186. *4-Thiopyridone and Derived Substances.*

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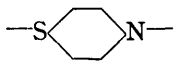
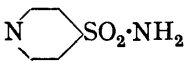
The object of this investigation was the preparation of pyridine-4-sulphonamide for a comparison of its therapeutic properties with sulphanilamide, to which it shows close structural similarity. This object has not been attained, since *sodium pyridine-*

4-*sulphonate* on treatment with phosphorus pentachloride gives 1-4′-pyridylpyridine-4-imine or 1-4′-pyridyl-4-pyridone depending on the manner in which the product is worked up. The starting material, 4-*thiopyridone*, has been characterised by the preparation of a number of derivatives and attempts to make the sulphonyl chloride or bromide by the action of chlorine or bromine on thiopyridone yielded *di-4-pyridyl sulphide*, *di-4-pyridyl disulphide*, and 4-chloropyridine. The results bring out the tendency of the pyridine nucleus to duplicate itself under the action of appropriate reagents, as has previously been observed by Arndt (*Ber.*, 1932, **65**, 92) and Koenigs and Greiner (*Ber.*, 1931, **64**, 1049).

THE remarkable success of the sulphanilamide group of drugs in the treatment of diseases of bacterial origin is a landmark in chemotherapy. The majority of the substances of proven activity contain the structure (I). The state of combination of the sulphur and nitrogen atoms can be widely varied with retention of activity, and certain French workers have suggested that the active bactericidal agent is the hydroxylamine formed by oxidation or reduction as the case may be. This view of the mechanism might be put to the test by the preparation of pyridine-4-sulphonamide (II), since if this substance was active, its activity could not be ascribed to the formation of a hydroxylamine. Apart from this consideration pyridine-4-sulphonamide, which shows close structural similarities to sulphanilamide (III), might itself possess desirable bactericidal properties. Unfortunately all attempts to prepare this substance have so far failed; the experimental results obtained are, however, not devoid of interest.


(I.)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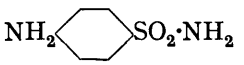
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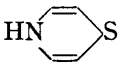
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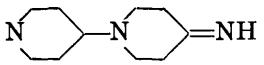
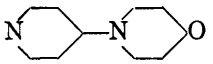
The starting material, 4-*thiopyridone* (IV), was obtained in 80% yield by the action of phosphorus pentasulphide on 4-pyridone. It was characterised by preparation of the S-*methyl* ether, the corresponding *sulphone*, the S-*methyl ether methiodide* and by the preparation of *pyridine-4-thioacetic acid*. On oxidation with hydrogen peroxide in presence of alkali it was quantitatively converted into *sodium pyridine-4-sulphonate*. By the action of phosphorus pentachloride on the anhydrous form of this salt under the mildest conditions there was no evidence for the formation of a sulphonyl chloride and on treatment with ammonia at −5° no sulphonamide was formed. The main product of the reaction was a new base, 1-4′-pyridylpyridine-4-imine (V), which formed well-crystallised salts, *e.g.*, a *mono-* and a *di-nitrate*, a *monohydrochloride*, a *dipicrate*, and a *diaurichloride*. The con-

(V.) 


(VI.)

stitution of the base follows since only *para*-positions are involved in the reaction and the base is quite different from di-4-pyridylamine, for a specimen of which for comparison purposes we are indebted to Prof. E. Koeings of Breslau. Furthermore, if the reaction product of sodium pyridine-4-sulphonate and phosphorus pentachloride is treated with water instead of ammonia, 1-4′-pyridyl-4-pyridone (VI) is formed as a very soluble base. It was characterised as its dipicrate and *aurichloride*. The properties of the base and picrate agree with those described by Arndt and Kalischek (*Ber.*, 1930, **63**, 587; Arndt, *ibid.*, 1932, **65**, 92) for this substance. There are small quantities of other substances produced in the reaction, two of which were identified through their picrates as 4-pyridone and 4-chloropyridine.

Sulphonyl chlorides and sulphonyl bromides have been obtained in some cases by the action of chlorine or bromine on a thiol in acetic acid solution (Zincke and Frohneberg, *Ber.*, 1910, **43**, 840). When this reaction was applied to 4-thiopyridone, *di-4-pyridyl sulphide*, m. p. 71°, and 4-chloropyridine were obtained by the action of chlorine and *di-4-pyridyl disulphide*, m. p. 75°, by the action of bromine.

We are indebted to Dr. L. Colebrook of Queen Charlotte's Maternity Hospital, Hammersmith, for examining ammonium pyridine-4-sulphonate and pyridine-4-thioacetic acid for

antistreptococcal activity in infected mice. Neither substance exhibited any curative action.

