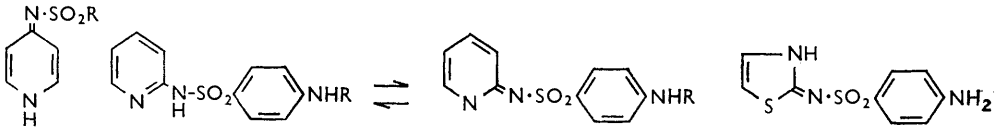
67. *Potentially Tautomeric Pyridines. Part III.*[1] 2-, 3-, *and* 4-*Methanesulphonamidopyridine.*

By R. Alan Jones and A. R. Katritzky.

The basicities and spectra of the compounds named in the title and alkylated derivatives of their alternative tautomeric forms show that the 2- and the 4-isomers exist largely in the imino-form and the 3-isomer predominantly in the sulphonamido-form.

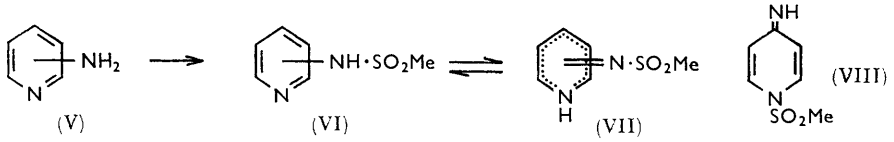
In Part II,[1] the tautomeric behaviour of acylaminopyridines was shown to resemble that of the corresponding aminopyridines and not the hydroxy-analogues. It was suggested that this was because the carbonyl group in pyrid-2- and -4-one acylimines is unable to conjugate simultaneously with the spare pair of electrons on the exocyclic nitrogen and with the aromatic system. Mesomerism involving sulphonyl groups is comparatively weak and thus for pyridone sulphonylimines (as I) destabilisation due to this factor should be unimportant, and therefore the tautomeric equilibrium should be displaced more in favour of the imine form. Shepherd, Bratton, and Blanchard [2] (who summarise earlier inconclusive work) showed by ultraviolet spectral comparison with the alkylated tautomers that acetylsulphapyridine existed in aqueous solution as 40% of form (II; R = Ac) and



(I) (II) (III) (IV)

60% of form (III; R = Ac), and that sulphathiazole existed predominantly as form (IV). Angyal and Warburton [3] reported similar findings for sulphathiazole and concluded that 30% of sulphapyridine existed as form (III; R = H) in aqueous solution (see also ref. 4). The above work was complicated by the occurrence in the sulpha-drugs of a second chromophore and basic centre.[5] We have now prepared 2-, 3-, and 4-methanesulphonamidopyridine and methylated derivatives of their alternative tautomeric forms and studied their spectra and basicities.

Recently Russian workers [6] have investigated infrared and ultraviolet spectra of 2-methanesulphonamidopyridine and 2- and 4-benzenesulphonamidopyridine and methylated derivatives of the fixed tautomeric forms. They conclude that the compounds exist in the imino-form in the solid state and predominantly so in aqueous solution. The present work confirms and amplifies these results.



(V) (VI) (VII) (VIII)

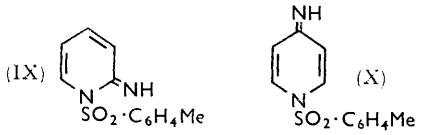
Preparation of Compounds.—2-, 3-, and 4-Aminopyridine reacted with methanesulphonyl chloride to give the corresponding methanesulphonamido-derivatives (V ⟶ VI, VII). These products were not the isomeric compounds methanesulphonylated at the ring nitrogen (cf. VIII) because each product could be converted into two methyl

