Spectral and Ionisation Constant Studies of Substituted 2-Hydroxypyridines (1,2-Dihydro-2-oxopyridines)

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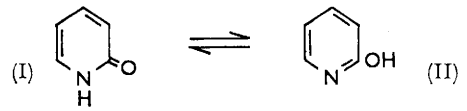
The ultraviolet and infrared spectra and the ionisation constants of the title compounds containing substituents (3-, 4-, 5-, and 6-Me; 3- and 5-Cl; 3,5-Cl_2; 3- and 5-Br; 3,5-Br_2; 5-I; 3,5-I_2; 3- and 6-OH; 3- and 6-O^-; 3- and 5-NO_2) have been determined. For all the compounds examined the pyridone form predominates. A number of the corresponding 2-methoxypyridines were also studied for reference.

THE parent compound commonly referred to as 2-hydroxypyridine is known to exist predominantly as the lactam tautomer 1,2-dihydro-2-oxopyridine ("2-pyridone") (I), and not as the hydroxy-compound (II),

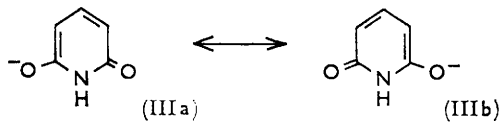


in aqueous [1-3] and non-aqueous [4] solution, and in the solid state.[5,6] Some evidence for the predominance of tautomer (I) has been obtained for a few substituted derivatives;[7,8] only one instance has been reported in which form (II) is preferred.[9] Claims (unsubstantiated in one case [9]) that both tautomers had been isolated in the solid state have been made for two derivatives.[10,11]

Ionisation Constants.—A substituted 2-hydroxypyridine in form (II) is expected [2] to have an acid strength similar to that of the corresponding 2-nitrophenol, *i.e.*, (II) with C·NO_2 in place of N. The ionisation constants in Table 1 show that these compounds are far weaker acids than this; 3- and 5-chloro-2-hydroxypyridine (two typical examples) are, in fact, slightly weaker acids than *o*- and *p*-chlorophenol, pK_a 8·5 and 9·4, respectively. This is the behaviour expected for the lactam structures (I).

2,6-Dihydroxypyridine is an apparent exception, being a much stronger acid than one would expect on this basis. However, the lactam form of this substance is best regarded as a derivative of glutacondialdehyde, H·CO·CH:CH·CH:C(OH)·H (acidic [12] pK_a 5·75) cyclised by replacement of the two terminal hydrogen atoms by –NH–; *i.e.*, the relatively high acid strength of (the hydroxyl group in) 2,6-dihydroxypyridine is attributable to stablisation of the anion [(IIIa) ⟷ (IIIb) according to resonance theory], and is by no means incompatible with a lactam structure for the neutral species. The first acidic ionisation of 2,3-dihydroxypyridine, too, is that of a hydroxyl group. In aqueous sodium hydroxide the second acidic ionisation constant is barely accessible for 2,6- and inaccessible for 2,3-dihydroxypyridine.

Substituted 2-hydroxypyridines are considerably weaker bases than the corresponding substituted 2-methoxypyridines, confirming the lactam structures of the former; the difference diminishes as the electron-withdrawing effect of the substituent(s) increases. 3-Substituted 2-hydroxypyridines are considerably weaker bases than their 5-substituted counterparts, as well as being weaker acids; presumably some kind of steric effect is operative here. Thus, 2-hydroxy-3-methylpyridine is actually a weaker base than 2-hydroxypyridine, and even slightly weaker than *N*-methyl-2-pyridone, pK_a 0·32.[2] The exact value of the equilibrium constant for the reaction (I) ⇌ (II), and for



the corresponding equilibrium between *O*-protonated and *N*-protonated cation (see following Paper), will have some effect [13] on the overall basic ionisation constants of a substituted 2-hydroxypyridine. This makes the interpretation of substituent effects here uncertain.

Electronic Spectra.—Table 1 shows also that, in the ultraviolet spectra of substituted 2-hydroxypyridines, the absorption maxima occur at considerably longer wavelengths than those of the corresponding 2-methoxypyridines. This confirms that the former are not hydroxy-tautomers (II). Two spectra of *N*-methylated derivatives,[14] which must have structures corresponding to (I), are included to illustrate their similarity to those of the hydroxypyridine spectra.

