10. *The Synthesis of Some Aryl Pyridyl Sulphones (Arylsulphonylpyridines).*

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During an investigation of methods for the synthesis of aryl pyridyl sulphones (or intermediate sulphides) the following routes have been examined: (i) interaction of 4-chloropyridine and sodium *p*-nitrothiophenoxide (cf. Burton and Davy, *J.* 1946, 542); (ii) introduction of the *p*-nitrobenzenesulphenyl (*p*-nitrophenylthio) group into the pyridine nucleus; (iii) interaction of an arylsulphinic acid with a chloropyridine (cf. Roblin, Williams, and Anderson, *J. Amer. Chem. Soc.*, 1941, **63**, 1930). In general, method (iii) was found to be the most satisfactory.

King and Ware (*J.*, 1939, 875) have shown that methyl iodide reacts rapidly with 4-thiopyridone yielding 4-methylthiopyridine hydriodide. We have investigated the alkylation using ethyl iodide and *n*-octyl bromide. With ethyl iodide ethylation is rapid, but with *n*-octyl bromide no reaction appears to occur in the absence of alkali; in presence of potassium hydroxide the resulting product is non-homogeneous. Comparison with thiophenol and *p*-nitrothiophenol shows that these both react normally in the presence of alkali to give *phenyl* and p-*nitrophenyl octyl sulphide*, respectively. We have already reported (*loc. cit.*) that interaction of 4-thiopyridone and *p*-chloronitrobenzene (I) in presence of alkali is anomalous, leading to 4 : 4′-dinitrodiphenyl sulphide, which presumably arises from the decomposition of 4-thiopyridone to alkali sulphide which then reacts with (I). The alternative route, *viz.*, interaction of 4-chloropyridine (II) and sodium *p*-nitrothiophenoxide (III), has, curiously enough, led to the same abnormal product, although Bambas (*J. Amer. Chem. Soc.*, 1945, **67**, 668) has shown that (III) and 5-bromo-2-nitropyridine interact normally. The mechanism of the reaction whereby 4 : 4′-dinitrodiphenyl sulphide arises from (II) and (III) is not easy to envisage; presumably the SNa group of (III) is partly replaced by chlorine to give (I), which then reacts with unchanged (III).

The use of *p*-nitrobenzenesulphenyl chloride for the introduction of the *p*-nitrophenylthio-group into a reactive molecule is well known (cf. *inter al.*, Zincke, *Annalen*, 1913, **400**, 9; Smiles *et al.*, *J.*, 1931, 2207, 3264; 1932, 1040, 1488; Burton and Hoggarth, *J.*, 1945, 468), but this method does not appear to have been extended to the pyridine series. The reactions with the readily available ethyl 4 : 6-dihydroxy-2-methylpyridine-5-carboxylate (for constitution see Späth and Koller, *Ber.*, 1925, **58**, 2124) and 4 : 6-dihydroxy-2-methylpyridine were studied, the former in some detail. The insolubility of the dihydroxymethylpyridine in the usual inert solvents was a great disadvantage, since the reaction did not proceed satisfactorily in a non-homogeneous phase. In hot nitrobenzene–chloroform the sulphenyl chloride and the ester interacted smoothly, and the expected *ethyl* 4 : 6-*dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate* was obtained. This was characterised by acid hydrolysis to 4 : 6-*dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine* (IV); formation of this showed the absence of the p-$NO_2{\cdot}C_6H_4{\cdot}S{\cdot}N<$ grouping, which could arise from the pyridone form of the original ester. The *p*-nitrophenylthio-ester was also characterised by the preparation of a *diacetate*, thus affording further proof of the above structure; a compound analysing as a *monoacetate* was also obtained. Both acetates were hydrolysed by acid to (IV), thus excluding the possibility of the monoacetate being a pyridone derivative (assuming that hydrolysis was not accompanied by a migration). Oxidation of the monoacetate and the diacetate gave the same compound, analysing as *ethyl* 4 : 6-*dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*-5-*carboxylate*, the

phenolic character being shown by its ready solubility in cold dilute sodium hydroxide and its insolubility in cold aqueous sodium bicarbonate. The loss of acetyl groups during oxidation is probably concerned with the presence of the " ethyl acetoacetate " grouping in the molecule. Attempts to reacetylate this sulphone-ester proved unsuccessful; either the acetylation did not proceed at all, or the sulphone was destroyed. Acid hydrolysis of the sulphone-ester gave 4 : 6-*dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*.