[1] Part II, Jones and Katritzky, *J.*, 1959, 1317.
[2] Shepherd, Bratton, and Blanchard, *J. Amer. Chem. Soc.*, 1942, **64**, 2532.
[3] Angyal and Warburton, *Austral. J. Sci. Res.*, 1951, **44**, 93.
[4] Sheinker and Kuznetsova, *Zhur. fiz. Khim.*, 1957, **31**, 2656.
[5] Cf. Vandenbelt and Doub, *J. Amer. Chem. Soc.*, 1944, **66**, 1633.
[6] Sheinker, Peresleni, Zosimova, and Pomerantsev, *Russ. J. Phys. Chem.*, 1959, **33**, 303.

derivatives, in which the sulphonyl group was attached to the exocyclic nitrogen atoms (see below), and the ultraviolet spectra of the cationic species resemble those of one of the methylated derivatives (of known structure, see below) in the same series.

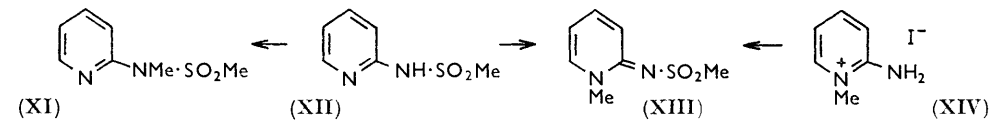
Angyal and his co-workers [7] also provided evidence that, while sulphonylation of amino-heteroaromatic compounds occurs initially on the ring-nitrogen atom, the products rearrange spontaneously to the isomers with the sulphonyl group attached to the exocyclic nitrogen atom.

Grammaticakis [8] assigned the structures (IX) and (X) to sulphonamides from 2- and 4-aminopyridine because their ultraviolet spectra differ from those of acylaminopyridines.



It appeared more likely that these products have the (tautomeric) toluenesulphonamidopyridine structure, and the similarity of their ultraviolet spectra to those of the analogous methanesulphonamido-compounds (Fig. 1) supports this view.

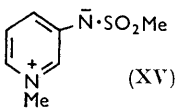
2-Methanesulphonamidopyridine and diazomethane gave two products; that obtained in lower yield was identical with the product obtained by use of dimethyl sulphate and



alkali and was shown to be (XIII) by its formation from 2-amino-1-methylpyridinium iodide (XIV). Further, 2-(*N*-methylmethanesulphonamido)pyridine (XI) gave the bands characteristic of the 2-substituted pyridine ring [9] at 1594 (220), 1576 (65), 1472 (210), 1441 (160), 1277 (70), (—), (—), 991 cm.$^{-1}$ (35); † the other bands were characteristic of the NMe·SO_2Me substituent.[10]

4-Methanesulphonamidopyridine also gave two products with diazomethane; structures were assigned on the basis of the infrared spectra. 4-(*N*-Methylmethanesulphonamido)-pyridine showed bands characteristic of the 4-substituted pyridine ring [11] at 1595 (300), 1564 (50), 1497 (120), 1432 (20), (—), 996 (75), 815 (85) and those of the NMe·SO_2Me substituent.[10]

Only one product was isolated from the reaction of 3-methanesulphonamidopyridine with diazomethane; its infrared spectrum showed bands at 1587 * (25), 1577 (30), 1483 (140), 1426 (125), (—), 1127 * (35), 1106 (15), (—), 1023 (75), 805 * (35) characteristic of the 3-substituted pyridine nucleus.[12] The isomeric zwitterion (XV) was obtained as the perchlorate *via* the action of methotoluene-*p*-sulphonate.



(XV)

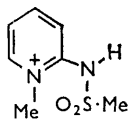
Basicity Measurements (Table 1).—4-Methanesulphonamidopyridine is a considerably weaker base than 4-(*N*-methylmethanesulphonamido)pyridine, but is comparable in strength to 1-methylpyrid-4-one methanesulphonylimine. Quantitatively the results indicate that the imino-form predominates by a factor of *ca.* 40 in the tautomeric equilibrium.

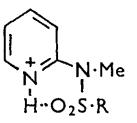
† For the significance of asterisks see Table 3; figures in parentheses denote ϵ_A values.

