875. N-*Oxides and Related Compounds. Part V.* The Tautomerism of* 2- *and* 4-*Amino- and -Hydroxy-pyridine* 1-*Oxide.*

By J. N. GARDNER and A. R. KATRITZKY.

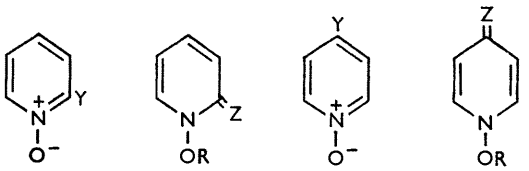
The basicities of the oxides named in the title and alkylated derivatives of their tautomers show that the 2- and 4-amino-compounds exist as such; the 4-hydroxy-compound is a mixture of comparable amounts of both tautomers in aqueous solution but the method fails with 2-hydroxypyridine 1-oxide. Previous work is reviewed. Ultraviolet and infrared evidence supports these conclusions and shows that 2-hydroxypyridine 1-oxide exists as strongly hydrogen-bonded 1-hydroxypyrid-2-one. The 2-amino-1-methoxypyridinium cation comes rapidly into equilibrium with hydroxyl ion; slow decomposition to 2-aminopyridine competes with this. The measured tautomeric constants are compared with those of the corresponding pyridines.

THE tautomerism of 2- and 4-amino- and 2- and 4-hydroxy-pyridine 1-oxide (I and III; Y = NH_2 or OH) with the alternative 1-hydroxypyridone imine and 1-hydroxypyridone forms (II and IV; R = H, Z = NH or O), has already been much investigated.[1-8] But in all cases where a decision was reached objections can be raised to its validity, as discussed below. Therefore the basicities of the parent compounds have been compared with those of alkylated derivatives of both forms, not only to find the predominant tautomer at equilibrium, but also to measure the stability difference between the forms,[9,10] and to compare the results with the published [10,11] information in the pyridine series.

* Papers by Katritzky (*J.*, 1956, 2063, 2404; 1957, 191) and by Katritzky, Randall, and Sutton (*J.*, 1957, 1769) are regarded as Parts I, II, III, and IV, respectively, of this series.

[1] Ochiai and Hayashi, *J. Pharm. Soc. Japan*, 1947, **67**, 151; *Chem. Abs.*, 1951, **45**, 9540; cf. Hayashi, *J. Pharm. Soc. Japan*, 1951, **71**, 213 (in German).
[2] Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67.
[3] Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2091.
[4] Hirayama and Kubota, *J. Pharm. Soc. Japan*, 1953, **73**, 140; *Chem. Abs.*, 1953, **47**, 4196.
[5] Jaffe, *J. Amer. Chem. Soc.*, 1955, **77**, 4445.
[6] *Idem*, *ibid.*, p. 4448.
[7] Costa, Blasina, and Sartori, *Z. phys. Chem.* (*Frankfurt*), 1956, **7**, 123.
[8] Katritzky, *J.*, 1957, 191.
[9] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.
[10] Angyal and Angyal, *J.*, 1952, 1461.
[11] Albert and Phillips, *J.*, 1956, 1294.

Preparation of Compounds.—Reduction of 4-nitropyridine 1-oxide gave 4-amino-pyridine 1-oxide,[12] converted by methyl toluene-*p*-sulphonate into a quaternary salt



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

which with perchloric acid gave 4-amino-1-methoxypyridinium perchlorate. 4-Chloro-pyridine 1-oxide with mono- and di-methylamine gave 4-mono- and 4-di-methylamino-pyridine 1-oxide; the latter was converted into quaternary salts as above.

Compounds in the 2-amino-series were prepared by known [8] methods, as were those of the 4-hydroxy-series,[2,13] except that 1-methoxypyrid-4-one was obtained from 4-hydroxy-pyridine 1-oxide with sodium methoxide and methyl toluene-*p*-sulphonate.

2-Chloropyridine 1-oxide with sodium benzyloxide gave 1-benzyloxypyrid-2-one as the only product isolated, instead of the expected 2-benzyloxypyridine 1-oxide. Shaw reported [2] that the latter was partially isomerised by hydrochloric acid. Catalytic reduction of 1-benzyloxypyrid-2-one gave 2-hydroxypyridine 1-oxide. However, with sodium methoxide and ethoxide, 2-chloropyridine 1-oxide gave the 2-methoxy- and the 2-ethoxy-compound as expected. 1-Methoxypyrid-2-one was prepared as for the 4-isomer above.

Results.—The pK values in Table 1 were determined by potentiometric titration, except for values below *ca.* 2 where the spectrometric method was used. Table 1 also

TABLE 1.