Reduction of both sulphones was most unsatisfactory; amorphous, dark-coloured products were obtained.

Roblin, Williams, and Anderson (*loc. cit.*) have shown that *p*-acetamidobenzenesulphinic acid (usually as its potassium salt) reacts readily with various reactive halogen compounds to give *p*-acetamidophenyl sulphones. We have shown that 4-chloropyridine (Wibaut and Brockman, *Rec. Trav. chim.*, 1939, **58**, 885) reacts smoothly with *p*-acetamido-, *p*-cyano-, and *p*-acetamidomethyl-benzenesulphinic acids and with *p*-toluenesulphinic acid (as neutral salts) to give 4-*p*-acetamido-(V), 4-p-*cyano*-(VI), and 4-p-*acetamidomethyl-phenylsulphonylpyridine* (VII) and 4-p-*tolylsulphonylpyridine*, respectively. Hydrolysis of (V) occurred readily (cf. *loc. cit.*), but we were not able to hydrolyse (VII) satisfactorily to the corresponding amino-compound (VIII). Oxidation of (V) with perbenzoic acid proceeded slowly and gave the N-*oxide* which was hydrolysed, but with more difficulty than (V), by acid to 4-p-*aminophenylsulphonylpyridine* N-*oxide*. Attempts to reduce (VI) by sodium and alcohol to 4-*p*-aminomethylphenylsulphonylpyridine [*i.e.*, (VIII)] were also unsuccessful.

Interaction of *p*-acetamidobenzenesulphinic acid and 4 : 6-dichloro-2-methylpyridine was also examined. With equimolecular amounts of the reagents, 6(or 4)-*chloro*-4(or 6)-p-*acetamidophenylsulphonyl*-2-*methylpyridine* was produced; this was hydrolysed satisfactorily to the *amino*-compound. With 2 mols. of the sulphinic acid, a mixture resulted, but a little 4 : 6-*bis*-p-*acetamidophenylsulphonyl*-2-*methylpyridine* was isolable; this could not be hydrolysed satisfactorily.

Experimental.

4-*Methylthiopyridine*.—Following the method of King and Ware (*loc. cit.*), 4-methylthiopyridine hydriodide was obtained in needles (from alcohol), m. p. 183°, and not 170° as reported by these authors (Found : C, 28·8; H, 3·1. Calc. for C_6H_8NIS : C, 28·4; H, 3·2%).

4-*Ethylthiopyridine Hydriodide*.—4-Thiopyridone (4·44 g.) was dissolved in boiling alcohol (50 c.c.), the solution cooled to 60°, and ethyl iodide (6·3 g.) in alcohol (10 c.c.) added. On cooling, the *hydriodide* separated (7·5 g.) After crystallisation from alcohol, this had m. p. 164—165° (Found : C, 32·0; H, 3·9. $C_7H_{10}NIS$ requires C, 31·5; H, 3·7%).

4-*Ethylsulphonylpyridine*.—The base, liberated from the foregoing hydriodide (7·5 g.) with sodium hydroxide solution, was extracted with ether, the ethereal solution dried (BaO), and the residual oil oxidised with a slight excess of 3% permanganate, the mixture being evaporated to dryness, care being taken not to overheat the residue. The latter was extracted with ether; on evaporation of the ether, an oil, which solidified on standing, was obtained. Crystallisation from ligroin–acetone gave the *compound* in white needles (1·8 g.), m. p. 29° (Found : C, 49·4; H, 5·7. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%).