Experimental.

4-Pyridone.—Chelidonic acid was prepared as described in "Organic Synthesis," **17**, 40.* For the successful decarboxylation of chelidamic acid to 4-pyridone it is essential to have pure chelidamic acid. The following process (compare Lerch, *Monatsh.*, 1884, **5**, 402) gives almost quantitative yields. Chelidonic acid (20 g.), m. p. 266—267°, in dilute aqueous ammonia (100 c.c.; 10%) was heated on the water-bath for 4 hours, and the mixture evaporated to dryness under reduced pressure. The residue was dissolved in water (100 c.c.), and hydrochloric acid (10 c.c.; 32%) added to the boiling solution in insufficient quantity to produce a permanent precipitate. At this stage the solution was treated with charcoal, and the chelidamic acid precipitated by addition of hydrochloric acid in excess (20 c.c.; 32%).

Batches of chelidamic acid (50 to 60 g.) were heated at 200° in a distillation flask immersed in an oil-bath until all the water had been driven off. The temperature was then raised to 260°; evolution of carbon dioxide took place smoothly. When this process was over, the 4-pyridone was distilled at 3 mm. (yield, 95%).

4-Thiopyridone.—Finely powdered 4-pyridone (40 g.) was intimately ground with finely powdered phosphorus pentasulphide (81 g.). (The use of a 40-mesh sieve for both components is an advantage, as it lowers the temperature of reaction considerably.) When the mixture was heated to 60—70°, a vigorous reaction ensued. The reddish-brown crystalline mass was decomposed by water (100 c.c.), and the solution filtered and neutralised to about p_H 6 by addition of 50% sodium hydroxide solution (80 c.c.). After a few hours some crude 4-thiopyridone separated and was collected and the remainder was extracted from the aqueous salt solution by mixing it with several portions of alcohol until the extracts were no longer yellow. The crude 4-thiopyridone was dissolved in the combined alcoholic extracts, and the solution then evaporated to dryness. A solution of the residue in boiling absolute alcohol (100 c.c.) (charcoal) was filtered and concentrated for crystallisation; yield 43·5 g., 86%. *4-Thiopyridone* crystallises well from methyl alcohol in pale yellow, flattened, hexagonal plates, m. p. 186° with previous sintering. It sublimed readily and was easily soluble in water (Found :† C, 54·0, 54·1; H, 4·6, 4·7; N, 13·0, 13·2. C_5H_5NS requires C, 54·0; H, 4·5; N, 12·6%). The *picrate* separated from water in pale yellow needles, m. p. 222° (decomp.) with reddening at about 155° (Found : C, 39·0, 39·0; H, 2·5, 2·4; N, 17·2, 17·3. $C_5H_5NS,C_6H_3O_7N_3$ requires C, 38·8; H, 2·4; N, 16·5%).

4-Methylthiopyridine.—4-Thiopyridone (2·22 g.) was dissolved in boiling alcohol (20 c.c.) and when the temperature had fallen to 50° methyl iodide (2·9 g.) in alcohol (5 c.c.) was added. On cooling, a quantitative yield of *4-methylthiopyridine hydriodide* separated. For analysis it was crystallised from ethyl alcohol, in which it was sparingly soluble, separating in orange-yellow prisms, m. p. 170° (Found : C, 28·4, 28·6; H, 3·5, 3·3; N, 5·9, 5·9. C_6H_7NS,HI requires C, 28·4; H, 3·2; N, 5·5%). The free *base* was extracted from an alkaline solution with ether. The ethereal solution was dried over barium oxide and on evaporation gave an oil, which crystallised on cooling to 0° and then separated from light petroleum in colourless prismatic needles, m. p. 44—45° (Found : C, 56·8, 57·0; H, 5·6, 5·4; N, 10·9, 10·8. C_5H_7NS requires C, 57·5; H, 5·6; N, 11·2%). The *picrate*, chrome-yellow prismatic needles from water, melted at 245° (Found : C, 40·8, 40·8; H, 3·1, 3·0; N, 15·4, 15·3. $C_5H_7NS,C_6H_3O_7N_3$ requires C, 40·7; H, 2·9; N, 15·8%).