Compound	pK_a	Spread (±)	Concn. (M)	Wave-length [e] (mμ)	pK_a of corresp. pyridine	pK_a less pyridine pK_a
4-Aminopyridine 1-oxide	3·69 [b]	0·03	0·0083	—	9·17 [f]	−5·48
4-Methylaminopyridine 1-oxide	3·85	0·03	0·0074	—	—	—
4-Dimethylaminopyridine 1-oxide	3·88	0·07	0·0077	—	—	—
4-Amino-1-methoxypyridinium perchlorate [a]	>11	—	0·0075	—	12·5 [f]	*ca.* 0
4-Dimethylamino-1-methoxypyridinium perchlorate [a]	>11	—	0·0073	—	—	—
2-Aminopyridine 1-oxide	2·67	0·04	0·096	—	6·86 [f]	−4·19
2-Methylaminopyridine 1-oxide	2·61	0·07	0·0088	—	—	—
2-Dimethylaminopyridine 1-oxide	2·27	0·08	0·011	—	—	—
2-Amino-1-methoxypyridinium perchlorate [a]	12·4 [c]	—	—	—	12·2 [f]	*ca.* 0
2-Methylamino-1-methoxypyridinium toluene-*p*-sulphonate [a]	>11	—	0·0086	—	—	—
4-Hydroxypyridine 1-oxide	2·45 [d]	0·03	0·096	—	3·27 [g]	—
4-Methoxypyridine 1-oxide	2·05	0·06	0·097	—	6·62 [g]	−4·57
4-Benzyloxypyridine 1-oxide	1·99	0·05	0·095	—	—	—
1-Methoxypyrid-4-one	2·57	0·08	0·092	—	3·33 [g]	−0·76
1-Benzyloxypyrid-4-one	2·58	0·05	0·095	—	—	—
2-Hydroxypyridine 1-oxide	−0·8	0·2	$9·6 \times 10^{-5}$	295	0·75 [g]	—
2-Methoxypyridine 1-oxide	1·23	0·08	$7·1 \times 10^{-5}$	247	3·28 [g]	−2·05
2-Ethoxypyridine 1-oxide	1·18	0·18	$7·1 \times 10^{-5}$	247	—	—
1-Benzyloxypyrid-2-one	−1·7	0·1	$5·5 \times 10^{-5}$	295	—	—
1-Methoxypyrid-2-one	−1·3	0·2	$1·2 \times 10^{-4}$	300	0·32 [g]	−1·53

[a] Values for these compounds refer to back-titrations with alkali. [b] Lit.,[14] 3·65,[4] 3·54. [c] See text. [d] Lit.,[14] 2·36. [e] An entry in this column signifies that the determination was spectrometric (otherwise potentiometric). [f] Ref. 10. [g] Ref. 11.

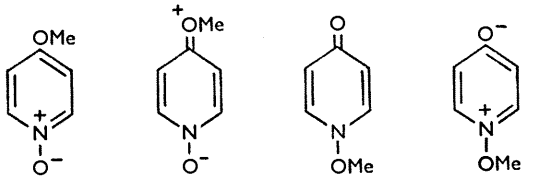
gives the initial concentration of the base from which thermodynamic pK values can be calculated (cf. ref. 11). Values for 1-methoxypyrid-2- and -4-one imines were obtained by

[12] Cf. Kato, Hamaguchi, and Oiwa, *Pharm. Bull.* (*Japan*), 1956, **4**, 178.
[13] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[14] Jaffe and Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.

back-titration of the corresponding 1-methoxy-2- and -4-aminopyridinium salts, as the former compounds could not be isolated.

In the 2- and the 4-amino-series, if it is assumed that the true basicities of the separate tautomeric forms (*e.g.*, 2-aminopyridine 1-oxide and 1-hydroxypyrid-2-one imine) are unchanged by *O*- or *N*-alkylation, the above results show [10,11] that the amino-forms are preferred by factors of at least 10^8 and 10^7 respectively, which are far too large to be materially affected by the above assumption.