The spectrum of neutral 2,6-dihydroxypyridine (now obtained for the first time; that previously [8] measured was of the mono-anion) is quite different from that of 2,6-diethoxypyridine,[8] which shows clearly that it is predominantly in the lactam form (I) and not the

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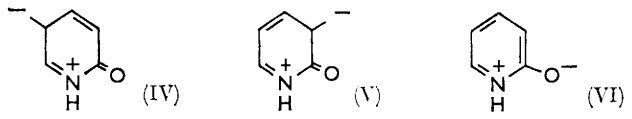
hydroxy-form (II). That 2,3-dihydro-6-hydroxy-4-methylfuro[2,3-*b*]pyridine in water exists largely [9] as the hydroxy-form (II) is thus not a consequence of its being an alkylated derivative of 2,6-dihydroxypyridine.

The simplest of the substituent effects on the ultraviolet spectra of 2-pyridones are shown by 3-NO_2 which displaces the 294 mμ band strongly, and 5-NO_2 which displaces the 224 mμ band very strongly, to longer wavelengths. Thus, in terms of the theory which



(IV) (V) (VI)

associates electronic absorption of this type with enhanced contributions from certain zwitterion structures,[15] the excited state produced by the 224 mμ transition contains a large contribution from (IV), and that produced by the 294 mμ transition a large contribution from (V). [(IV) and (V) are the respective canonical forms invoked in connection with electrophilic substitution in the 3- and 5-positions in 2-pyridone.[16]]

For saturated 3- and 5-substituents (*i.e.*, "non-conjugating" ones, in this context) the position is less straightforward; both bands are often displaced more by a 5- than a 3-substituent. As in comparable disubstituted benzenes, the substituent effect increases with the inductomeric and direct field polarisability of the substituent: [17] H < Me < Cl < Br < I; OH < O^-. The 4-methyl and 4-hydroxy [8] substituents, remarkably, displace the 294 mμ band to shorter rather than longer wavelengths.

Infrared Spectra.—The principal bands in these are listed in Table 2. Raman spectra were obtained only for the highly water-soluble methyl-2-pyridones, and are not listed. A very intense infrared band in the range 1710—1640 $cm.^{-1}$ is shown by all, and a second one above 1600 $cm.^{-1}$ by some 2-pyridones here studied (anions excepted). Substituted 2-methoxypyridines, by contrast, rarely show prominent bands above 1600 $cm.^{-1}$,

TABLE 1

Ionisation constants (in water at 20°) and ultraviolet spectra

Subst.	pK_a Acidic	pK_a Basic	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	pH (solvent)
Substituted 1,2-dihydro-2-oxopyridines					
—	11·70 ± 0·03	0·77 ± 0·02	224, 294	3·85, 3·75	5
3-Me	12·59 ± 0·03	0·20 ± 0·02	226, 294	3·75, 3·83	7
4-Me	12·23 ± 0·04	1·14 ± 0·02	226, 290	3·69, 3·76	7
5-Me	12·01 ± 0·01	1·13 ± 0·02	227, 302	3·91, 3·76	7
1-Et, 5-Me [a]			? 305	? 3·74	(H_2O)
6-Me	12·45 ± 0·03	1·12 ± 0·03	225, 301	3·86, 3·89	7
3-OH	9·00 ± 0·01	0·22 ± 0·09	234, 297	3·61, 3·87	5
6-OH	4·52 ± 0·01	1·00 ± 0·03	225, 306	3·83, 3·89	2·8
3-O^-	?		255, 310	3·81, 3·96	12
6-O^-	~15		234, 322	3·92, 4·17	7
3-Cl	10·40 ± 0·02	−2·03 ± 0·15	229, 303	3·72, 3·84	5
5-Cl	9·87 ± 0·02	−0·07 ± 0·02	233, 310	4·00, 3·70	5
3,5-Cl_2	8·48 ± 0·05	−2·40 ± 0·13	238, 320	3·83, 3·80	5
3-Br	10·42 ± 0·01	−2·15 ± 0·15	230, 306	3·66, 3·87	5
5-Br	10·03 ± 0·03	−0·06 ± 0·02	233, 310	3·98, 3·66	5
1-Me, 5-Br [a]			235, 313	3·91, 3·65	(H_2O)
3,5-Br_2	8·43 ± 0·03	−2·45 ± 0·13	216, *236*,[c] 323	4·27, *3·80*, 3·80	5
5-I	9·93 ± 0·02	0·00 ± 0·02	235, 316	4·24, 3·63	5
3,5-I_2 [b]	?	?	236, 332	? ?	5
3-NO_2	8·52 ± 0·03	−4·00 ± 0·15	257, 362	3·40, 3·85	5
5-NO_2	7·97 ± 0·03	−2·45 ± 0·15	211, 301, *314*[c]	3·93, 4·03, *4·02*	5
Substituted 2-methoxypyridines					
—		3·28 ± 0·06	~212, 269	~3·7, 3·53	7
5-Me		3·73 ± 0·03	217, 280	3·85, 3·56	7
3-OH	8·65 ± 0·01	2·10 ± 0·01	221, 280	3·76, 3·76	5
3-O^-			242, 296	3·95, 3·83	12
6-OEt [d]			217, 277	3·70, 3·70	(H_2O)
3-Cl		? [e]	220, 278	3·82, 3·69	5
5-Cl		1·18 ± 0·03	223, 284	4·00, 3·55	5
3,5-Cl_2		−1·4 ± 0·1	229, 292	3·95, 3·69	(MeOH)
3-Br		? [e]	220, 280	3·78, 3·71	5
5-Br		1·14 ± 0·02	222, 284	4·01, 3·54	5
3,5-Br_2		−1·50 ± 0·06	227, 294	3·98, 3·73	(MeOH)
5-I		1·51 ± 0·02	231, 290	4·16, 3·47	7