[7] Angyal, Morris, and Warburton, *Austral. J. Sci. Res.*, 1952, **5**, *A*, 367, 374.
[8] Grammaticakis, *Bull. Soc. chim. France*, 1959, 480.
[9] Katritzky and Hands, *J.*, 1958, 2202.
[10] Katritzky and Jones, *J.*, 1960, 4497.
[11] Katritzky and Gardner, *J.*, 1958, 2198.
[12] Katritzky, Hands, and Jones, *J.*, 1958, 3165.

3-Methanesulphonamidopyridine is weaker as a base than anhydro-3-methanesulphonamido-1-methylpyridinium hydroxide by 1·12 pK units, and weaker than 3-(N-methylmethanesulphonamido)pyridine by 0·53 pK unit. This indicates that for the potentially tautomeric compound, the non-zwitterionic form (as VI) predominates over the zwitterionic by a factor of *ca.* 4—13.

For the 2-series, the situation is complicated by different amounts of hydrogen-bonding and steric hindrance in the various cations (XVI—XVIII). The relatively high basicity


(XVI)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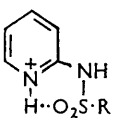
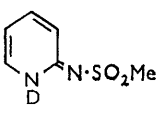

(XVIII)


(XIX)

of 2-(N-methylmethanesulphonamido)pyridine reflects the need to lose a hydrogen-bonded proton from the cation. The somewhat lower basicity of 2-methanesulphonamidopyridine could be explained if the compound existed predominantly in the imino-form, and

TABLE 1. pK_a *of sulphonamidopyridines.*

Pyridine derivative	pK_a [a]	Stand. devn.	Concn. (10^{-4}M)	Wavelength (mμ)
2-Methanesulphonamido-	1·10	0·11	0·43	310
2-(N-Methylmethanesulphonamido)-	1·73	0·07	0·60	289
1-Methylpyrid-2-one methanesulphonylimine	−0·33	0·04	0·31	312
3-Methanesulphonamido-	3·43	0·03	449·0	—
2-(N-Methylmethanesulphonamido)-	3·94	0·02	433·8	—
Anhydro-3-methanesulphonamido-1-methylpyridinium hydroxide	4·55	0·01	164·1	—
4-Methanesulphonamido-	3·64	0·06	222·2	—
4-(N-Methylmethanesulphonamido)-	5·14	0·04	111·6	—
1-Methylpyrid-4-one methanesulphonylimine	3·42	0·12	90·0	—
2-Methanesulphonamido-	8·02	0·01	145·5	—
3-Methanesulphonamido-	7·02	0·06	170·6	—
4-Methanesulphonamido-	9·07	0·08	222·2	—

[a] Arithmetical mean of six values. The first nine entries refer to proton addition, the last three to proton loss. [b] An entry in this column signifies that the determination was spectrometric; otherwise it was potentiometric.

TABLE 2. *Ultraviolet spectra* (*wavelengths in* mμ).

		Ions						Neutral species [b]			
	Pyridine derivative	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$
1	2-Methanesulphonamido-	221	10·5	286	11·5			241	11·6	310	7·2
2		239	13·7	291	5·0						
3	2-(N-Methylmethanesulphonamido)-	227	6·4	289	7·7			220	5·9	265	3·5
4	1-Methylpyrid-2-one methanesulphonylimine	221	13·2	283	14·8			243	10·9	311	6·6
5	3-Methanesulphonamido-	205	17·4	234	6·3	284	4·2	263	3·2	320	0·3
6		244	11·5	292	3·0						
7	3-(N-Methylmethanesulphonamido)-	214	8·8	240	4·3	280	3·3	266	2·7		
8	Anhydro-3-methanesulphonamido-1-methylpyridinium hydroxide	208	22·2	236	6·0	287	3·9	262	14·1	325	3·6
9	4-Methanesulphonamido-			253	18·3			281	25·2		
10				253	17·2						
11	4-(N-Methylmethanesulphonamido)-			263	18·1			236	7·9		
12	1-Methylpyrid-4-one methanesulphonylimine			257·5	18·5			287	27·3		