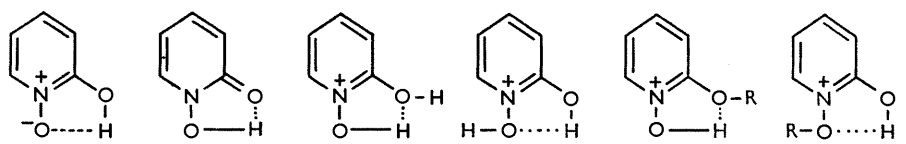
In the 4-hydroxy-series, qualitatively the results show that there can be little difference in stability between the hydroxy- and the pyridone forms. Quantitatively, interpretation



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

is more difficult: as the pK of 4-methoxypyridine 1-oxide is *lower* than that of 4-hydroxypyridine 1-oxide, the methyl group in the former must (whatever the tautomeric composition of the latter) have a base-weakening effect. The pK's of aniline and hydroxy- and methoxy-aniline show (see discussion in ref. 11) that, whereas the inductive effects are approximately equal, the mesomeric effect of hydroxyl is considerably more base-strengthening than is that of methoxyl (by about 0·3 pK unit in *o*- and *p*-substituted anilines). The two main canonical forms of 4-methoxypyridine 1-oxide are (V) and (VI), those of 1-methoxypyrid-4-one are (VII) and (VIII), showing that mesomerism involving the methoxyl group is much more important in the former compound where the methyl group can be expected to exert a considerable base-weakening effect. Thus the intrinsic pK of the 1-hydroxypyrid-4-one tautomer should be close to the homologue value of 2·57, but the 4-hydroxy-tautomer should be more strongly basic than 4-methoxypyridine 1-oxide (pK 2·05) by at least 0·3 units. It is concluded that 4-hydroxypyridine 1-oxide exists in aqueous solution as a mixture of comparable amounts of *N*-oxide and pyridone forms.

The 2-hydroxy-series is still more complicated. In whichever form it exists, 2-hydroxypyridine 1-oxide will be strongly hydrogen-bonded (IX or X) (see below and compare tropolone [15]). In addition (in distinction to the 2-amino-series) there are two possible structures for the protonated species (XI and XII). The pK values of the alternative alkylated derivatives show that (XIV) can lose its proton more readily than (XIII); this probably indicates that form (XI) is more stable than (XII) (although it is the loss of a

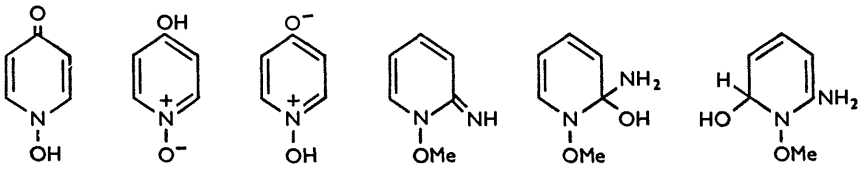


(IX) (X) (XI) (XII) (XIII) (XIV)

different proton), but (XI) may lose a proton to give either (IX) or (X). The stability of the hydrogen bond in (IX or X) may be obtained by considering how much more readily (XI) loses its proton than (XIII). Using $\Delta F = -RT \ln K$, we find ΔF to be *ca.* 3 kcals./mole. The above conclusions will now be compared with evidence on the position of tautomerism that has been obtained in other ways.

The Hammett Equation.—Jaffe [5] calculated that the intrinsic pK's of 4-hydroxy- and 4-amino-pyridine 1-oxide, existing as such, would be 1·68 and 2·22, both values being considered to be low because of uncertainties in the σ values for OH and NH_2 to be used in

the Hammett equation. He measured the actual pK's as 2·36 and 3·65 (cf. Table 1) and concluded (very unconvincingly) that this showed that 4-hydroxypyridine 1-oxide existed as such and not as 1-hydroxypyrid-4-one, and that 4-aminopyridine 1-oxide existed either as such or possibly as an equilibrium mixture with the pyridone imine (the latter was considered less probable on grounds of resonance and bond energies).

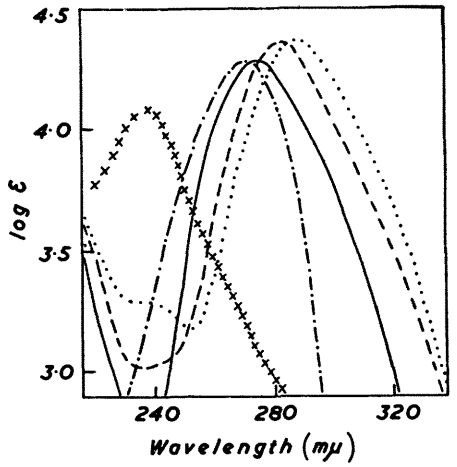


(XV) (XVI) (XVII) (XVIII) (XIX) (XX)

The Molecular-orbital Calculation.—It must be concluded that Jaffe's calculation [6] which showed 2- and 4-hydroxypyridine 1-oxide to be more stable than the corresponding 1-hydroxypyrid-2- and -4-ones by *ca.* 20 kcals./mole (*i.e.*, corresponding to a ratio of *ca.* 10^{14} between the forms) was not sufficiently refined.

