393. *Chemotherapeutic Agents of the Sulphone Type. Part V. 2 : 5-Disubstituted Derivatives of Pyridine.*

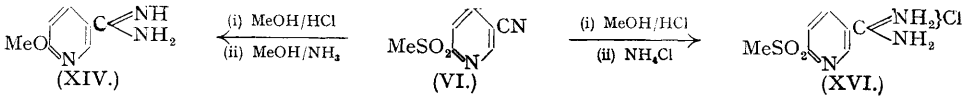
By H. S. Forrest and James Walker.

Replacement of the benzene ring in *p*-methylsulphonylbenzamidine hydrochloride, *p*-methylthiobenzamidine hydrochloride, and *p*-methylsulphonylaniline by a pyridine ring greatly reduced antibacterial activity in each case. Relatively marked antibacterial activity has been observed in some mercaptopyridines. A facile replacement of a methylsulphonyl substituent by a methoxy-group in the 2-position of the pyridine ring has been observed.

Numerous reports have shown that the isosteric replacement of an aromatic ring in an essential metabolite affords a substance with antagonistic properties, and the wide generality of this biological discrimination has been borne out by studies on adenine, guanine, hypoxanthine, riboflavin, thiamin, nicotinic acid (and amide), phenylalanine, and *p*-aminobenzoic acid (for references, see Roblin, *Chem. Reviews*, 1947, **38**, 255; Woolley, *Physiol. Rev.*, 1947, **27**, 308). In the case of antibacterial agents, whether modelled on essential metabolites or otherwise, it is impossible to state in advance of experiment what will be the precise effect of similar replacement on biological activity. Comparative figures do not appear to be available for the activities of aminopyridinesulphonamides (*e.g.*, Naegeli *et al.*, *Helv. Chim. Acta*, 1938, **21**, 1746; Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1695; Caldwell, Tyson, and Lauer, *ibid.*, 1944, **66**, 1479; B.P. 516,288) relative to the activities of the corresponding benzenoid analogues but the replacement of the benzene ring in sulphonamides by isosteric heterocyclic rings probably has a dystherapeutic effect generally (Tullar, quoted by Naegeli *et al.*, *loc. cit.*; Backer and de Jonge, *Rec. Trav. chim.*, 1943, **62**, 163). Among diamidines, the (bis)pyridine analogue of pentamidine has less than half the activity of the benzenoid compound (Gregory, Holt, and Slack, *J.*, 1947, 87). On the other hand, the antitubercular activities of 5-amino-2-alkoxypyridines and *p*-aminophenyl alkyl ethers are approximately equal for the same alkyl radical (C_4—C_6) (Feinstone *et al.*, *J. Pharmacol.*, 1947, **89**, 153). The work described in the present paper was undertaken, in part, to see if the outstanding antibacterial activity of some of the benzene derivatives studied in previous parts (*J.*, 1945, 630, 633) was shared by their pyridine analogues.

6-Chloronicotinamide (I) was dehydrated with phosphoryl chloride to give 2-chloro-5-cyanopyridine (II), which has been prepared by Rath (*Annalen*, 1931, **487**, 127) by a lengthier process, and the latter reacted smoothly with thiourea to give S-(*5-cyano-2-pyridyl*)*thiouronium chloride* (III). Decomposition of (III) with alkali afforded 5-cyano-2-mercaptopyridine (IV), which was obtained by Rath (*loc. cit.*) in much poorer yield from (II) and potassium hydrogen sulphide. Methylation of (IV) afforded *5-cyano-2-methylthiopyridine* (V), which yielded *5-cyano-2-methylsulphonylpyridine* (VI) on oxidation with potassium permanganate. Traces

of 6-*methylsulphonylnicotinamide* (VII) were formed during the oxidation and the possibility of postponing dehydration until the last stage in the preparation of (VI) suggested itself. As the amide group in (I) activates the chlorine atom less powerfully than the cyano-group does that in (II), reaction between (I) and thiourea was slower and less complete than the corresponding reaction of (II), but the resulting S-(5-*carbamyl*-2-*pyridyl*)*thiouronium chloride* (VIII) afforded easy access to 6-*mercaptonicotinamide* (IX), 6-*methylthionicotinamide* (X), (VII), and (VI). In the oxidations of thioethers with potassium permanganate described in this paper it was found that only $\frac{3}{5}$ of the oxygen usually available in acid solution appeared to be utilised and good yields of sulphones resulted on augmenting the amount of permanganate used on that basis. Oxidation of (X) with hydrogen peroxide only proceeded as far as 6-*methylsulphinylnicotinamide* (XI), the melting point of which, in contrast to the usual ascending series (thioether, sulphoxide, sulphone), was higher than that of (VII). Considerable difficulty was experienced in preparing amidines from (IV) and (V), owing to the ready precipitation of the starting materials as hydrochlorides at the outset with consequent recovery of substantial amounts of unchanged nitrile, and only moderate yields of 6-*mercaptonicotinamidine hydrochloride* (XII) and 6-*methylthionicotinamidine benzoate* (XIII) were obtained. Conversion of (VI) into the iminoether hydrochloride appeared to proceed more completely using methyl alcohol, and methyl-alcoholic ammonia, allowing of a higher concentration of ammonia, was used in the second stage of the Pinner process for amidine formation. Unexpectedly, however, the product proved to be 6-methoxynicotinamidine (XIV), which was characterised as the *benzoate* and