[a] Substituted *N*-methyl derivative; data from Bradlow and Vanderwerf.[14] [b] Not sufficiently soluble in water to permit the determination of ionisation constants or extinction coefficients. [c] Inflexions in italics. [d] 2,6-Diethoxypyridine; data from den Hertog *et al.*[8] [e] Hydrolysis in acid too rapid to permit determination of ionisation constants.

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TABLE 2

Infrared spectra of substituted 1,2-dihydro-2-oxopyridines [a]

	I		II		III		IV		V		VI		VII	
Subst.	NH	str.	"C=O str." [c]		"NH i.p. bend" [c]		"C=C str. I" [c]		"C=C str. II" [c]		skel.	str.	CH i.p. bend	
—	3080	0·7	1649 1641	2·0	1607	1·3	1577	2·4	1540	0·6	1434 1420	0·6	1364	0·2
4-Me [d] ...	2815	0·8	1657	2·0	1621	2·0	+ 1613	2·0	1536	0·8	1454	1·0	1335	0·3
6-Me [d] ...	2770	0·55	1671	1·5			1611	0·9	1551	0·3	1434	0·6	1371	0·25
6-OH [e] ...	3085 2925	0·6	1640	0·9			1585	0·45	1537	0·2	1442	0·3	1336	0·45
6-O$^-$	3085	0·3	1639	2·0			+ 1621	2·1			1450	0·4	1360 1320	2·0 0·4
3-Me [d] ...	2780	0·7	1658 1641	2·0	1598 infl.		1610	1·9	1571	0·5	1423	0·4	1350	0·25
3-OH [f] ...	3165	0·75	1665	2·0	1620 infl.		1613	1·0	1578	0·9	1447	0·2		
3-Cl	2780	0·5	1656	1·6			1612	0·7	1546	0·3	1471	0·3	1325	0·3
3-Br	2805	0·4	1656 1649	2·0			1610	0·8	1540	0·25	1462	0·3	1323	0·3
3-NO$_2$ [g] ...	3160	0·55	1706 1655	1·25 0·9	1637	0·7	1590	1·2	1551	1·3	1471	0·2	1309 1297	0·9
5-Me [d] ...	2940 2825	0·8	1656	1·8			1613	2·0	1548	1·3	1463	1·3	1357	0·25
5-Cl	2820	0·7	1656 1640	1·7 2·0			1607	2·1	1542	0·8	1470	1·1	1340	0·4
5-Br	2815	0·5	1640	1·7			1605	1·6	1536	1·0	1459	0·8	1340	0·3
5-I.....	2810	0·45	1637	1·7			1602	1·1	1534	0·75	1455	0·8	1339	0·2
5-NO$_2$ [g]	2820	0·4	1692 1668	1·7			1629	1·5	1562	0·55	1430	0·55		
3,5-Cl$_2$ ...	3060	0·55	1698	0·95	1632	0·3	1588	0·95	1532	0·5	1438	0·4	1304 1292	0·2
3,5-Br$_2$ ...	3085	0·45	1689	0·9	1625	0·15	1583	0·95	1527	0·3	1430	0·25	1301	0·3
3,5-I$_2$ ...	2725	0·3	1636	2·0			1593	0·3	1524	0·45	1459	0·2	1308	0·3