4-Methylsulphonylpyridine.—4-Methylthiopyridine (0·8 g.) in dilute acetic acid (20%) was shaken with aqueous permanganate (3%) until a permanent pink colour appeared. The slight excess was removed with sulphur dioxide, the solution evaporated to dryness, and the residue extracted with ether in presence of 2N-sodium hydroxide. The ethereal solution was dried over barium oxide and on distillation gave an 80% yield of the crystalline *sulphone*, which separated from hexane in needles, m. p. 81° (Found : C, 46·1, 46·0; H, 4·7, 4·5; N, 8·9, 8·8. $C_6H_7O_2NS$ requires C, 45·8; H, 4·5; N, 8·9%).

Pyridine-4-thioacetic Acid.—4-Thiopyridone (1·1 g.) in water (5 c.c.), when mixed with chloroacetic acid (0·94 g.) in water (5 c.c.), set to a paste. Sodium bicarbonate (0·84 g.) was added and when evolution of carbon dioxide had ceased the product was collected and washed with water; yield, 95%. It crystallised from boiling water, in which it was sparingly soluble, in

* Ethyl acetonedioxalate is therein (p. 41) wrongly described as ethyl chelidonate.

† All analyses except Na values are micro.

small, colourless, prismatic needles, m. p. 270° (efferv.) (Found: C, 50·5, 50·3; H, 4·2, 4·3; N, 8·9, 8·8. $C_7H_7O_2NS$ requires C 49·7; H, 4·2; N, 8·3%). The *sodium* salt crystallised from 60% alcohol in colourless parallelepipeds (Found: Na, 11·9. $C_7H_6O_2NSNa$ requires Na, 12·0%).

4-Methylthiopyridine Methiodide.—4-Methylthiopyridine (1·25 g.) was digested on the water-bath for 4 hours with methyl iodide (4 g.) in alcohol (10 c.c.). The cooled solution set to a mass of crystals of the *methiodide*. This salt was very soluble in water, but crystallised from ethyl alcohol in prismatic needles, m. p. 177° (Found: C, 31·2, 31·4; H, 3·7, 3·7. $C_7H_{10}NIS$ requires C, 31·4; H, 3·8%).

Sodium Pyridine-4-sulphonate.—4-Thiopyridone (55·5 g.), dissolved in 2N-sodium hydroxide (250 c.c.), was treated, dropwise, with "perhydrol" (171 c.c.; 30% H_2O_2) with external cooling. Reaction was completed by heating on the water-bath. On concentration successive crops of *sodium pyridine-4-sulphonate* were collected; yield, almost quantitative. The salt was very readily soluble in water and crystallised in needles containing water of crystallisation (Found: Loss at 145°, 16·4. $C_5H_4O_3NSNa,2H_2O$ requires H_2O, 16·6%. Found for the dried solid: Na, 12·7. $C_5H_4O_3NSNa$ requires Na, 12·7%).

1-4′-Pyridylpyridine-4-imine (V).—Anhydrous, finely powdered sodium pyridine-4-sulphonate (9·06 g.) and phosphorus pentachloride (10·4 g.) were heated in a bath to 90°; a vigorous reaction then occurred, accompanied by distillation of a mixture containing phosphorus oxychloride and thionyl chloride (8·1 g.), the last traces of volatile products being removed by suction. The residual solid brown mass was cooled and straightway added to 28% aqueous ammonia (100 c.c.) cooled to −5°. There was no marked rise of temperature. The deep violet solution was separated from a dark by-product (1·2 g.) and evaporated with 2N-sodium hydroxide (20 c.c.) at 50° under reduced pressure until all free ammonia had been removed; it was then made faintly acid with hydrochloric acid and evaporated to dryness under reduced pressure. The solid residue was boiled with dry methyl alcohol, and the solution filtered from inorganic salts (5·2 g.) and concentrated, whereby unchanged sodium pyridine-4-sulphonate (2·55 g.) and *pyridylpyridineimine hydrochloride* (1·6 g.) were obtained. The solvent of the residual mother-liquor was replaced by water and on addition of sodium nitrate *pyridylpyridineimine dinitrate* (1·5 g.) was obtained, and finally, by careful addition of picric acid to the mother-liquor, *pyridylpyridineimine dipicrate* (0·17 g.). The yield of pyridylpyridineimine allowing for recovered sodium pyridinesulphonate is 61%. When 1·3 molecular proportions of phosphorus pentachloride were used, there was an increase in the weight of pyridylpyridineimine salts obtained. When the ammonium salts were not removed by sodium hydroxide, a 30% yield of *ammonium pyridine-4-sulphonate* was obtained, which crystallised from methyl alcohol, in which it was sparingly soluble, or preferably from water, in which it was very soluble, in long needles, m. p. 257° (efferv.) (Found for solid dried in a high vacuum at 80°: C, 33·7, 33·9; H, 4·5, 4·5; N, 15·5, 15·5. $C_5H_8O_3N_2S$ requires C, 34·1; H, 4·6; N, 15·9%). From the mother-liquors, pyridylpyridineimine salts could be isolated as described above.