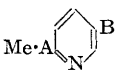


acetate, formed by displacement of the methylsulphonyl radical of (VI) by a methoxy-group, the identity of the salts being confirmed by comparison with authentic specimens. It was anticipated that displacement had taken place during imino-ether formation since nucleophilic displacement of potential anions occupying activated positions in heterocyclic compounds is catalysed by acids (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127; Tomisek and Christensen, *ibid.*, 1945, **67**, 2112; Walker, unpublished); similarly, the chlorine atom in 5-chloroacridine is fairly stable to hydrolysis (Graebe and Lagodzinski, *Annalen*, 1892, **276**, 48; Magidson and Grigorowski, *Ber.*, 1933, **66**, 866), but, when a formal positive charge rests on the nitrogen atom, hydrolysis takes place in aqueous solution with extreme readiness, as in the conversion of 5-chloro-*N*-methylacridinium chloride into *N*-methylacridone (Fischer and Demeler, *Ber.*, 1899, **32**, 1307). As a model, 5-*nitro*-2-*methylsulphonylpyridine* (XV), in which the activating forces would be comparable with those obtaining in (VI), was submitted to the conditions used for imino-ether formation and it was recovered unchanged. Treatment with methyl-alcoholic ammonia under the conditions used for the second stage of amidine formation, however, afforded 5-nitro-2-aminopyridine together with a small amount of 5-nitro-2-methoxypyridine, recalling the behaviour of 1-chloro-2 : 4-dinitrobenzene, to which (XV) bears some analogy, in reacting with alcoholic ammonia to give 2 : 4-dinitroaniline (Willgerodt, *Ber.*, 1876, **9**, 978) and with methyl-alcoholic potassium hydroxide to give 2 : 4-dinitroanisole (*idem*, *ibid.*, 1879, **12**, 763). It is noteworthy, too, that 1-chloro-2 : 4-dinitrobenzene reacts with aqueous-alcoholic sodium sulphite to give 2 : 4-dinitrobenzenesulphonic acid (D.R.-P. 65,240), while 2-chloro-5-nitropyridine with sodium sulphite in aqueous methyl alcohol affords 5-nitro-2-methoxypyridine and not the expected product (Caldwell and Kornfeld, *loc. cit.*). It was then conclusively shown that displacement of the methylsulphonyl group in applying the orthodox Pinner process to (VI) had taken place during the second phase of the reaction by the successful preparation of 6-*methylsulphonylnicotinamidine hydrochloride* (XVI), with no evidence of simultaneous formation of (XIV), by avoiding the use of free ammonia following the technique of Barber and Slack (*J. Amer. Chem. Soc.*, 1944, **66**, 1607).

Access to a series of aminopyridyl alkyl thioethers was obtained through *S*-(5-nitro-2-pyridyl)thiouronium chloride and 5-nitro-2-mercaptopyridine (XVII). The latter, which need not be isolated, was alkylated with the appropriate alkyl halides to give 5-*nitro*-2-*methylthio*- (XVIII), -2-*ethylthio*- (XIX), -2-n-*propylthio*- (XX), and -2-n-*butylthio*-*pyridine* (XXI); these were reduced with tin and hydrochloric acid to give the corresponding 5-*amino*-2-*methylthio*- (XXII), -2-*ethylthio*- (XXIII), -2-n-*propylthio*- (XXIV), and -2-n-*butylthio*-*pyridine* (XXV), which were further characterised, apart from (XXII), as *hydrochlorides*. The thioethers (XVIII) and (XXI) were oxidised with potassium permanganate to (XV) and 5-*nitro*-2-n-

butylsulphonylpyridine (XXVI) respectively and these, on catalytic reduction, afforded 5-*amino*-2-*methylsulphonyl*- (XXVII) and -2-n-*butylsulphonyl-pyridine* (XXVIII). Reaction between (II) and the appropriate alkoxides readily yielded 5-*cyano*-2-*methoxy*- (XXIX) and -2-n-*butoxy-pyridine* (XXX), which by the normal process of amidine formation, afforded (XIV)-*hydrochloride* and 6-n-*butoxynicotinamidine hydrochloride* (XXXI); catalytic reduction gave 5-(2-*methoxypyridyl*)- (XXXII) and 5-(2-n-*butoxypyridyl*)-*methylamine hydrochloride* (XXXIII). (XXXI) and (XXXIII) were prepared for the specific purpose of comparison with 5-amino-2-butoxypyridine, the marked antitubercular action of which, first reported by Feinstone (*Proc. Soc. Exp. Biol. Med.*, 1946, **63**, 153), has been confirmed under certain conditions in this laboratory (Forrest, Hart, and Walker, *Nature*, 1947, **160**, 94).