[a] Nos. 2, 6, and 10 are anions measured in N-NaOH; the remainder are cations. Nos. 1, 3, and 4 were measured in 20N-H_2SO_4; Nos. 5, 7, and 8 in N-H_2SO_4; and Nos. 9, 11, and 12 in 10N-H_2SO_4. [b] All measured in a phosphate buffer of pH 10, except 1 (pH 4·6), 5 (pH 5·15), and 9 (pH 6·5).

thus the cation (XVIII) lost principally the non-bonded proton. The low basicity of 1-methylpyrid-2-one sulphonylimine presumably arises from steric effects which are unfavourable for cation formation. pK_a values of the sulphonamido-compounds as acids are also recorded in Table 1; the 3-isomer is a somewhat stronger acid than the other two compounds because it exists mainly in the sulphonamido-form.

FIGS. 1—4.

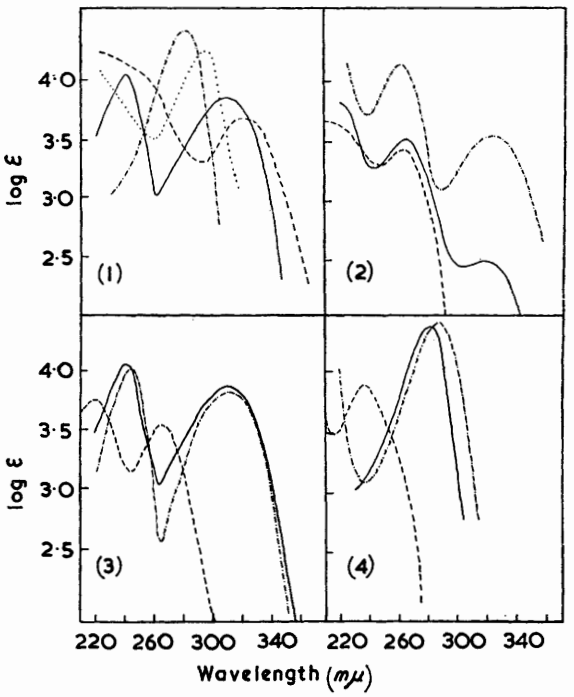


FIG. 1. —— 2-*Methanesulphonamidopyridine at* pH 4·6. – – – 2-*Toluene*-p-*sulphonamidopyridine in* 95% *ethanol*. — · — · — 4-*Methanesulphonamidopyridine at* pH 6·5. . . . 4-*Toluene*-p-*sulphonamidopyridine in* 95% *ethanol*.

FIG. 2. —— 3-*Methanesulphonamidopyridine at* pH 5·15. – – – 3-(N-*Methylmethanesulphonamido*)-*pyridine at* pH 10. — · — · — *Anhydro*-3-*methanesulphonamido*-1-*methylpyridinium hydroxide in* N-NaOH.

FIG. 3. —— 2-*Methanesulphonamidopyridine at* pH 4·6. – – – 2-(N-*Methylmethanesulphonamido*)-*pyridine at* pH 10. — · — · — 1-*Methylpyrid*-2-*one methanesulphonylimine at* pH 10.

FIG. 4. —— 4-*Methanesulphonamidopyridine at* pH 6·5. – – – 4-(N-*Methylmethanesulphonamido*)-*pyridine at* pH 10. — · — · — 1-*Methylpyrid*-4-*one methanesulphonylimine at* pH 10.

Ultraviolet Spectra (Table 2).—In each series, the spectra of the cations are similar, indicating their similar structure. For the 4-series, the spectrum of the potentially tautomeric compound closely resembles that of the fixed imine. It can be seen (Fig. 4) that *ca.* 3% of the other tautomeric form would be difficult to detect by this method.

For the 3-series (Fig. 2) the spectrum of the potentially tautomeric compound resembles that of the exocyclic *N*-methyl compound, but absorption is found in the 325 mμ region and calculation indicates a ratio of *ca.* 9 : 1 of pyridine to betaine structure.