Phenyl Octyl Sulphide.—Thiophenol (11·0 g.) was added to a solution of sodium (2·3 g.) in alcohol (50 c.c.) followed by a solution of *n*-octyl bromide (19·3 g.) in alcohol (25 c.c.). The solution was boiled for 1 hour, filtered from sodium bromide, and the product distilled; the *sulphide* had b. p. 175°/18 mm. (18·5 g.) (Found : C, 76·1; H, 10·1; S, 14·2. $C_{14}H_{22}S$ requires C, 75·7; H, 9·9; S, 14·4%). Oxidation of 8·2 g. with perhydrol (20 c.c.) in acetic acid (50 c.c.) at 100° for ¾ hour gave the *sulphone* (7·5 g.), b. p. 230°/19 mm. (Found : C, 66·1; H, 8·8; S, 12·5. $C_{14}H_{22}O_2S$ requires C, 66·15; H, 8·65; S, 12·6%).

p-*Nitrophenyl Octyl Sulphide*.—*n*-Octyl iodide (or the equivalent amount of bromide) (7·8 g.) and sodium *p*-nitrothiophenoxide (6·0 g.), were dissolved in alcohol (25 c.c.) and benzene (25 c.c.) and the solution was boiled for 3 hours. The solvent was evaporated, water added, and the product extracted with ether. The ethereal solution was dried (Na_2SO_4), the ether distilled, and the residue dissolved in ligroin (b. p. 40—60°), from which the *sulphide* separated in pale yellow prisms, m. p. 35° (3 g.) (Found : C, 63·1; H, 8·0; N, 5·5; S, 12·15. $C_{14}H_{21}O_2NS$ requires C, 62·9; H, 7·9; N, 5·24; S, 12·0%).

The sulphide (4 g.) in acetic acid (40 c.c.) was oxidised with perhydrol (9·0 c.c.) for 45 minutes at 100°. The *sulphone* was precipitated with water and crystallised from alcohol, forming yellow needles (4 g.), m. p. 52° (Found : C, 56·1; H, 7·1; N, 5·0; S, 10·8. $C_{14}H_{21}O_4NS$ requires C, 56·2; H, 7·0; N, 4·7; S, 10·7%).

p-*Aminophenyl Octyl Sulphone*.—The nitro-sulphone (5·2 g.), iron powder (15 g.), alcohol (100 c.c.), water (15 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated, with stirring, under reflux for 3 hours. The mixture was made alkaline with ammonia, and the liquid filtered hot and evaporated to dryness. The residue was dissolved in boiling dilute hydrochloric acid (charcoal) and the amine liberated with sodium hydroxide. The *sulphone* (3·5 g.) formed needles, m. p. 105°, from alcohol (Found : C, 62·3; H, 8·5; N, 5·4; S, 12·0. $C_{14}H_{23}O_2NS$ requires C, 62·5; H, 8·55; N, 5·2; S, 11·9%).

Interaction of 4-Chloropyridine and Sodium p-*Nitrothiophenoxide*.—Sodium *p*-nitrothiophenoxide (3 g.) and 4-chloropyridine (2 g.) were dissolved in alcohol (60 c.c.) and boiled for 16 hours. The mixture was poured into water and the product collected. Crystallisation from alcohol gave pale yellow needles (1·1 g.) of 4 : 4′-dinitrodiphenyl sulphide, m. p. and mixed m. p. 156°.

Ethyl 4 : 6-*Dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate*.—*p*-Nitrobenzenesulphenyl chloride (from 15·4 g. of pure 4 : 4′-dinitrodiphenyl disulphide) in dry chloroform (100 c.c.) was added to a solution of ethyl 4 : 6-dihydroxy-2-methylpyridine-5-carboxylate (19·7 g.) in warm nitrobenzene (200 c.c.) and the solution heated on the steam-bath for 20 hours during which time a solid slowly separated. The mixture was filtered whilst still hot, giving 12 g. of solid (*A*). On cooling, a further 8 g. (*B*) was obtained. Crystallisation of (*A*) from 2-methoxyethanol gave nearly colourless needles, m. p. 261° (decomp.) (Found : N, 8·0; S, 8·9), and of (*B*) needles, m. p. 256° (Found : C, 51·2; H, 4·2; N, 7·9; S, 8·9. $C_{15}H_{14}O_6N_2S$ requires C, 51·4; H, 4·0; H, 8·0; S, 9·1%), no depression in m. p. being observed on admixture of the two samples of the *ester*.