Tests for *in vitro* antibacterial activity were kindly carried out on the substances described in the present paper by Drs. A. T. Fuller and P. D'Arcy Hart. The over-all result of these tests was to indicate that the pyridine analogues were markedly inferior in activity to the corresponding benzenoid compounds. For example, (XVI) and (XIII) had only about 1% of the antibacterial activity of the corresponding highly active benzene analogues, *p*-methylsulphonyl- and *p*-methylthio-benzamidine hydrochloride (*J.*, 1945, 633), and (XXVII) had about a quarter of the activity of the similarly substituted benzene derivative (*ibid.*, p. 630). The more significant antibacterial titres are recorded in the Table and the feature which emerges



(XVI) A = SO_2; B = $C(NH_2){:}NH_2\}Cl$
(XIII) A = S; B = $C(NH_2){:}NH_2\}Cl$
(XXVII) A = SO_2; B = NH_2

is the high activity of the thiols and also that of (III). *p*-Aminothiophenol has been shown by Green and Bielschowsky (*Brit. J. Exp. Path.*, 1942, **23**, 13) to have marked antibacterial activity *in vitro* but to be less active than the corresponding disulphide; this observation is difficult to understand since bacterial cultures are usually strongly reducing systems and the latter would be expected to suffer reduction to the former therein. As the antibacterial activity

Antibacterial activity in vitro.

Minimal inhibiting concentrations in mg. of drug per 100 c.c. of culture medium.

	X	Y.	Organism.	* *Strep. haemolyt.*		* *Staph. aureus.*	* *Bact. coli.*	* *Cl. welchii.*	† *Myc. tuberculosis.*	† *Myc. phlei.*
			Medium.	a.	b.	a.	a.	a.	c.	d.
(III)	$S{\cdot}C(NH_2){:}NH_2\}Cl$	CN		2	50	2	10	100	2·5	—
(IV)	SH	CN		1	>100	2	20	5	1·3	—
(V)	CH_3S	CN		200	200	>200	>200	100	—	20
(II)	Cl	CN		>200	>200	>200	>200	200	—	20
(VI)	CH_3SO_2	CN		50	50	100	50	50	20	—
(VIII)	$S{\cdot}C(NH_2){:}NH_2\}Cl$	$CO{\cdot}NH_2$		10	500	200	500	1000	20	—
(IX)	SH	$CO{\cdot}NH_2$		1	>50	>50	>50	50	—	—
(X)	CH_3S	$CO{\cdot}NH_2$		5	200	>200	>200	200	—	—
(XXXIV)[e]	SH	NH_2		1	>50	2	10	75	20	
(XXII)	CH_3S	NH_2		200	>200	500	500	200	20	0·6
(XXIV)	C_3H_7S	NH_2		50	200	150	200	500	20	
(XXV)	C_4H_9S	NH_2		50	200	50	100	200	20	
(XII)	SH	$C(NH_2){:}NH_2\}Cl$		10	100	50	80	500	20	
(XXXI)	C_4H_9O	$C(NH_2){:}NH_2\}Cl$		10	100	100	100	50	20	
(XXXIII)	C_4H_9O	$CH_2{\cdot}NH_3\}Cl$		50	50	200	200	100	20	
(XXXV)[f]	SH	H		2	100	20	20	1000	20	

* Tests by Dr. A. T. Fuller.
† Tests by Dr. P. D'Arcy Hart.
— Not active at 20 mg./100 c.c.
a Nutrient broth.
b Blood.
c Albumin " Tween 80 " (Dubos) and albumin (Dubos).
d Broth (surface culture).
e Prepared following Rath (*loc. cit.*).
f Prepared following Phillips and Shapiro (*J.*, 1942, 584).

in both cases was counteracted by *p*-aminobenzoic acid it is not easy to decide how much, if any, of the net observed activity was contributed by the thiol or disulphide group, and how

much of the activity was of the " sulphonamide " type; on the other hand, the disulphide was inhibited in the presence of blood, plasma, or as little as 5% of serum. Similarly, the thiols described in the present paper showed reduced activity in the presence of blood. A number of thiols and disulphides in the thiazole series have been shown to possess antibacterial activity *in vitro* (Gibbs and Robinson, *J.*, 1945, 925) and the activity was ascribed to the thiol and disulphide group in these cases, while 3 : 3′-dipyridyl disulphide has been claimed as an antibacterial agent (B.P. 582,638); the degree of activity of these compounds appears to be comparable with, or slightly higher than, that of (III), (IX), 5-amino-2-mercaptopyridine (XXXIV), or 2-mercaptopyridine (XXXV), as far as comparison between tests carried out in one laboratory and those carried out in another allows. Replacement of the amino-group in 5-amino-2-butoxypyridine by the amidine group, in (XXXI), or by the aminomethyl group, in (XXXIII), reduced antitubercular activity markedly.

Experimental.

6-*Chloronicotinamide* (I).—Methyl coumalate (50 g.), prepared in one operation from malic acid following Ruzicka's technique for the ethyl ester (*Helv. Chim. Acta*, 1921, **4**, 504), was converted into 6-hydroxynicotinic acid (36·2 g.) according to v. Pechmann and Welsh (*Ber.*, 1884, **17**, 2391). The latter, m. p. 303°, was of adequate purity for the next stage, which has advantages over the method described by Mills and Widdows (*J.*, 1908, **93**, 1379). 6-Hydroxynicotinic acid (30 g.) was treated cautiously with phosphoryl chloride (50 c.c.) and the mixture heated for 2½ hours on the water-bath. Excess phosphoryl chloride was removed under reduced pressure and the resulting brown gum was dissolved in acetone (50 c.c.) and added slowly to cooled aqueous ammonia (100 c.c.; *d* 0·88). After standing for 30 minutes, the mixture was diluted with water and the crude product collected. Recrystallisation from spirit (norite) afforded colourless rectangular plates (26·6 g.), m. p. 208° (Found: C, 46·2; H, 3·1. Calc. for $C_6H_5ON_2Cl$: C, 46·0; H, 3·2%). Rath (*loc. cit.*) records m. p. 205° and Mills and Widdows (*loc. cit.*) record m. p. 211°.