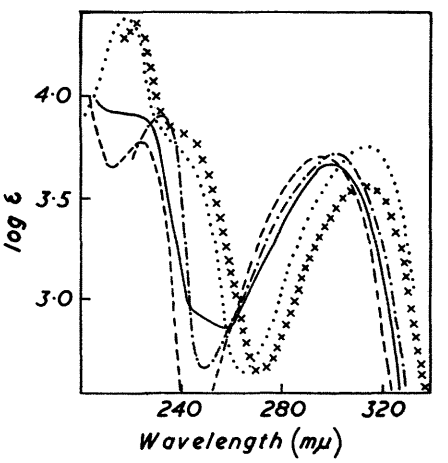
Hirayama and Kubota [4] appear to have deduced from resonance-energy considerations that 4-aminopyridine 1-oxide exists as such.

FIG. 1. *Solvent*: 0·1N-*sodium hydroxide.*



———— 4-*Aminopyridine* 1-*oxide.*
— — — — 4-*Methylaminopyridine* 1-*oxide.*
. . . . . 4-*Dimethylaminopyridine* 1-*oxide.*
— · — · — 4-*Amino*-1-*methoxypyridinium perchlorate.*
× × × × × 4-*Aminopyridine.*

FIG. 2. *Spectrum of* 2-*hydroxypyridine* 1-*oxide.*



———— *in* H_2O.
— — — — *in* 0·01N-H_2SO_4.
. . . . . *in* 0·01N-NaOH. 2-*Aminopyridine* 1-*oxide.*
— · — · — *in* 0·1N-HCl.
× × × × × *in* 0·1N-NaOH.

Ultraviolet Spectra.—Ochiai considered [1] that, because the spectrum of 4-hydroxypyridine 1-oxide showed little change in acid or alkaline solution, there was little contribution from the pyridone form (XV) but the " benzenoid form " (XVI) and/or the " betaine form " (XVII) were important.

Shaw showed [2] that the spectra of 4-hydroxypyridine 1-oxide and both possible benzyl (also true of methyl-) derivatives were all too similar to indicate the structure of the first. Fig. 1 shows that this holds also in the 4-amino-series.

Shaw,[2] and Spring and his co-workers,[3] independently concluded that the spectra in ethanol of 2-hydroxypyridine 1-oxide and alkylated derivatives showed that the parent

existed as 1-hydroxypyrid-2-one. The dangers of measuring the absorption of acids or bases of appreciable strength in unbuffered solvents are known.[16] Fig. 2 shows the neutral molecule and anion spectra of 2-hydroxypyridine 1-oxide (lit.,[2] pK_a 5·9; we find 5·99 ± 0·05 by potentiometric titration, c = 0·0098M) and the spectrum in unbuffered water (the latter is not reproducible). Acid strengths are lower in ethanol,[17] increasing the chance of obtaining the neutral form in unbuffered solvent. In Table 2, data from the literature are compared with spectra in 0·01N-ethanolic sulphuric acid and sodium ethoxide, indicating (although pK_a and pK_b in ethanol are unknown) that the first were essentially spectra of the neutral form.

FIG. 3. *Solvent*: 20N-*sulphuric acid* (except 2-*ethoxypyridene* 1-*oxide in* 10N *acid*).

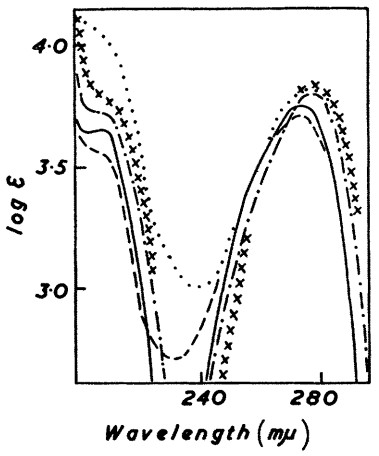
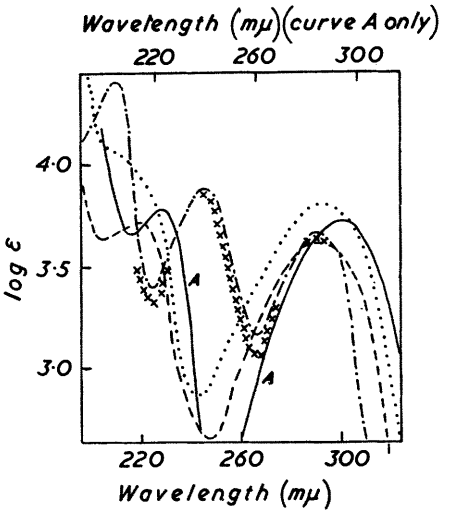


FIG. 4. *Solvent*: *water* (*except* 2-*hydroxypyridine* 1-*oxide in* 0·01N-H_2SO_4).