	VIII		IX [b]		X [b]		XI [b]		XII [b]		XIII		XIV [b]		XV [b, h]	
Subst.	skel.	str.									CH o.p. bend					
—	1244	0·8	1156	0·8	1098	0·45	981	0·65	845	0·05	780	1·5			729	0·4
4-Me	1248	0·25	1170	0·7			971	0·55	848	0·55	778	0·85	755	0·5	731	0·15
6-Me	1251	0·05	1168	0·45			998	0·35	810	0·3	799	0·5			733	0·1
	1212	0·25														
6-OH ...	1261		1143		1095		1026		860		802				719	
6-O$^-$	1264	infl.	1163	0·8			991	0·2	865	0·3	775	0·5			710	0·6
3-Me	1255	0·4	1164	0·05			986	0·4	885	0·6	775	1·3			735	0·1
	1230	0·6														
3-OH ...					1049	0·4			845	0·45	752	1·2			696	0·15
3-Cl	1246	0·25	1170	0·05	1046	0·6	982	0·15	876	0·4	774	0·6	756	0·35	671	0·3
3-Br	1242	0·25	1170	0·05	1031	0·65	982	0·15	866	0·3	770	0·6	752	0·4	648	0·25
3-NO$_2$ ...	1223	1·2	1141	0·25	1065	0·25	971	0·05	880	0·15	765	0·7			659	0·2
					1045	0·15										
5-Me	1237	0·4	1146	0·2			979	0·5			846	0·8	759	1·4		
5-Cl	1233	0·35	1141	0·2			990	0·45			842	0·6			668	1·3
5-Br	1231	0·3	1142	0·2			990	0·35			844	0·55				
5-I.....	1232	0·3	1146	0·2			987	0·25			844	0·45				
5-NO$_2$ ...	1252	0·85	1133 1119	0·7			1000 984	0·3			836	0·8	761	0·6	654	0·9
3,5-Cl$_2$ ...	1234	0·65	1120	0·35	1049	0·3					846	0·65	747	0·4	753	0·4
															651	0·3
3,5-Br$_2$ ...	1231	0·55	1100	0·3	1031	0·1					841	0·55	747	0·1	699	0·5
3,5-I$_2$ ...	1249	0·2	1088	0·02	1025	0·2	960	0·05			864	0·35	748	0·1	670	0·3

[a] Wavenumbers in cm.$^{-1}$. Intensities, in optical density units, are comparable only within each spectrum. Minor bands that are observed only for a small number of derivatives are not listed. [b] Bands listed in this column are not necessarily due to similar vibrations. [c] These four vibrations are usually intermixed; see text. [d] CH_3 bending bands, near 1480 and 1380 cm.$^{-1}$, are not listed. [e] Potassium chloride disc. From 1300 to 750 cm.$^{-1}$ this spectrum shows distortions (broad absorptions and sharp deep minima, such as sometimes accompany strong hydrogen-bonding in solids). [f] Very intense bands, apparently associated with OH in-plane bending and C–O stretching, occur at 1375, 1295, and 1190 cm.$^{-1}$. [g] The NO_2 stretching bands occur at 1506 and 1348 for the 3-, and at 1503 and 1362 cm.$^{-1}$ for the 5-nitro-compound. [h] Bands in this column probably include ONO scissoring and CCl and CBr stretching bands.

the highest aromatic skeletal stretching frequency encountered being 1615 cm.$^{-1}$ for a fairly prominent band for the 5 methyl derivative. Substitution by heavy atoms depresses this frequency to, *e.g.*, 1579 cm.$^{-1}$ in 5-iodo- and 1571 cm.$^{-1}$ in 3,5-dibromo-2-methoxypyridine.