4 : 6-*Dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine*.—The above ester (*A* or *B*) (2 g.) was boiled with concentrated hydrochloric acid (40 c.c.) and 2-methoxyethanol (30 c.c.) for 6 hours. On cooling, the *product* crystallised in minute needles (1·2 g.), m. p. 294° (decomp.) (Found : C, 51·6; H, 3·8; N, 9·8; S, 11·6. $C_{12}H_{10}O_4N_2S$ requires C, 51·8; H, 3·6; N, 10·1; S, 11·5%).

Ethyl 4 : 6-*Diacetoxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate*.—The above ester (*B*) (10 g.) was heated on the steam-bath with fused sodium acetate (10 g.) and acetic anhydride (75 c.c.) for 4 hours. The reaction mixture was poured into water giving an oil, which solidified on being stirred. Crystallisation from alcohol gave the *diacetyl* derivative as fine needles (8·5 g.), m. p. 123° (Found : C, 52·6; H, 4·1; N, 6·5; S, 7·2. $C_{19}H_{18}O_8N_2S$ requires C, 52·5; H, 4·1; N, 6·5; S, 7·4%). Attempted acetylation with boiling acetic anhydride caused profound decomposition.

Ethyl 6(or 4)-*Hydroxy*-4(or 6)-*acetoxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate*.—Acetylation of (*A*) under similar conditions to the above gave the *monoacetyl* derivative as nearly colourless needles (10 g.), m. p. 176° (Found : C, 51·7; H, 4·4; N, 7·3; S, 8·1. $C_{17}H_{16}O_7N_2S$ requires C, 52·0; H, 4·1; N, 7·1; S, 8·2%), soluble in cold dilute sodium hydroxide. Further acetylation could not be accomplished. Acetylation of (*A*) and (*B*) was carried out several times with the same results.

Ethyl 4 : 6-*Dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*-5-*carboxylate*.—The diacetate (8 g.) in glacial acetic acid (50 c.c.) and acetic anhydride (15 c.c.) was oxidised with perhydrol (8·5 c.c.) at 100° for ½ hour, during which time a solid slowly separated. The cooled reaction mixture was diluted with water, and the solid collected. After crystallisation from acetic acid, the *product* (5 g.) had m. p. 276° (decomp.) (Found : C, 47·1; H, 3·6; N, 7·3; S, 7·9. $C_{15}H_{14}O_8N_2S$ requires C, 47·1; H, 3·7; N, 7·3; S, 8·4%). Similar oxidation of the monoacetate gave the same product, m. p. and mixed m. p. 276°.

4 : 6-*Dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*.—The ester-sulphone (1·5 g.) was boiled with concentrated hydrochloric acid (30 c.c.) and 2-methoxyethanol (40 c.c.) for 6 hours. A white solid slowly separated, and was thrown out completely on cooling (1·1 g.). This *compound* had m. p. 303° (decomp.), and was completely insoluble in all the common solvents (Found : C, 47·3; H, 3·6; N, 9·0; S, 10·0. $C_{12}H_{10}O_6N_2S$ requires C, 46·5; H, 3·2; N, 9·0; S, 10·3%).

4-p-*Cyanophenylsulphonylpyridine*.—Sodium *p*-cyanobenzenesulphinate (27·5 g.) in water (250 c.c.) was added to a solution of 4-chloropyridine (16·2 g.) in alcohol (50 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 3½ hours. The *sulphone* separated on cooling (26·5 g.), and, after crystallisation from alcohol, formed pale yellow needles, m. p. 182° (Found : N, 11·1; S, 13·0. $C_{12}H_8O_2N_2S$ requires N, 11·5, S, 13·1%).

4-p-*Tolylsulphonylpyridine*.—4-Chloropyridine (3 g.) in alcohol (25 c.c.) was added to a solution of *p*-toluenesulphinic acid (4·1 g.) and potassium hydroxide (1·5 g.) in water (50 c.c.). Traces of copper powder and iodine were added, and the solution was refluxed for 1½ hours. On cooling, the *sulphone* separated and, after crystallisation from alcohol, formed colourless needles (4·5 g.), m. p. 137—138° (Found : C, 61·4; H, 4·7. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%).

p-*Acetamidomethylbenzenesulphinic Acid*.—*p*-Acetamidomethylbenzenesulphonyl chloride (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459) (29 g.) was shaken for 2 hours with a solution of sodium sulphite ($Na_2SO_3,7H_2O$) (60 g.) in water (120 c.c.) with frequent addition of 50% sodium hydroxide solution to keep the mixture slightly alkaline. The solution was filtered and acidified with sulphuric acid. The product was collected, and, after crystallisation from a small volume of water, formed white needles (10 g.), m. p. 138—139° (decomp.).