2-*Chloro*-5-*cyanopyridine* (II).—6-Chloronicotinamide (30 g.) was refluxed with phosphoryl chloride (75 c.c.) in chloroform (250 c.c.) for 2½ hours. Solvent and excess phosphoryl chloride were removed by distillation and the residue was treated with melting ice, the resulting precipitate being collected. Crystallisation from spirit afforded colourless hexagonal plates (24 g.), m. p. 117—118° (Found: C, 52·0; H, 2·4. Calc. for $C_6H_3N_2Cl$: C, 52·0; H, 2·2%). Rath (*loc. cit.*) records m. p. 115°.

S-(5-*Cyano*-2-*pyridyl*)*thiouronium Chloride* (III).—2-Chloro-5-cyanopyridine (21·6 g.) was added to a warm solution of thiourea (12 g.) in absolute alcohol (200 c.c.) and the mixture was refluxed for 2 hours. The product (32 g., m. p. 190—192°), which separated on cooling, was collected. The *compound* crystallised from absolute alcohol in thin yellow prisms with pointed ends, m. p. 192° (Found: C, 39·1; H, 2·9; N, 26·4. $C_7H_6N_4S,HCl$ requires C, 39·1; H, 3·2; N, 26·1%).

5-*Cyano*-2-*mercaptopyridine* (IV).—*S*-(5-Cyano-2-pyridyl)thiouronium chloride (9·8 g.) was shaken with 2N-aqueous sodium hydroxide (25 c.c.) for about 15 minutes. A further quantity of 2N-sodium hydroxide (25 c.c.) was added and the solution was filtered and acidified with acetic acid, affording a pure product in practically quantitative yield. The substance separated from a large volume of alcohol in long yellow needles, m. p. 255° (Found: C, 53·3; H, 3·1. Calc. for $C_6H_4N_2S$: C, 53·0; H, 2·9%). Rath (*loc. cit.*) records m. p. 252° and U.S.P. 1,753,658 records m. p. 245°.

5-*Cyano*-2-*methylthiopyridine* (V).—(*a*) 5-Cyano-2-mercaptopyridine (0·34 g.) was dissolved in N-sodium hydroxide (2·5 c.c.) and treated with methyl iodide (0·35 c.c.). Alcohol was added to homogeneity and the solution was kept at room temperature for 12 hours. The crystalline product (0·32 g.) was collected. The *compound* separated from 50% alcohol in colourless needles, m. p. 78° (Found: C, 56·2; H, 4·0; N, 18·5. $C_7H_6N_2S$ requires C, 56·0; H, 4·0; N, 18·7%).

(*b*) *S*-(5-Cyano-2-pyridyl)thiouronium chloride (11 g.) was shaken with N-sodium hydroxide (51 c.c.) for 30 minutes. An equal volume of N-sodium hydroxide was added, and the solution was filtered and treated with methyl iodide (7·2 g.) and a little alcohol. There was a slight rise in temperature and a rapid separation of crystals took place. After standing overnight the product, m. p. 76—78°, was collected; the yield was quantitative.

5-*Cyano*-2-*methylsulphonylpyridine* (VI).—(*a*) 5-Cyano-2-methylthiopyridine (9 g.) was dissolved in acetone (60 c.c.) and 2N-sulphuric acid (100 c.c.) was added. Aqueous potassium permanganate solution (12·6 g. in 250 c.c.) was then run into the stirred mixture over a period of 30 minutes, a slight rise in temperature being observed. Manganese dioxide was thereafter destroyed with sulphur dioxide and the product (5·1 g., m. p. 131—133°) was collected, a further quantity (5·4 g.) being obtained on concentrating the filtrate. Crystallisation from absolute alcohol afforded the *cyano-sulphone* in the form of colourless needles (9·5 g.), m. p. 133° (Found: C, 46·2; H, 3·5; N, 15·4. $C_7H_6O_2N_2S$ requires C, 46·2; H, 3·3; N, 15·4%).

Further examination of the oxidation mother-liquors afforded a small amount of impure 6-methylsulphonylnicotinamide.

(*b*) 6-Methylsulphonylnicotinamide (3 g.) (see below) was treated with phosphoryl chloride (7 c.c.) in chloroform (25 c.c.) and the suspension was refluxed for 3 hours. The reaction mixture was worked up in the usual way, the residue being crystallised from absolute alcohol to give the cyano-sulphone (2·16 g.), m. p. and mixed m. p. 133°.

S-(5-*Carbamyl*-2-*pyridyl*)*thiouronium Chloride* (VIII).—6-Chloronicotinamide (33·5 g.), thiourea (17·7 g.), and absolute alcohol (350 c.c.) were heated on the water-bath under reflux for 6 hours, when a gradual separation of crystals and colouring of the solution occurred. After cooling, the product (46·4 g., m. p. 195°) was collected and a further quantity (1·2 g.) was obtained from the filtrate. The

compound separated from glacial acetic acid in pale yellow needles, m. p. 195° (Found: N, 23·8. $C_7H_8ON_4S,HCl$ requires N, 24·1%).