Pyridylpyridineimine hydrochloride crystallises readily from water in long prismatic needles, m. p. 100°, but when dried has m. p. 280° (Found for air-dried material: C, 44·4, 44·4; H, 5·9, 5·7; Cl, 12·9, 12·9; loss at 100°, 22·9. $C_{10}H_9N_3,HCl,3\frac{1}{2}H_2O$ requires C, 44·3; H, 6·3; Cl, 13·1; $3·5H_2O$, 23·3%. Found for solid dried at 100°: C, 58·0, 58·2; H, 4·9, 5·0; N, 20·6, 20·5; Cl, 16·7, 16·8. $C_{10}H_9N_3,HCl$ requires C, 57·8; H, 4·9; N, 20·3; Cl, 17·1%). This salt also crystallises from water in plates which again correspond to a hydrate with $3\frac{1}{2}H_2O$ (Found: C, 44·4, 44·3; H, 5·8, 6·0; Cl, 12·9, 13·1%). Both crystalline forms give the same dipicrate. The dinitrate is a characteristic salt not very soluble in water and crystallising in needles, m. p. 226° (decomp.) (Found: C, 40·5, 40·3; H, 3·8, 3·6; N, 23·7, 24·0. $C_{10}H_9N_3,2HNO_3$ requires C, 40·4; H, 3·7; N, 23·6%). The *mononitrate*, needles, also obtainable by the action of ammonium nitrate on a soluble salt, has m. p. 255° (decomp.) (Found: C, 51·3, 51·1; H, 4·3, 4·2; N, 23·4, 23·6. $C_{10}H_9N_3,HNO_3$ requires C, 51·3; H, 4·3; N, 23·9%). The dipicrate is sparingly soluble in water and crystallises in small prisms with some fasciation. It melts at 216° when air-dried but at 227° (decomp.) when previously dried at 100°. This property is probably connected with the hydration of the picrate (Found: C, 40·8, 40·9; H, 2·8, 2·9; N, 19·1, 19·3. $C_{10}H_9N_3,2C_6H_3O_7N_3,H_2O$ requires C, 40·8; H, 2·7; N, 19·5%). 1-4′-Pyridylpyridine-4-imine is liberated as an oil, which gradually crystallises in needles, on addition of a strong alkali to a concentrated solution of a salt. This form is probably hydrated and melts at 70°. It is very difficult, owing to its great solubility, to free it from traces of inorganic salts. An anhydrous form, m. p. about 160°, can however be obtained in small quantities from organic solvents. This form is also obtained by micro-sublimation or distillation. The base is, however, unstable

to heat, readily forming red uncrystallisable oils. The anhydrous form, m. p. 160°, gives the characteristic nitrate. The hydrated form of the base, dissolved in N-hydrochloric acid and treated with aurichloric acid solution (5%) in excess, gives a *diaurichloride*, needles, m. p. 280° (Found: C, 14·5, 14·6; H, 1·5, 1·5; N, 5·2, 5·1; Au, 46·1, 46·0, 46·2. $C_{10}H_9N_3,2HAuCl_4$ requires C, 14·1; H, 1·3; N, 4·9; Au, 46·3%).

1-4′-*Pyridyl*-4 *pyridone* (VI).—When sodium pyridine-4-sulphonate (9·06 g.) and phosphorus pentachloride were allowed to react exactly as described in the previous experiment and the dry reaction product was added to ice-cold water instead of ammonia, 1-4′-pyridyl-4-pyridone was the main product instead of pyridylpyridineimine. When the aqueous solution was treated with picric acid (8 g.), pyridylpyridone dipicrate (6·7 g.; m. p. 195°) was obtained as the main product. On crystallisation from water the pure dipicrate had m. p. 202° (Found: C, 40·8, 40·8; H, 2·5, 2·5; N, 17·4, 17·2. Calc. for $C_{10}H_8ON_2,2C_6H_3O_7N_3,H_2O$: C, 40·7; H, 2·5; N, 17·3%). Arndt and Kalischek (*Ber.*, 1930, **63**, 593) give m. p. 198° and record an analysis, for nitrogen only, in agreement with an anhydrous dipicrate. The *aurichloride*, prepared from the base regenerated from the pure picrate, crystallised in tufts of very small needles, m. p. about 226° (Found: C, 22·4, 22·3; H, 1·9, 1·9; Au, 35·7, 35·8. $C_{10}H_8ON_2,HAuCl_4,2H_2O$ requires C, 21·9; H, 2·4; Au 36·0%).