4-p-*Acetamidomethylphenylsulphonylpyridine*.—A solution of the above sulphinic acid (10·65 g.) and potassium hydroxide (2·8 g.) in water (50 c.c.) was added to a solution of 4-chloropyridine (5·7 g.) in alcohol (10 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 20 minutes. The *sulphone* separated on cooling, and, after crystallisation from water, formed minute needle-shaped crystals (9·3 g.), m. p. 170—171° (Found : N, 9·4; S, 10·8. $C_{14}H_{14}O_3N_2S$ requires N, 9·7; S, 11·0%).

4-p-*Aminophenylsulphonylpyridine* N-*Oxide*.—4-*p*-Acetamidophenylsulphonylpyridine (5·52 g.) dissolved in chloroform (530 c.c.) was added to 70 c.c. of a chloroform solution of perbenzoic acid containing 0·4 g. of active oxygen. The solution was kept for two weeks in the refrigerator (unreacted perbenzoic acid being determined iodometrically at frequent intervals). The chloroform solution was evaporated to one third of its volume and shaken with excess of sodium carbonate solution; a colourless solid then separated. This was collected, and on crystallising from alcohol formed small agglomerations of flattened needles (3·6 g.), m. p. 242—243° (Found : C, 53·9; H, 4·2; N, 10·4; S, 10·9. $C_{13}H_{12}O_4N_2S$ requires C, 53·4; H, 4·1; N, 9·6; S, 10·9%). The *acetamido-sulphone oxide* was hydrolysed by boiling with concentrated hydrochloric acid (50 c.c.) and water (10 c.c.) for 6 hours; the *product* after crystallisation from alcohol, had m. p. 244—245° (decomp.) (Found : N, 11·5; S, 13·2. $C_{11}H_{10}O_3N_2S$ requires N, 11·2; S, 12·8%), depressed to 209—210° on admixture with the acetyl derivative.

6(or 4)-*Chloro*-4(or 6)-p-*aminophenylsulphonyl*-2-*methylpyridine*.—4 : 6-Dichloro-2-methylpyridine (Collie *et al.*, *J.*, 1892, 725; 1895, 408) (5·1 g.) in alcohol (100 c.c.) was added to a solution of acetamidobenzenesulphinic acid (6·3 g.) and potassium hydroxide (1·75 g.) in water (250 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 15 hours. The solution was cooled, and the solid (10 g.) collected. Crystallisation from aqueous 2-methoxyethanol gave the *compound* as lustrous, white needles, m. p. 250—252° (Found : C, 52·5; H, 4·6; N, 8·9; S, 10·1.

$C_{14}H_{13}O_3N_2ClS$ requires C, 51·8; H, 4·0; N, 8·6; S, 9·9%). Hydrolysis with 6N-hydrochloric acid gave the *amino-sulphone* which, crystallised from alcohol, had m. p. 172° (Found: C, 51·3; H, 3·9; N, 10·2; S, 11·1. $C_{12}H_{11}O_2N_2ClS$ requires C, 51·0; H, 3·9; N, 9·9; S, 11·3%).

4: 6-*Bis*-p-*acetamidophenylsulphonyl*-2-*methylpyridine*.—*p*-Acetamidobenzenesulphinic acid (12·5 g.), and potassium hydroxide (3·53 g.) were dissolved in water (150 c.c.) and added to a solution of **4**: 6-dichloro-2-methylpyridine (3 g.) in alcohol (75 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 20 hours. The alcohol was evaporated, and on cooling a white solid separated. After three crystallisations from 2-methoxyethanol the *compound* formed lustrous, hair-like, white needles, m. p. 275—276°, unchanged by further crystallisation (Found: C, 53·5; H, 4·9; S, 13·1. $C_{22}H_{21}O_6N_3S_2$ requires C, 54·2; H, 4·3; S, 13·1%).

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