6-*Mercaptonicotinamide* (IX).—The preceding thiouronium salt (2·8 g.) was decomposed with 2N-sodium hydroxide, following the technique used in the analogous case described above, and the product (1·5 g.) was isolated in the normal way. The *thiol* crystallised from a large volume of water in pale yellow needles, m. p. 266—268° (Found: C, 46·8; H, 3·6. $C_6H_6ON_2S$ requires C, 46·7; H, 3·9%).

6-*Methylthionicotinamide* (X).—*S*-(5-Carbamyl-2-pyridyl)thiouronium chloride (29 g.) was decomposed with alkali and the resulting thiol methylated directly. The *product* (16·4 g.) separated from water in colourless needles, m. p. 166—167° (Found: C, 50·0; H, 4·8; N, 17·0. $C_7H_8ON_2S$ requires C, 50·0; H, 4·8; N, 16·7%).

6-*Methylsulphonylnicotinamide* (VII).—(*a*) 6-Methylthionicotinamide (6 g.), suspended in a mixture of acetone (40 c.c.) and excess of 2N-sulphuric acid, was oxidised with aqueous potassium permanganate (7·6 g. in 150 c.c.) and the product (6·9 g.) collected. The *compound* separated from 80% alcohol in rectangular plates, m. p. 210° (Found: C, 42·2; H, 3·9; N, 13·9. $C_7H_8O_3N_2S$ requires C, 42·0; H, 4·0; N, 14·0%).

(*b*) 6-Methylthionicotinamide (2 g.) in acetone (10 c.c.) was treated cautiously with 30% hydrogen peroxide (6 c.c.) and the mixture was then heated on the water-bath for 3 hours After concentration and cooling, the product (2·03 g.) was collected. As the m. p. was not sharp the product was re-treated with hydrogen peroxide under the same conditions and again isolated. Recrystallisation from 80% alcohol afforded clusters of colourless needles, m. p. 224—226°, depressed on admixture with the sulphone prepared in (*a*) (above). Analysis showed the substance to be the sulphoxide, 6-*methylsulphinylnicotinamide* (XI) (Found: C, 45·7; H, 4·6; N, 15·0. $C_7H_8O_2N_2S$ requires C, 45·6; H, 4·3; N, 15·2%), which gave the sulphone, m. p. and mixed m. p. 209—210°, on further oxidation with potassium permanganate.

6-*Mercaptonicotinamidine Hydrochloride* (XII).—5-Cyano-2-mercaptopyridine (5 g.), chloroform (13 c.c.), and absolute alcohol (6 c.c.) were mixed and saturated at 0° with dry hydrogen chloride. After standing at 0° for 60 hours, solvent and excess hydrogen chloride were removed in a vacuum and the yellow powdery residue was kept for 5 days at 37° in contact with 10% alcoholic ammonia (70 c.c.). The solid product from this stage was mixed with the residue obtained by evaporation of the alcoholic ammonia and the bulked material was crystallised from a large volume of water, affording two crops (2·6 g. and 0·35 g.) of unchanged starting material, followed by the desired amidine hydrochloride (1·07 g.). The *compound* separated from a small volume of water in yellow needles, m. p. 290°, but did not give precise analytical figures (Found: C, 38·5; H, 3·3; N, 22·6. $C_6H_7N_3S,HCl$ requires C, 38·0; H, 4·2; N, 22·2%). The *benzoate*, obtained by double decomposition in aqueous solution, separated from water in yellow plates, m. p. 266° (decomp.), giving precise analytical figures (Found: C, 56·6; H, 4·7; N, 15·1. $C_6H_7N_3S,C_7H_6O_2$ requires C, 56·7; H, 4·7; N, 15·3%).

Attempts to increase the extent of the conversion of nitrile by the use of larger volumes of chloroform, or of dioxan, were ineffective.

6-*Methylthionicotinamidine Benzoate* (XIII).—5-Cyano-2-methylthiopyridine (5 g.), dry dioxan (25 c.c.), and methyl alcohol (1·3 c.c.) were mixed and saturated at 0° with dry hydrogen chloride and the mixture was kept for 10 days in the refrigerator. Crude imino-ether hydrochloride, freed from solvent and excess hydrogen chloride in a vacuum, was treated with saturated methyl alcoholic ammonia (75 c.c.) at 37° for 7 days. The solution was evaporated to dryness, the residue taken up in water, brought to pH 5 with hydrochloric acid, and filtered from unchanged nitrile (2·8 g.). On evaporating the aqueous solution to dryness the resulting syrupy hydrochloride could not be induced to crystallise. The *benzoate*, however, obtained by double decomposition in aqueous solution, separated from water in rectangular plates, m. p. 248°, softening at 236° (Found: C, 58·0; H, 5·3; N, 14·5. $C_7H_9N_3S,C_7H_6O_2$ requires C, 58·1; H, 5·2; N, 14·5%). The *acetate*, similarly prepared, crystallised from water in colourless needles, m. p. 224—226° (Found: N, 18·1. $C_7H_9N_3S,C_2H_4O_2$ requires N, 18·5%).

A number of modifications of the above experiment were tried but none gave any greater conversion of nitrile.