For the 2-series (Fig. 3) the spectrum of the potentially tautomeric compound shows that it exists largely in the imino-form, but some absorption is found in the 265 mμ region which indicates *ca.* 10% may be present in the sulphonamidopyridine form.

Infrared Spectra.—The infrared spectra of crystalline 2- and 4-methanesulphonamidopyridine closely resemble those of the corresponding 1-methylpyrid-2- and -4-one methanesulphonylimines and show distinct differences from those of the *N*-methylmethanesulphonamido-compounds.[10] The spectra of the imino-compounds are given in Table 3, with tentative assignments based on previous work.[10,13] The band near 1640 cm.$^{-1}$ is assigned to a ring mode; many pyridones and pyridthiones show a ring mode considerably above 1600 cm.$^{-1}$.[13] The spectrum of the deuterated derivative (XIX) differed most from that of the non-deuterated compound in the 1600—1500 cm.$^{-1}$ region where bands at 1563, 1528, and 1503 cm.$^{-1}$ appear in place of the shoulder at 1619 cm.$^{-1}$ and band at 1534 cm.$^{-1}$. Thus, an NH deformation mode presumably lies in this region, but as the *N*-methyl compounds

TABLE 3. *Infrared spectra of sulphonamidopyridines.*

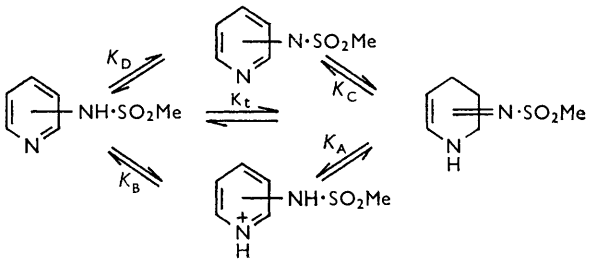
2-Series				4-Series		
1-Methyl [a]		Potential tautomer [b]	1-Methyl [c]	Potential tautomer [b]	Tentative assignment
ν (cm.$^{-1}$)	ε_A	ν (cm.$^{-1}$)	ν (cm.$^{-1}$)	ν (cm.$^{-1}$)	
1643	340	1636s	1644vs	1636s	Ring stretch
1556	190	1620*s		1615m	νC=N and NH def?
1521	340	1535m	1515vs		
1470*	45	1465m			Ring stretch
1454	145	1430w	1436m		
1418	15				
1376	195	1394s, 1365s	1380vs	1352s	SO_2 sym. stretch also one ring mode and one βCH
1323	115	1331m	1320m	1337s	
1287	100	1291s		1312s	
1265	220	1271s	1258s	1281m	
		1250s		1273m	
1189	45		1197s	1192m	βCH or Me rock
1176	30	1165w			
1122*	250	1119vs	1115*s	1116s	SO_2 asym. stretch
1110	400	1100*m	1104vs	1095*m	
1062	35				?
1030	30	1037m	1027m	1017w	N–S stretch
		997s		994w	Ring breathing
967	300	970s	965vs	966m	C–S stretch
		945m	939s		?
			832s	828w	γCH
807	115	803s			?

[a] Measured as a 0·189M-solution in $CHCl_3$ in a 0·106 mm. cell. [b] Nujol mull. [c] Satd. solution in $CHCl_3$ in a 0·106 mm. cell. * Shoulder.

also absorb strongly here the νC=N vibrational frequency is also assigned to this region. The asymmetric SO_2 stretching vibration is at frequencies lower than those (1158—1146 cm.$^{-1}$) for sulphonamido-compounds;[10] for 1-methylpyrid-2-one methanesulphonylimine this band showed the expected shift towards lower frequencies as the proton-donor ability of the solvent increased.[14] All the compounds showed several strong bands in the 1400—1250 cm.$^{-1}$ region; the solvent shift method did not clearly indicate which were due to the SO_2 symmetric stretching mode. The band at 970—965 cm.$^{-1}$ is tentatively assigned to the C–S stretching mode; similar bands were found for the sulphonamido-compounds.[10] The N–S stretching vibrational mode is probably at 1037—1017 cm.$^{-1}$; its position could be considerably different from that (912—866 cm.$^{-1}$) found for sulphonamido-compounds.[10]