The NH stretching frequency [18] in solid substituted 2-pyridones seems to depend mainly on intermolecular packing as it affects hydrogen bonding. Simple substituent effects can rarely be discerned. Often, but not always, an NH stretching frequency near 3100 cm.$^{-1}$ is accompanied by a band IV near 1585 cm.$^{-1}$, and NH stretching near 2800 cm.$^{-1}$ by a band IV near 1610 cm.$^{-1}$. The NH in-plane bending, near 1610 cm.$^{-1}$, is probably mixed appreciably with other vibrations of similar frequency.

Only one appreciably intense infrared band in the range 1500—1400 cm.$^{-1}$ is observed regularly for substituted 2-pyridones. The medium intensity band of 2-pyridone at 1460 cm.$^{-1}$, and its counterpart in a series of *N*-substituted derivatives, were attributed to a skeletal stretching vibration by Katritzky and Jones,[19] who sought to interpret the infrared spectrum of 2-pyridone on the basis of benzene-type skeletal vibrations; however, this band seems to be associated with the presence of four adjacent hydrogen atoms. If skeletal vibrations like those in benzene are to occur, either all six or, alternatively,[20] each set of three alternate skeletal bond stretching force constants should be roughly equal (giving either pseudo-D_{6h} or pseudo-D_{3h} skeletal symmetry). This is realised for 2-pyridone (I) only if structure (VI) makes a large contribution, in which case, however, a localised CO stretching vibration should have a stretching frequency much below that of an ordinary amide [cf. Cook; [21] in a pure form (VI) pure ν(CO stretching) would be no higher than 1380 cm.$^{-1}$]. Katritzky and Jones [19] nevertheless assigned the 2-pyridone band near 1650 cm.$^{-1}$ to C=O stretching; Bell, Shoffner, and Bauer,[22] however, assigned it to pseudo-aromatic skeletal stretching.

A more orthodox approach to the 2-pyridone vibrations was taken by Bellamy and Rogasch,[23] who assigned the 1698—1658 cm.$^{-1}$ band and the 1606 + 1585 cm.$^{-1}$ doublet of the *N*-methyl derivative to C=O and C=C stretching, respectively, because the former, but not the latter, band is strongly sensitive to the polarity of the solvent. To be more precise, on this basis the 2-pyridone bands at 1577 and 1540 cm.$^{-1}$ would be attributable to out-of-phase and in-phase C=C stretching, respectively; both here and for the *N*-methyl derivative,[24] the most intense Raman band in this region is at 1542 cm.$^{-1}$. Furthermore, substituents in 2-pyridone should alter the C=O stretching frequency in the normal manner, in accordance with their polar effects, while not affecting the C=C bands greatly.

The observed frequencies do not conform to such a neat pattern. For example, within the series 3-Me, 3-Cl, and 3-Br, and 5-Me, 5-Cl, 5-Br, and 5-I, the " C=O stretching " frequency shows a mass effect rather than the polar effect expected for a localised vibration of a highly polar bond. Extensive coupling between C=O and (in-phase) C=C stretching was previously proposed for 4-pyridone,[3,25] where the bond arrangement clearly favours this.* It now appears that appreciable C=O/C=C/C=C coupling occurs in 2-pyridones. The extent and manner of this coupling, which must also include components from other vibrations, vary from one substituted derivative to another. If the substituent(s) are strongly electron withdrawing, a localised C=O stretching motion is probably approached; but it is to be noted that 5-NO_2 raises both of the " C=C stretching " frequencies above their normal values. 3,5-Di-iodo substitution differs conspicuously from 3,5-dichloro and 3,5-dibromo substitution in lowering, instead of strongly raising, the " C=O stretching " frequency; the electron withdrawing effect of iodine is here masked by either a strong mass effect, or by the high polarisability of iodine (which is strongly manifested in electronic spectra [17]).

