6 g., 55%) separated in clusters of irregular plates, m. p., after falling to powder at 100°, 158—160° (Found: C, 49·7; H, 6·4; N, 25·1. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·5; N, 24·9%). The urethane *picrate* crystallised from water in microscopic saffron rhombs, m. p. 148—150° (Found, after drying at 70°/0·01 mm.: N, 21·5. $C_7H_{11}O_2N_3,C_6H_3O_7N_3$ requires N, 21·1%). When the moist azide was used, ethyl 3-methylpyrazole-5-carboxylate was the reaction product.

5-Amino-3-methylpyrazole.—The urethane (25·5 g.) was heated with hydrated barium hydroxide (143 g.) in water (150 c.c.) under reflux for 3½ hours; the solution was then cooled, saturated with carbon dioxide, and filtered from barium salts. The filtrate was fractionated under reduced pressure, and the aminopyrazole (9·6 g., 65%) collected at 213°/14 mm. as a very viscous syrup which on keeping formed highly deliquescent crystals, m. p. 94°. The amine *picrate* crystallised from water in microscopic yellow needles, m. p. 205—209° (Found: N, 25·3. $C_4H_7N_3,C_6H_3O_7N_3$ requires N, 25·8%).

5-p-Aminobenzenesulphonamido-3-methylpyrazole.—*p*-Acetamidobenzenesulphonyl chloride (10·2 g.) was added to a solution of the amine (4·24 g.) in dry dioxan (30 c.c.) and pyridine (4·5 c.c.), which next day was diluted with water. The crude acetyl derivative (10·55 g., 81·5%) was collected, washed, and dried at 100°, and a portion (6·33 g.) heated for 3 hours on a steam-bath with potassium hydroxide (3·9 g.) in water (30 c.c.). Neutralisation with acetic acid precipitated the *aminobenzenesulphonamide* (2·7 g., 50%), which crystallied from aqueous alcohol in long needles, m. p. 253—254° (Found: N, 22·6; S, 13·2. $C_{10}H_{12}O_2N_4S$ requires N, 22·2; S, 12·7%).

2 : 5-Diketo-3 : 4 : 6 : 1-bis-(3′-methylpyrazolo)piperazine.—A pyridine solution of 3-methylpyrazole-5-carboxylic acid (1 mol.) and *p*-acetamidobenzenesulphonyl chloride (1 mol.) was heated for 30 minutes at 100° and then diluted with water. The precipitated solid, crystallised from acetic acid, yielded the *piperazine* as feathery masses of microscopic yellow rhombic plates decomposing above 270° (Found: C, 55·2; H, 3·7; N, 25·6. $C_{10}H_8O_2N_4$ requires C, 55·5; H, 3·7; N, 25·9%). The identical compound was also obtained from the pyrazolecarboxylic acid by the action of *p*-nitrobenzoyl chloride–pyridine.

p-Phthalimidobenzenesulphonyl Chloride.—Phthalanil (30 g.) was shaken and heated on a steam-bath with chlorosulphonic acid (30 c.c.) for 2 hours. When cool, the *sulphonyl chloride* (27·2 g., 95%) was isolated by pouring on ice, collected, and dried in a vacuum over sulphuric acid. Crystallisation from chlorobenzene gave acicular plates, m. p. 234—237° (Found: N, 4·6; Cl, 10·6. $C_{14}H_8O_4NClS$ requires N, 4·4; Cl, 11·0%).

p-Phthalimidobenzenesulphonanilide.—The phthalimidobenzenesulphonyl chloride (9·7 g.) and aniline (6·1 g.) were refluxed in acetone (30 c.c.) for 2 hours, and the *anilide* (11·5 g., 100%) isolated by addition of water. It crystallised from acetic acid in truncated hexagonal plates, m. p. 219—221° (Found: C, 62·9; H, 3·9; N, 7·3; S, 7·9. $C_{20}H_{14}O_4N_2S$ requires C, 63·5; H, 3·7; N, 7·4; S, 8·5%).

Hydrolysis of p-Phthalimidobenzenesulphonanilide.—Removal of the phthalyl group by heating the anilide (4·7 g.) on a steam-bath first with hydrazine hydrate (0·62 g.) in alcohol (20 c.c.) and then with hydrochloric acid (50 c.c. of 10%) gave, in small yield, *p*-aminobenzenesulphonanilide, m. p. 190—192°, not depressed by an authentic specimen.

The anilide (3·76 g., 0·01 mol.) was added to 2N-sodium hydroxide (50 c.c.) maintained at 100°, and at 15 minute intervals 5 c.c. portions were removed, added to 2N-hydrochloric acid (20 c.c.) and ice, and titrated with sodium nitrite solution (0·1022N) standardised against sulphanilic acid. A comparative experiment with *p*-acetamidobenzenesulphonanilide demonstrated the greater rate of hydrolysis of the latter.

p-Phthalimidobenzenesulphonanilide.				*p*-Acetamidobenzenesulphonanilide.	
Time (mins.).	Titre (c.c.).	Time (mins.).	Titre (c.c.).	Time (mins.).	Titre (c.c.).
15	1·8	90	6·8	15	7·5
30	3·2	105	7·3	30	8·5
45	4·5	120	7·7	45	8·8
60	5·5	600	9·3	300	8·8
75	6·2				

1-p-Phthalimidobenzenesulphonamido-1 : 3 : 4-triazole.—The aminotriazole (0·84 g.) (Ruhemann and Stapleton, J., 1899, **75**, 1132) and the phthalylsulphonyl chloride (3·4 g.) were heated at 100° in dioxan (25 c.c.) and pyridine (1 c.c.) for 2 hours, and the *sulphonamide* precipitated by addition of water. The product could not be crystallised and was therefore purified by treating its solution in alkali with charcoal, filtering and acidifying it (Found: S, 8·3. $C_{16}H_{11}O_4N_5S$ requires S, 8·7%). The compound was destroyed by all attempts to hydrolyse the phthalyl group.

1-p-Acetamidobenzenesulphonamido-1 : 3 : 4-triazole.—A mixture of 1-amino-1 : 3 : 4-triazole (4·08 g.) and *p*-acetamidobenzenesulphonyl chloride (11·4 g.) in dry dioxan (25 c.c.) and pyridine (5 c.c.), after standing overnight, deposited a gum which solidified when triturated with water. The *acetamidosulphonamide* (7·6 g., 59%) crystallised from water

in flat prisms, m. p. 205° (decomp.) (Found: S, 11·4. $C_{10}H_{11}O_3N_5S$ requires S, 11·4%). Hydrolysis at 100° with 20% hydrochloric acid gave the sulphanilamide (yield 60%) crystallising from water in needles, m. p. 225° (decomp.) (Found: C, 40·4; H, 4·0; S, 13·1. Calc. for $C_8H_9O_2N_5S$: C, 40·2; H, 3·8; S, 13·4%). Anderson, Faith, Marson, Winnek, and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2902) give m. p. 237° (corr.).

The authors thank Imperial Chemical Industries, Ltd., for a grant.

DYSON PERRINS LABORATORY, OXFORD. [*Received, September 7th*, 1944].