FIGS. 3 & 4. ———— 2-*Hydroxypyridine* 1-*oxide*. — · — · — 2-*Methoxypyridine* 1-*oxide*.
× × × × × 2-*Ethoxypyridine* 1-*oxide*. ····· 1-*Benzyloxypyrid*-2-*one*.
— — — — 1-*Methoxypyrid*-2-*one*.

Figs. 3 and 4 give spectra of cationic and neutral 2-hydroxypyridine 1-oxide and alkylated derivatives. Those of the cations are similar (cf. the expected difference in hydrogen-bonding). In 2-aminopyridine 1-oxide, methyl substitution of amino-groups

TABLE 2. *Ultraviolet spectra of* 2-*hydroxypyridine* 1-*oxide in ethanol.*

Solvent	λ_1	ε_1	$\lambda_{infl.}$	ε_i	λ_2	ε_2
EtOH [2]	228	7200	—	—	305	4600
EtOH [3]	228	6500	—	—	305	4000
0·01N-H_2SO_4–EtOH	230	6500	—	—	303	4750
0·01N-NaOEt–EtOH	225	23,200	244	5700	323	6800

causes bathochromic shifts [8] of *ca.* 8 mμ, the bathochromic effect of *C*-alkyl groups (*ca.* 5 mμ) is well known,* and *p*-methoxydiphenyl has $\lambda_{max.}$ 260 compared with 256 for *p*-hydroxydiphenyl.[18] In Fig. 4 the spectrum of 2-hydroxypyridine 1-oxide is displaced by 6 mμ relatively to the alkylated derivatives; it is thus difficult to deduce its structure. However, the spectral effect of *O*-alkylation varies; often no shift or a hypsochromic shift

* However, introduction of methyl groups into the 2-, 3-, or 4-position in pyridine causes shifts of +6·5, +5, and −3·5 mμ respectively [Ikekawa, Maruyama, and Sato, *Pharm. Bull.* (*Japan.*), 1954, **2**, 209].

[15] Koch, *J.*, 1951, 512.
[16] See, *e.g.*, Farmer and Thomson, *Chem. and Ind.*, 1957, 112.
[17] Brown, McDaniel, and Häfliger in Braude and Nachod's "Determination of Organic Structures by Physical Methods," Academic Press, New York, 1955, p. 619 ff.
[18] Burawoy, Cais, Chamberlain, Liversedge, and Thompson, *J.*, 1955, 3727.

is shown, *e.g.*, 3-methoxy- ($\lambda_{max.}$ 223, 262, and 299) and 3-hydroxy-pyridine 1-oxide (224·5, 263·5, 304);[19] this appears to be especially true in chelated phenols.[18] Thus Spring's [3] and Shaw's [2] evidence, while suggestive, is less conclusive than has been accepted (see, *e.g.*, ref. 6).

The changes in the spectra of 2-amino- and 2-hydroxy-pyridine 1-oxide from (dilute) acid to alkaline solution are similar (Fig. 2). It is known that the change in the former compound is loss of a proton from the *N*-oxide-oxygen atom of the cation, to give 2-aminopyridine 1-oxide as such; this perhaps indicates that the proton in 2-hydroxypyridine 1-oxide is more strongly bound to *N*-oxide oxygen.

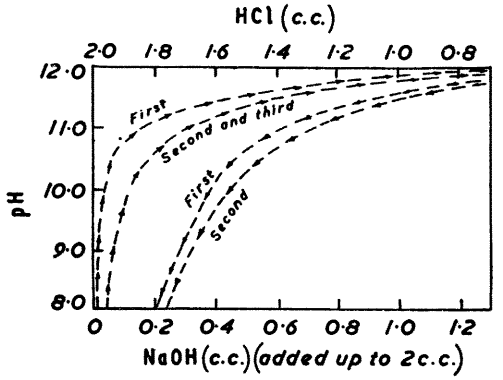
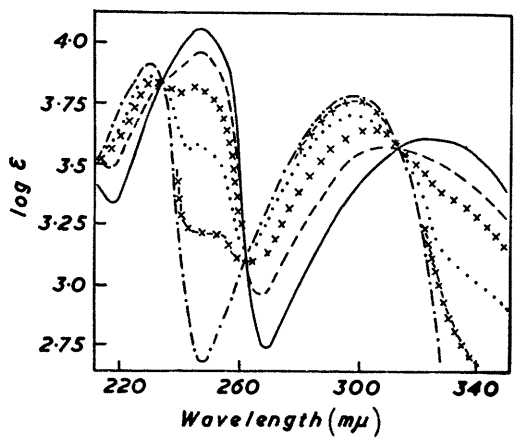