The most intense Raman band [3] of 2-pyridone and its 3-methyl derivative occurs at 1260 cm.$^{-1}$, and a corresponding infrared band of reasonably constant frequency is found for the other derivatives. This is attributed to a skeletal stretching motion, tentatively suggested to contain a large amount of C-4–C-5 stretching. The vibration at 1434 cm.$^{-1}$ in 2-pyridone is suggested to be largely an all-out-of-phase stretching motion of the C–N–C–C system. The strong Raman band [3] of 2-pyridone at 850 cm.$^{-1}$ (the infrared counterpart of which is exceedingly weak) is now attributed in the main to all-in-phase stretching of the C–N–C–C system; a previous assignment of this band to hydrogen out-of-plane bending [25,26] must be discarded, because in the Raman spectrum [24] of *N*-methyl-2-pyridone (which has the same number of nuclear hydrogen atoms) this band occurs at 757 cm.$^{-1}$; the 3-methyl derivative shows it at 744 cm.$^{-1}$. The frequencies of the other major infrared bands vary amongst the substituted derivatives, and with the number of hydrogen atoms; no assignments are suggested for them.

Added in Proof.—The predominance of the hydroxy-

* Solvent effects on bond stretching frequencies [23] do not always enable one to distinguish between a vibration localised in one bond and one extending over several. For example, a large changing dipole moment, and hence a strong sensitivity to solvent polarity, seem likely for the 4-pyridone vibration in which the C=O bond stretches while the C=C bonds contract.

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tautomer (II) for a second substituted 2-hydroxypyridine, the 3,6-dichloro-4,5-diphenyl derivative, has just been reported (P. I. Mortimer, paper read to Royal Australian Chemical Institute Heterocyclic Symposium, Canberra, August 16th, 1966).

EXPERIMENTAL

All the substituted 2-hydroxypyridines examined are described in the literature, but several of the 2-methoxypyridines are new or not adequately described.

2-Methoxy-5-methylpyridine.— 2-Chloro-5-methylpyridine [27] (10 g.) and sodium methoxide (from 7·5 g. of sodium) in dry methanol (45 ml.) were refluxed for 24 hr. Neutralisation with methanolic hydrogen chloride, removal of the sodium chloride, evaporation, and distillation gave 2-methoxy-5-methylpyridine, b. p. 163—165°/722 mm. (2·2 g., 24%). Dissolved in anhydrous ether, with dry hydrogen chloride it gave the (extremely hygroscopic) *hydrochloride* which was recrystallised from methanol–ether (Found: C, 52·8; H, 6·3; Cl, 21·6; N, 8·8. $C_7H_{10}ClNO$ requires C, 52·7; H, 6·3; Cl, 22·2; N, 8·8%).

3-Chloro-2-methoxypyridine.—2,3-Dichloropyridine [28] (25 g.) and sodium methoxide (from 12 g. of sodium) in dry methanol (140 ml.) were refluxed for 5 hr. Neutralisation with methanolic hydrogen chloride, removal of the sodium chloride, evaporation, addition of water, ether extraction, and distillation gave *3-chloro-2-methoxypyridine* (12 g., 50%), b. p. 107—109°/52 mm. (Found: C, 50·4; H, 4·1; Cl, 25·2; N, 9·6. C_6H_6ClNO requires C, 50·2; H, 4·2; Cl, 24·7; N, 9·8%).

3-Bromo-2-methoxypyridine.—This *compound* was prepared from 3-bromo-2-chloropyridine,[29] in 63% yield, in the same manner as the 3-chloro-derivative; it had b. p. 98·5—100°/26 mm. (Found: C, 38·6; H, 3·1; Br, 44·0; N, 7·4. C_6H_6BrNO requires C, 38·3; H, 3·2; Br, 42·5; N, 7·4%).

5-Chloro-2-methoxypyridine.—Into a solution of 2-methoxypyridine (2·18 g.) and anhydrous sodium acetate (1·64 g.) in glacial acetic acid (6 ml.) at 100°, chlorine (1·42 g., measured by increase in weight of solution) was passed. Water was added, followed by enough 5-N-sodium hydroxide to make the solution alkaline; ether extraction, drying, and distillation gave crude 5-chloro-2-methoxypyridine, collected over the boiling range 167—180°. It was purified by passing hydrogen chloride into an ethereal solution and recrystallising the *hydrochloride* from methanolic hydrogen chloride; it had m. p. 121° (eff.) (150 mg., 4%) (Found: C, 40·1; H, 4·0; Cl, 41·5. $C_6H_7Cl_2NO$ requires C, 40·0; H, 3·9; Cl, 39·4%).