Attempted Preparation of 6-*Methylsulphonylnicotinamidine Hydrochloride. Formation of* 6-*Methoxynicotinamidine* (XIV).—5-Cyano-2-methylsulphonylpyridine (6·06 g.), methyl alcohol (1·3 c.c.), and dioxan (25 c.c.) were treated for 6 days at 0° with dry hydrogen chloride (3·5 g.), and the crude imino-ether hydrochloride was set aside with saturated methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. The ammoniacal solution was evaporated to dryness and the residue was taken up in water, adjusted to pH 5—6, and filtered from a small quantity (0·5 g.) of 5-cyano-2-methoxypyridine, identified by comparison with an authentic specimen (see below), m. p. and mixed m. p. 94°. The crude amidine hydrochloride (5 g.), obtained by evaporating the filtrate to dryness and extraction from ammonium chloride with absolute alcohol, showed no tendency to crystallise. The *benzoate*, obtained by double decomposition in aqueous solution, however, separated from water in rectangular plates, m. p. 253° (Found: C, 61·2; H, 5·4; N, 15·6. $C_7H_9ON_3,C_7H_6O_2$ requires C, 61·5; H, 5·5; N, 15·4%); the analytical figures indicated the substance to be 6-methoxynicotinamidine benzoate, and no depression of the m. p. was observed on admixture with an authentic specimen (see below).

Similarly, the *acetate*, prepared by double decomposition, separated from water in colourless needles, m. p. 246—248°, not depressed on admixture with an authentic specimen of 6-methoxynicotinamidine acetate (Found: C, 50·9; H, 6·2; N, 19·7. $C_7H_9ON_3,C_2H_4O_2$ requires C, 51·2; H, 6·2; N, 19·9%).

6-*Methylsulphonylnicotinamidine Hydrochloride* (XVI).—5-Cyano-2-methylsulphonylpyridine (5 g.) was converted into crude imino-ether hydrochloride in the usual way during 12 days at 0°. After removal of the solvent (dioxan) and excess hydrogen chloride, the free imino-ether base was liberated with ice-cold 0·5N-sodium carbonate (100 c.c.) and extracted with ice-cold chloroform. The extract was washed with water and evaporated in a vacuum. The residue was dissolved in warm alcohol (75 c.c.) and treated with aqueous ammonium chloride solution (1·6 g. in 25 c.c.) at 37° for 60 hours. Unchanged ammonium chloride (0·25 g.) was precipitated with acetone at 0° and the filtrate was evaporated to dryness. Unchanged starting material (1·05 g.) remained undissolved on extracting the residue with water and the aqueous solution was taken to complete dryness. The *amidine hydrochloride* was

extracted with hot absolute alcohol and then crystallised from a very small volume of water, when colourless rectangular plates (2·2 g.) separated, m. p. 238° (Found : N, 17·9. $C_7H_9O_2N_3S$,HCl requires N, 17·8%).

The *benzoate* separated from water in long rectangular plates, m. p. 210° (Found : C, 52·3; H, 4·6; N, 13·0. $C_7H_9O_2N_3S$,$C_7H_6O_2$ requires C, 52·3; H, 4·7; N, 13·1%). The *acetate* crystallised from water in fine needles, m. p. 196—198° (Found : N, 15·9. $C_7H_9O_2N_3S$,$C_2H_4O_2$ requires N, 16·2%).

Action of Methyl-alcoholic Ammonia on 5-Nitro-2-methylsulphonylpyridine. Formation of 5-Nitro-2-amino- and 5-Nitro-2-methoxy-pyridine.—5-Nitro-2-methylsulphonylpyridine (5 g.) was kept at 37° for 4 days with 14% methyl-alcoholic ammonia (70 c.c.) in a pressure bottle. The mixture was evaporated to dryness and the residue was crystallised from alcohol, affording 5-nitro-2-aminopyridine (2·35 g.), m. p. 184° alone and in admixture with an authentic specimen (Found : N, 30·2. Calc. for $C_5H_5O_2N_3$: N, 30·2%). On steam-distillation of the mother-liquors a colourless solid (0·4 g.) separated in the distillate and was collected; this substance was shown by m. p. and mixed m. p. (110°) to be 5-nitro-2-methoxypyridine (Found : N, 18·2. Calc. for $C_6H_6O_3N_2$: N, 18·2%). Finally, a further quantity (0·85 g.) of 5-nitro-2-aminopyridine was obtained from the steam-distillation still-residue.

5-Nitro-2-mercaptopyridine (XVII).—*S*-(5-Nitro-2-pyridyl)thiouronium chloride (23·4 g.) (Surrey and Lindwall, *J. Amer. Chem. Soc.*, 1940, **62**, 1697) was suspended in water (50 c.c.) and 2N-sodium hydroxide (50 c.c.) was run into the stirred mixture. Stirring was continued for 15 minutes and the dark red suspension was then heated on the water-bath for 5 minutes to complete the decomposition of the thiouronium salt. A further quantity (50 c.c.) of 2N-sodium hydroxide was added, and the solution, filtered from some 5 : 5′-dinitro-2 : 2′-dipyridyl disulphide (1·2 g., m. p. 132—135°), gave the thiol (14·2 g.), m. p. 186—188°, on acidification with concentrated hydrochloric acid. Caldwell and Kornfeld (*loc. cit.*) record m. p. 188—191°.