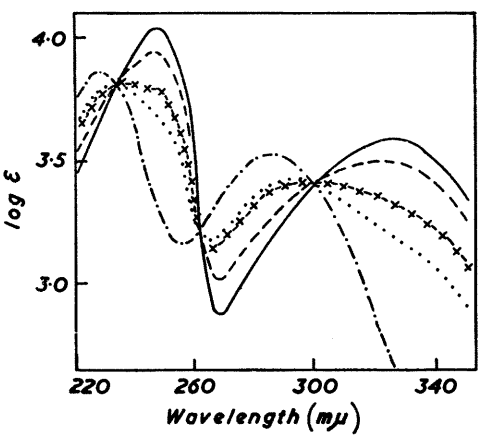
FIG. 5. *Hysteresis in titration of 2-amino-1-methoxypyridinium perchlorate with alkali.*

FIG. 6. *Variation of spectrum of 2-amino-1-methoxypyridinium perchlorate with* pH.



——— 3N- *and* N-, — — — 0·1N-, × × × × 0·03N-, · · · · · · 0·01N-, *and* ×—×—× 0·003N-*Sodium hydroxide.* —·—·— *Water,* 0·01N- *and* 0·1N-*hydrochloric acid.*

FIG. 7. *Variation of spectrum of 2-amino-1-methoxypyridinium perchlorate with time (in* N-*sodium hydroxide).*



——— *After* 8 *min.,* — — — 60 *min.,* ×—×—× 115 *min.,* · · · · · 180 *min.,* —·—·— 1250 *min.*

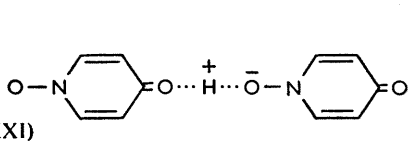
One of us has concluded [8] from ultraviolet spectra comparisons that 2-aminopyridine 1-oxide exists in the amino-form. In the potentiometric titrations, all the 1-methoxypyridinium salts (but not 2-aminopyridine 1-oxide) showed hysteresis (cf., *e.g.*, Fig. 5). It was at first thought that the non-superimposition of the forward- and backward-titration curves for 2-amino-1-methoxypyridinium perchlorate was due to decomposition, which would invalidate the previous [8] conclusions. In a detailed study of the spectrum of this compound in aqueous alkali, it was found to vary with both hydroxyl-ion concentration and time (Figs. 6 and 7). The first product (XVIII or possibly XIX or XX) behaves as a base

[19] Prins, *Rec. Trav. chim.*, 1957, **76**, 58.

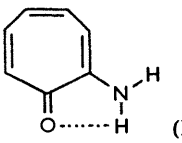
(pK 12·4 from Fig. 6), shown to be in equilibrium with starting material; adding acid at once (but not after 48 hr.) to the salt in 0·1N-alkali gave the curve for acid solutions. The slow reaction is possibly decomposition into 2-aminopyridine and formaldehyde, a reaction known for compounds of this type.[20] This reaction did not occur *via* (XVIII) because the rate of appearance of the decomposition product spectrum was similar in N- and 0·1N-alkali (decomposition at the alkali concentration used in the titrations was negligible in the time required for titration). The curve previously given [8] for 2-amino-1-methoxypyridinium perchlorate in 0·1N-sodium hydroxide is misleading, but the true curve for (XVIII) is different from the curves for 2-dimethylamino-, 2-monomethylamino-, and 2-aminopyridine 1-oxide (themselves similar [8]), and this is further evidence for the existence of 2-aminopyridine 1-oxide as such.

The ultraviolet spectrum of 2-aminopyridine 1-oxide does not vary with time or alkali concentration; 1-methoxypyridinium perchlorate shows marked changes, at present under investigation. Hysteresis in the titrations of 2 : 6-dihydroxypteridine with alkali has been explained by " covalent hydration." [21] Ochiai *et al.*[22] record the decomposition of 4-amino-1-methoxy-pyridinium and -quinolinium iodide to pyridine or quinoline and formaldehyde on treatment with silver oxide; Oda [23] states that the quinolinium salt is not easily decomposed by alkalis.