The picric acid mother-liquors were carefully fractionated and gave a small quantity (0·19 g.) of 4-*pyridone picrate*, m. p. 240° (Found: C, 40·4, 40·7; H, 2·4, 2·4; N, 17·5, 17·4. $C_5H_5ON,C_6H_3O_7N_3$ requires C, 40·7; H, 2·5; N, 17·3%). Arndt and Kalischek (*loc. cit.*) describe this picrate, m. p. 238°, but give no analysis. A third picrate, obtained in smaller quantity (75 mg.) as fine needles, containing chlorine, proved to be 4-*chloropyridine picrate*, m. p. 146° (Found: C, 38·7, 38·8; H, 2·2, 2·3. $C_5H_4NCl,C_6H_3O_7N_3$ requires C, 38·5; H, 2·1%). A fourth picrate (82 mg.), m. p. 222° (Found: C, 40·9, 40·9; H, 2·6, 2·5; N, 18·7, 18·9%), could not be identified.

Action of Chlorine on 4-*Thiopyridone*.—Thiopyridone (5 g.) in 90% acetic acid (50 c.c.) was treated with an excess of chlorine at room temperature. The clear solution was evaporated to dryness under reduced pressure below 50°, and the residue decomposed with 28% aqueous ammonia (100 c.c.) at 0°. The oil which separated was taken up in ether and finally fractionated. It gave 4-chloropyridine, b. p. 50°/11 mm., as a mobile colourless liquid with an odour similar to that of pyridine. When kept, this fraction deposited orange amorphous flocks, but the picrate, m. p. 147°, was stable (Found: C, 38·4, 38·7; H, 2·1, 2·1; Cl, 10·8, 10·5. Calc.: C, 38·5; H, 2·1; Cl, 10·4%). A higher fraction (0·9 g.), b. p. 155°/1·5 mm., rapidly set to a crystalline mass, m. p. 71°, and proved to be *di*-4-*pyridyl sulphide* (Found: C, 64·0, 63·9; H, 4·3, 4·4; S, 18·2. $C_{10}H_8N_2S$ requires C, 63·8; H, 4·3; S, 17·7%). It gave a *dipicrate*, m. p. 229°, crystallising from methyl alcohol in glistening needles (Found: C, 41·0, 41·1; H, 2·5, 2·5; N, 17·9. $C_{10}H_8N_2S,2C_6H_3O_7N_3$ requires C, 40·9; H, 2·2; N, 17·3%).

Action of Bromine on 4-*Thiopyridone*.—Thiopyridone (1·11 g.) in glacial acetic acid (35 c.c.) was treated dropwise with 6 atoms of bromine (4·8 g.). There was immediate deposition of an orange-yellow solid. The flask was sealed and kept at 37° for 2 months. The solvent was removed under reduced pressure, and the residual solid treated with 30% aqueous ammonia (250 c.c.) at −10°. A crystalline base separated (0·7 g.), which proved to be *di*-4-*pyridyl disulphide*, m. p. 74—75°, depressed by admixture with dipyridyl sulphide to 48° (Found: C, 54·8; H, 3·5. $C_{10}H_8N_2S_2$ requires C, 54·5; H, 3·7%). This base was readily soluble in most solvents except ligroin and low-boiling petroleum. It crystallised from water in plates. The *dipicrate* was obtained in needles, usually twinned, by mixing the components in methyl alcohol; it was very sparingly soluble in all boiling solvents and had m. p. 231° (Found: C, 39·0, 39·1; H, 2·2, 2·2; S, 9·7, 9·6. $C_{10}H_8N_2S_2,2C_6H_3O_7N_3$ requires C, 38·9; H, 2·1; S, 9·4%). The original ammoniacal liquors on concentration to a very small volume gave a further quantity of the same disulphide (0·11 g.).

The same disulphide was obtained in an attempt to prepare the sulphinic acid by the action of hydrogen peroxide on 4-thiopyridone in the presence of zinc oxide. On acidification with hydrochloric acid a *zincichloride* separated, m. p. above 300° (Found: C, 27·0, 27·0; H, 2·7, 2·6; Cl, 33·2, 32·9. $C_{10}H_8N_2S_2,H_2ZnCl_4,\frac{1}{2}H_2O$ requires C, 27·4; H, 2·5; Cl, 32·4%). The base was regenerated by alkali and ether and proved identical with that obtained by the action of bromine and gave an identical picrate.

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