Discussion.—The above results indicate that, in aqueous solution, K_{imino}/K_{amino} = *ca.* 10, 0·1, and 30 in the 2-, 3-, and 4-series respectively. By using the pK_a values of Table 1,

[13] Katritzky and Jones, *J.*, 1960, 2947.
[14] Bellamy and Williams, *Trans. Faraday Soc.*, 1959, **55**, 14.



and following Mason,[15] the pK_a values for the individual tautomers can now be calculated (cf. scheme):

	pK_A	pK_B	pK_C	pK_D
2-Series	1·1	2·1	8·0	7·0
3-	4·5	3·5	6·0	7·0
4-	3·6	5·1	9·1	7·6

For the imino-compounds, the strength as acids (K_C) decreases in the order 3- > 2- > 4-substituted, and as bases (K_A) in the order 3- > 4- > 2-. The zwitterion would be expected to be the strongest, both as an acid and as a base, because the zwitterionic species is intrinsically less stable. Of 2- and 4-analogues, the proximity of the two nitrogen atoms in the 2-compound makes it the stronger acid and the weaker base.

For the amino-compounds as bases (K_B), the effect of the NH·SO_2Me group appears to be mainly inductive because the order is 4- > 3- > 2-. For the compounds as acids (K_D) the order is 2- ~ 3- > 4-, which again indicates inductive interaction although the 3-derivative is a surprisingly strong acid.

Experimental

2-Methanesulphonamidopyridine.—Methanesulphonyl chloride (1·15 g.) was added dropwise to 2-aminopyridine (0·94 g.) in pyridine (1·25 c.c.) at 0°. After 24 hr. at 20°, the mixture was added to water (3 c.c.); the resulting sulphonamide (1·25 g., 72%) crystallised from water in needles, m. p. 203—204° (lit.,[6] m. p. 204—206°) (Found: C, 41·9; H, 4·7; N, 16·2. Calc. for $C_6H_8N_2O_2S$: C, 41·9; H, 4·7; N, 16·3%).

1-Methylpyrid-2-one Methanesulphonylimine.—(*a*) 2-Methanesulphonamidopyridine (1·0 g.) and dimethyl sulphate (0·8 g.) in acetone (37 c.c.) were refluxed over potassium carbonate (1·7 g.) for 2 hr. Insoluble material was filtered off and the filtrate was evaporated. The residue was taken up in benzene and boiled with carbon. Evaporation then gave the *sulphonylimine* (0·35 g., 32%) which crystallised from chloroform in needles, m. p. 142·5—144° (lit.,[6] m. p. 146—147°, no analysis given) (Found: C, 45·3; H, 5·7; N, 15·3. $C_7H_{10}N_2O_2S$ requires C, 45·2; H, 5·4; N, 15·1%).

(*b*) 2-Amino-1-methylpyridinium iodide (1·4 g.) in methanol (3 c.c.) was shaken with silver oxide (0·69 g.). After filtration and evaporation, the residue was treated with pyridine (1·0 c.c.) and methanesulphonyl chloride (0·7 g.). After 2 hr., water (2 c.c.) was added and the whole extracted with chloroform (10 c.c.). Evaporation of the extracts gave 1-methylpyrid-2-one methanesulphonylimine (0·28 g., 25%), m. p. and mixed m. p. 139—140°. The infrared spectrum was identical with that of material prepared above.

(*c*) Diazomethane (*ca.* 3 g. in 100 c.c. of ether) was added dropwise and with agitation to 2-methanesulphonamidopyridine (5·8 g.) in methanol (150 c.c.). After 30 min., volatile material was removed at 100°/20 mm. The residue was extracted with ether (*A*). The residual 1-methylpyrid-2-one methanesulphonylimine (0·28 g., 25%), crystallised from chloroform, had m. p. and mixed m. p. 138—139°.