5-Nitro-2-methylthiopyridine (XVIII).—*S*-(5-Nitro-2-pyridyl)thiouronium chloride (46·8 g.) was suspended in water (100 c.c.) and decomposed with two successive portions of 2N-sodium hydroxide (each 100 c.c.) in the manner described above. The solution, filtered from disulphide (2 g.), was heated on the water-bath with methyl iodide (29 g.) and absolute alcohol (30 c.c.) until the colour practically disappeared (*ca.* 15 minutes). The product was collected after cooling. The *compound* separated from spirit in pale yellow rectangular plates (31·7 g.), m. p. 115° (Found : N, 16·2. $C_6H_6O_2N_2S$ requires N, 16·5%).

5-Nitro-2-ethylthiopyridine (XIX).—Obtained in a similar manner in 91% yield using ethyl iodide, the *compound* crystallised from methyl alcohol in yellow rectangular plates, m. p. 60° (Found : N, 15·1. $C_7H_8O_2N_2S$ requires N, 15·2%).

5-Nitro-2-n-propylthiopyridine (XX).—Obtained in 91% yield using *n*-propyl iodide, the *compound* was obtained as a yellow oil, b. p. 116°/0·5 mm. (Found : N, 14·0. $C_8H_{10}O_2N_2S$ requires N, 14·1%).

5-Nitro-2-n-butylthiopyridine (XXI).—Obtained in 87% yield using *n*-butyl iodide, the *compound* was obtained as a yellow oil, b. p. 140°/1 mm. (Found : C, 51·3; H, 5·6. $C_9H_{12}O_2N_2S$ requires C, 50·9; H, 5·7%).

5-Nitro-2-methylsulphonylpyridine (XV).—5-Nitro-2-methylthiopyridine (12 g.) was treated with potassium permanganate using the technique described above for analogous oxidations. The *sulphone* separated from absolute alcohol in colourless rhombs (13·3 g.), m. p. 115° (Found : N, 13·9. $C_6H_6O_4N_2S$ requires N, 13·9%). The m. p. was depressed to 95° on admixture with the starting material.

5-Nitro-2-n-butylsulphonylpyridine (XXVI).—5-Nitro-2-*n*-butylthiopyridine (15·5 g.) was oxidised in the same manner. The *sulphone* was isolated as an oil (15·6 g.), b. p. 182°/0·5 mm., which solidified in the receiver; it then crystallised from a very small volume of methyl alcohol in elongated pale yellow plates, m. p. 58° (Found : N, 11·5. $C_9H_{12}O_4N_2S$ requires N, 11·5%).

5-Amino-2-methylthiopyridine (XXII).—5-Nitro-2-methylthiopyridine (5 g.) was reduced with granulated tin (7 g.) and 15% hydrochloric acid (36 c.c.) on the water-bath for an hour. The mixture was cooled, saturated with hydrogen sulphide, and filtered. The *amine*, isolated by addition of excess caustic alkali and extraction with ether, separated from benzene–ligroin in light brown needles (2·42 g.), m. p. 71—72° (Found : N, 20·1. $C_6H_8N_2S$ requires N, 20·0%).

5-Amino-2-ethylthiopyridine (XXIII).—5-Nitro-2-ethylthiopyridine (5 g.) was reduced in the same manner. The *amine* distilled as a viscous yellow oil (3 g.), b. p. 126°/1 mm. (Found : N, 17·9. $C_7H_{10}N_2S$ requires N, 18·1%). The *dihydrochloride*, obtained by dissolving the base in the calculated amount of alcoholic hydrochloric acid, separated from absolute alcohol in small blunt needles, m. p. 175—176° (Found : N, 12·6. $C_7H_{10}N_2S$,2HCl requires N, 12·4%).

5-Amino-2-n-propylthiopyridine (XXIV).—5-Nitro-2-*n*-propylthiopyridine (7·5 g.) similarly afforded the *amine* as a viscous yellow oil (3·6 g.), b. p. 142°/1 mm. (Found : N, 16·5. $C_8H_{12}N_2S$ requires N, 16·7%). The *hydrochloride* crystallised from alcohol in rectangular plates, m. p. 154° (Found : N, 13·3. $C_8H_{12}N_2S$,HCl requires N, 13·6%).

5-Amino-2-n-butylthiopyridine (XXV).—In this case the lower solubility of 5-nitro-2-*n*-butylthiopyridine (5 g.) in the reducing mixture necessitated the addition of an equal volume of glacial acetic acid. The *amine* was obtained as a pale yellow oil (2·8 g.), b. p. 184°/10 mm. (Found : C, 59·6; H, 7·8. $C_9H_{14}N_2S$ requires C, 59·3; H, 7·7%).

Neutralisation with the calculated volume of alcoholic hydrochloric acid afforded the *dihydrochloride*, which separated from methyl alcohol–ethyl acetate in clusters of colourless needles, m. p. 139—141° (Found : N, 11·4. $C_9H_{14}N_2S$,2HCl requires N, 11·0%). Repeated recrystallisation from the same solvent mixture caused hydrolysis to the *monohydrochloride* with fall in m. p. to 128—129° (Found : N, 12·6. $C_9H_{14}N_2S$,HCl requires N, 12·8%).