Infrared Spectra.—4-Amino- and 4-hydroxy-pyridine 1-oxide in the solid state have been studied by Costa, Blasina, and Sartori,[7] who concluded that the former could be interpreted on both the imino- or (more probably) the amino-structure. A band at 1648



(XXI)



(XXII)

and none at 1600 was adduced as evidence for the pyridone form in 4-hydroxypyridine 1-oxide but the spectrum was considered best explained by the hydrogen-bridged structure (XXI).

The above work was hindered by the insolubility of the compounds; we have now measured 2-hydroxy- and 2-amino- and 2- and 4-methylamino-pyridine 1-oxide in Nujol mulls and as 0·2M- (0·1 mm. cell) and 0·02M-solutions (1 mm. cell) in chloroform: the results for the 3 mμ region are shown in Table 3.

The spectrum of 4-methylaminopyridine 1-oxide shows strong intermolecular hydrogen-bonds in the solid state, partly broken up in 0·2M- and completely in 0·02M-solution. Both the position and the intensity of the unassociated imino-band agree with the values given by Goulden [24] for 2-methylaminopyridine (3450 cm.$^{-1}$, ε 100), showing that it exists in the methylamino-form.

2-Hydroxypyridine 1-oxide is shown to be strongly intramolecularly hydrogen-bonded, by its spectrum and molecular weight (cryoscopic in benzene, 109). Tropolone (pyridone is related to pyrrole as tropone is to benzene) shows [15] in dilute solution a broad band centred at *ca.* 3100 cm.$^{-1}$; β-diketone enols (containing a six-membered chelate ring) show [25] broad absorption centred at *ca.* 2700 cm.$^{-1}$. Koch concludes [15] from the hydrogen-bond strength (*ca.* 7 kcals./mole) that in tropolone the hydrogen atom is not (instantaneously) symmetrically placed; but is so on a time average (cf. ammonia and the bifluoride ion). The same should hold for 2-hydroxypyridine 1-oxide, but here disymmetry

[20] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[21] Albert, Lister, and Pedersen, *J.*, 1956, 4621; cf. Brown and Mason, *J.*, 1956, 3443.
[22] Ochiai, Katada, and Naito, *J. Pharm. Soc. Japan*, 1944, **64**, 210; *Chem. Abs.*, 1951, **45**, 5154.
[23] Oda, *J. Pharm. Soc. Japan*, 1944, **64**, 6; *Chem. Abs.*, 1951, **45**, 8523.
[24] Goulden, *J.*, 1952, 2939.
[25] Rasmussen, Tunicliffe, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.

enables one position to be filled on the average more than the other. Taking the evidence as a whole, the compound probably exists mainly as 1-hydroxypyrid-2-one.

2-Aminopyridine 1-oxide is shown to be intermolecularly hydrogen-bonded in the solid, but not in solution (no significant difference on dilution). The two bands of equal

TABLE 3. *Infrared spectra of substituted pyridine 1-oxides in 3 μ region.*

Subst.:	4-NHMe	2-OH	2-NH_2	2-NHMe
Nujol mull	3500—2600 (br) 3250 (sh), 2930	3200—2200 (br) 3070, 2940, 2400	3400—2800 (br) 3250 (sh), 3070 (sh), 2940	(Not measured)
$CHCl_3$ (0·2M) ...	3450 (55), 3240 (75)	3200—2300 (br)	3500 (70) 3360 (70)	3360 (65)
$CHCl_3$ (0·02M)...	3440 (90)	3200—2700 (br)	3480 (55) 3340 (50)	3360 (65)

(ε_A is given for solution spectra). br = broad region of absorption. sh = shoulder.

intensity at *ca.* 3490 and 3350 cm.$^{-1}$ indicate that it exists in the amino-form. Goulden,[24] and Angyal and Werner,[26] have shown that non-associated amino-pyridines, etc., absorb at *ca.* 3500 and 3400 cm.$^{-1}$ in solution.

2-Methylaminopyridine 1-oxide absorbs at 3360 cm.$^{-1}$, and the lowering of the frequency relatively to that of the (unassociated) 4-isomer shows that it is intramolecularly hydrogen-bonded.

The infrared spectrum of 2-aminotropone has been discussed by Japanese workers,[27] who record bands at 2·83 and 2·97 μ (3540 and 3370 cm.$^{-1}$), and consider that a weak hydrogen-bond was formed (XXII). Short [28] has shown that 1-aminoacridine (3494, 3390 cm.$^{-1}$) and 8-aminoquinoline (3493, 3389 cm.$^{-1}$) are intramolecularly hydrogen-bonded.