2-(N-Methylmethanesulphonamido)pyridine.—The ethereal extracts (*A*) above, on evaporation, gave the *pyridine* (4·4 g., 71%), b. p. 130—135° (bath)/0·1 mm., n^{23} 1·5370 (Found: C, 45·5; H, 5·6; N, 14·9. $C_7H_{10}N_2O_2S$ requires C, 45·2; H, 5·4; N, 15·1%).

3-Methanesulphonamidopyridine.—Methanesulphonyl chloride (1·2 g.) and 3-aminopyridine

[15] Mason, *J.*, 1958, 674.

(1·0 g.) were heated for 3 hr. at 100° in pyridine (1·3 c.c.). Addition of water (3 c.c.) gave the *sulphonamide* (1·6 g., 89%) which crystallised from water in plates, m. p. 140—141° (Found: C, 41·8; H, 4·8; N, 16·2%).

3-(N-*Methylmethanesulphonamido*)*pyridine*.—Ethereal diazomethane (*ca.* 0·5 g. in 25 c.c.) was added with agitation to 3-methanesulphonamidopyridine (1·0 g.) in methanol (25 c.c.) to give the *sulphonamide* (0·5 g., 45%) which distilled at 145—150° (bath)/0·06 mm. and solidified to plates, m. p. 62° (from ethanol) (Found: C, 45·1; H, 5·5; N, 14·9%).

3-*Methanesulphonamido*-1-*methylpyridinium Perchlorate*.—3-Methanesulphonamidopyridine (0·4 g.) and methyl toluene-*p*-sulphonate (0·44 g.) were kept at 120° for 10 hr. Cooling, and addition of 60% perchloric acid (1·0 c.c.), gave the *perchlorate* (0·4 g., 60%) which separated from ethanol as needles, m. p. 165·5—167° (Found: C, 29·8; H, 4·1; N, 10·1. $C_7H_{11}ClN_2O_6S$ requires C, 29·4; H, 3·9; N, 9·8%).

4-*Methanesulphonamidopyridine*.—4-Aminopyridine (2 g.) was refluxed with methanesulphonyl chloride (2·43 g.) in toluene (25 c.c.) for 2 hr. After cooling, the toluene was decanted from the oil, which, on being rubbed with ethanol (10 c.c.), solidified to give 4-*methanesulphonamidopyridine hydrochloride* (1·1 g., 25%), m. p. 251—253° (decomp.) (Found: C, 34·6; H, 4·5; N, 13·3. $C_6H_9ClN_2O_2S$ requires C, 34·5; H, 4·4; N, 13·4%). The hydrochloride (0·9 g.) in water (2 c.c.) was brought to pH 6·3 by 0·1N-sodium hydroxide. Continuous extraction with chloroform gave 4-*methanesulphonamidopyridine* (0·5 g., 66%), plates (from ethanol), m. p. 203—204° (Found: C, 41·4; H, 5·0; N, 16·3%).

1-*Methylpyrid*-4-*one Methanesulphonylimine and* 4-(N-*Methylmethanesulphonamido*)*pyridine*.—4-Methanesulphonamidopyridine hydrochloride (1·1 g.) under ethanol (20 c.c.) was shaken with excess of ethereal diazomethane. The resulting homogeneous mixture was evaporated and the oily residue extracted with ether. 1-*Methylpyrid*-4-*one methanesulphonylimine* (0·2 g., 20%) remained as an insoluble residue, m. p. 175·5—176° (from ethanol) (Found: C, 45·5; H, 5·3; N, 15·2%). The ethereal solution afforded 4-(N-*methylmethanesulphonamido*)*pyridine* (0·05 g., 5%), plates [from light petroleum (60—80°)], m. p. 53° (Found: C, 44·9; H, 5·7%).

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