5-Amino-2-methylsulphonylpyridine (XXVII).—5-Nitro-2-methylsulphonylpyridine (5 g.) was reduced at room temperature in methyl alcohol (200 c.c.) in the presence of palladised strontium carbonate (2 g.) with hydrogen at an initial pressure of 24 lbs./sq. in. Hydrogenation was complete in less than an hour. The *aminosulphone* crystallised from water in colourless leaflets, m. p. 171—173°, softening at 165° (Found : N, 16·3. $C_6H_8O_2N_2S$ requires N, 16·3%).

5-Amino-2-n-butylsulphonylpyridine (XXVIII).—When 5-nitro-2-*n*-butylsulphonylpyridine (5 g.)

was hydrogenated in the same way at 48 lbs./sq. in. pressure of hydrogen, reduction was complete in 10 minutes. The *amino-sulphone* separated from alcohol in colourless rhombs (4·2 g.), m. p. 97° (Found: N, 13·1. $C_9H_{14}O_2N_2S$ requires N, 13·1%).

5-Cyano-2-methoxypyridine (XXIX).—A solution of 2-chloro-5-cyanopyridine (13·9 g.) in a mixture of dioxan (50 c.c.) and methyl alcohol (50 c.c.) was added to a methyl-alcoholic solution of sodium methoxide (2·3 g. of sodium) and the mixture was refluxed for 30 minutes. After cooling, sodium chloride was removed and the filtrate was evaporated. The *compound* separated from absolute alcohol in colourless rectangular plates (12 g.), m. p. 94° (Found: N, 21·1. $C_7H_6ON_2$ requires N, 20·9%).

5-Cyano-2-n-butoxypyridine (XXX).—2-Chloro-5-cyanopyridine (13·9 g.) was similarly treated with sodium *n*-butoxide in *n*-butyl alcohol–dioxan. The *compound* was isolated as an oil, b. p. 140—150°/15 mm., which solidified on cooling to a mass of colourless needles, m. p. 24° (Found: C, 67·8; H, 6·8; N, 15·7. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·8; N, 15·9%).

6-Methoxynicotinamidine (XIV) *Hydrochloride*.—Crude imino-ether hydrochloride, prepared by treating 5-cyano-2-methoxypyridine (4·5 g.) with dry hydrogen chloride (4 g.) at 0° for 7 days in dioxan–methyl alcohol, was incubated with methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. On processing the product, unchanged starting material (1·9 g., m. p. and mixed m. p. 94°) was first recovered. Exhaustive evaporation and extraction with alcohol then gave a stiff residue (3·4 g.), which eventually crystallised. The *hydrochloride* separated, with considerable losses, from a small volume of methyl alcohol in colourless needles, m. p. 278—280° (Found: N, 22·4. $C_7H_9ON_3,HCl$ requires N, 22·4%).

The benzoate, m. p. 253°, and the acetate, m. p. 246—248°, both prepared by double decomposition in aqueous solution, were identical with the corresponding salts of the amidine derived from 5-cyano-2-methylsulphonylpyridine by the orthodox Pinner technique (see above).

5-(2-Methoxypyridyl)methylamine Hydrochloride (XXXII).—5-Cyano-2-methoxypyridine (5 g.) was reduced in methyl-alcoholic ammonia (100 c.c.) in the presence of Raney nickel (2 g.) at an initial hydrogen pressure of 42 lbs./sq. in. Reduction was complete in an hour. After removal of catalyst and solvents, the base was neutralised with one equivalent of alcoholic hydrochloric acid. The *hydrochloride* separated from spirit in colourless rectangular plates, m. p. 216—218° (Found: N, 15·8. $C_7H_{10}ON_2,HCl$ requires N, 16·0%).

6-n-Butoxynicotinamidine Hydrochloride (XXXI).—5-Cyano-2-*n*-butoxypyridine (7·6 g.) was treated with methyl alcohol (1·6 g.) and dry hydrogen chloride (5 g.) in dioxan (25 c.c.) at 0° for 7 days. The crude imino-ether hydrochloride was incubated with methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. On working up in the usual way, 6-n-*butoxynicotinamide* was first isolated, separating from spirit in clusters of colourless needles (1·5 g.), m. p. 158° (Found: N, 14·6. $C_{10}H_{14}O_2N_2$ requires N, 14·4%). The residue (6·5 g.), obtained on exhaustive evaporation and extraction with absolute alcohol, was crystallised from 1½ parts of water affording colourless irregular plates of the *hydrochloride monohydrate*, m. p. 95° (Found: N, 16·8; loss of weight at 100° in a vacuum, 7·0. $C_{10}H_{15}ON_3,HCl,H_2O$ requires N, 16·9; H_2O, 7·3%).

The *benzoate* separated from water in colourless rectangular plates, m. p. 228° (Found: C, 64·7; H, 6·5; N, 13·2. $C_{10}H_{15}ON_3,C_7H_6O_2$ requires C, 64·8; H, 6·7; N, 13·0%).

5-(2-n-Butoxypyridyl)methylamine Dihydrochloride (XXXIII).—Hydrogenation of 5-cyano-2-*n*-butoxypyridine was carried out in the same manner as described above for the analogous methoxy-compound. The monohydrochloride did not separate on the addition of one equivalent of alcoholic hydrochloric acid but the addition of a further equivalent afforded the *dihydrochloride*, which separated from *iso*propyl alcohol in colourless rectangular plates, m. p. 228° (Found: N, 12·8. $C_{10}H_{16}ON_2,2HCl$ requires N, 12·9%).

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