5-Bromo-2-methoxypyridine.—Dropwise addition of bromine (1·68 g.) in glacial acetic acid (2 ml.) to refluxing 2-methoxypyridine (1·09 g.) and anhydrous sodium acetate (0·82 g.) in glacial acid (3 ml.) followed by addition of water (10 ml.) and an excess of 5N-sodium hydroxide, ether extraction, and passage of dry hydrogen chloride into the dry ethereal solution gave *5-bromo-2-methoxypyridine hydrochloride*, m. p. 125—126° (eff.) (from methanolic hydrogen chloride) (1·1 g., 49%) (Found: C, 31·9; H, 3·0; Br, 35·3; Cl, 16·2; N, 6·0. $C_6H_7BrClNO$ requires C, 32·0; H, 3·15; Br, 35·6; Cl, 15·8; N, 6·3%).

When boiled with 60% hydrobromic acid for 4 hr. this compound was converted into 5-bromo-2-hydroxypyridine, m. p. and mixed m. p. 175—177°; this proves the halogen to be in the 5-position.

5-Iodo-2-methoxypyridine.—Iodine (10·2 g.) in glacial acetic acid (170 ml.) was slowly added to refluxing 2-methoxypyridine (4·36 g.) and silver acetate (9 g.) in glacial acetic acid (16 ml.). Silver iodide was filtered off, and concentrated hydrochloric acid added. Evaporation to dryness under reduced pressure, addition of water and an excess of sodium carbonate solution (20%), steam-distillation, chloroform extraction of the distillate, and distillation of the dried (Na_2SO_4) chloroform extracts gave 5-iodo-2-methoxypyridine, b. p. 106—108°/30 mm. (0·8 g., 8·5%), which was converted into the *hydrochloride* with (and recrystallised from) methanolic hydrogen chloride; needles, m. p. 146—147° (lit.,[30] 145—150°) (Found: C, 26·8; H, 2·35; Cl, 13·4; I, 45·4. Calc. for C_6H_7ClINO: C, 26·5; H, 2·6; Cl, 13·1; I, 46·7%).

3,5-Dichloro-2-methoxypyridine.—By the method described above for converting 2,3-dichloropyridine into 3-chloro-2-methoxypyridine, with slight variation (refluxing for 30 min., no ether extraction), 2,3,5-trichloropyridine was converted, in 50% yield, into *3,5-dichloro-2-methoxypyridine*, m. p. 38·5—40° (from aqueous ethanol) (Found: C, 40·0; H, 2·9; Cl, 38·9; N, 8·0. $C_6H_5Cl_2NO$ requires C, 40·5; H, 2·85; Cl, 39·8; N, 7·9%).

The compound obtained [31] by the action of diazomethane on 3,5-dichloro-2-hydroxypyridine and claimed [31] to be 3,5-dichloro-2-methoxypyridine differs from that here prepared (by an unambiguous route) in having an m. p. of 137—140°, which is almost the same as that (141°) of 3,5-dichloro-1,2-dihydro-1-methyl-2-oxopyridine.[32]

3,5-Dibromo-2-methoxypyridine.—This *compound*, prepared (75%) from 3,5-dibromo-2-chloropyridine, in the same manner as the dichloro-derivative, had m. p. 48·5—49° (from aqueous ethanol) (Found: C, 26·8; H, 1·85; Br, 59·3; N, 5·2. $C_6H_5Br_2NO$ requires C, 26·6; H, 1·9; Br, 59·8; N, 5·2%).

Spectra.—Ultraviolet, infrared, and Raman spectra were measured as before.[26,33] In the infrared, solids were examined in dispersion in potassium bromide discs (concn. 1 in 200), and liquids as thin films.

Ionisation Constants.—These were determined by potentiometric titration [2] if within the pK_a range 3—11, and spectrophotometrically if outside this range. Negative pK_a values were measured in water–sulphuric acid mixtures, Paul and Long's [34] H_0 scale being used.

We thank Professor A. Albert for helpful discussions, Messrs. A. Arandjelovic, D. T. Light, and K. Tratt for technical assistance, Dr. J. E. Fildes and her staff for microanalyses, and the Australian National University for a Research Scholarship to one of us (J. C. B. W.).

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