The infrared spectra in the 6—12·5 μ region of the compounds in Table 3 have been compared with those of the alkylated derivatives of both forms, and other pyridines and pyridine 1-oxides. The results, to be published separately, support the above conclusions.

TABLE 4. *Parts of amino- or hydroxy-form present per part of imino- or pyridone form.*

	4-Amino-	2-Amino-	4-Hydroxy-	2-Hydroxy-
Pyridine 1-oxide	$>10^7$	$>10^8$	*ca.* 1	(see text)
Pyridine	2×10^3 [a]	2×10^5 [a]	4×10^{-4} [b]	3×10^{-3} [b]

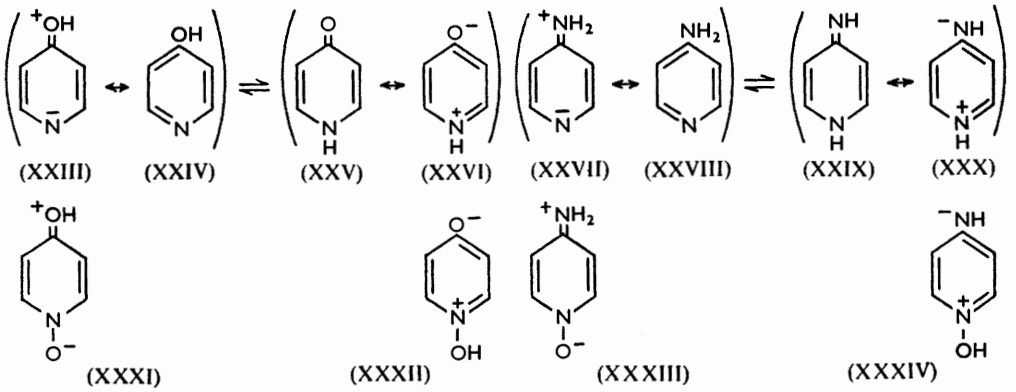
[a] Ref. 10. [b] Ref. 11.

Discussion.—Table 4 shows the proportions of the tautomers of 2- and 4-amino- and -hydroxy-pyridine and 1-oxides at equilibrium in solution as determined by basicity measurements. The usual explanation for the predominant existence of 4-hydroxypyridine in the pyridone form, but of, *e.g.*, 4-aminopyridine in the amino-form, is that in the tautomerism between the hydroxy- (XXIV) and pyridone form (XXV) account has to be taken of mesomerism with, respectively, (XXIII) and (XXVI). As negative charge is more stable on oxygen the equilibrium is swung in favour of the pyridone form. But in tautomerism of the aminopyridine (XXVIII) and 4-pyridone imine (XXIX), the form (XXX) is not much more stable than (XXVII) and the amino-form is favoured because of greater benzenoid resonance.

The influence of the oxygen atom in the corresponding pyridine 1-oxides can now be considered. The canonical form (XXXI) would be expected to be relatively more favoured than (XXIII), but (XXXII) less so than (XXVI); thus the equilibrium in the hydroxy-compounds should be less in favour of the pyridone form. In the amino-compounds, because (XXXIII) is relatively more favoured than (XXVII), and (XXXIV) less so than

[26] Angyal and Werner, *J.*, 1952, 2911.
[27] Nozoe, Seto, Takeda, Morosawa, and Matsumoto, *Proc. Japan, Acad.*, 1951, **27**, 556; *Chem. Abs.*, 1952, **46**, 7559; Kuratani, Tsuboi, and Shimanouchi, *Bull. Chem. Soc., Japan*, 1952, **25**, 250; *Chem. Abs.*, 1953, **47**, 8516.
[28] Short, *J.*, 1952, 4584.

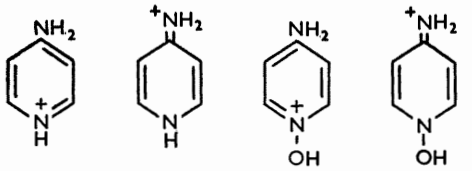
(XXX), the equilibrium would be expected to be still more in favour of the amino-form than in the pyridine series. Table 4 shows that this is so.



(XXIII) (XXIV) (XXV) (XXVI) (XXVII) (XXVIII) (XXIX) (XXX)

(XXXI) (XXXII) (XXXIII) (XXXIV)

The most important canonical forms of protonated 4-aminopyridine are (XXXV) and (XXXVI), those of protonated 4-aminopyridine 1-oxide are (XXXVII) and (XXXVIII), and it would be expected that the introduction of an *N*-oxygen atom would considerably lower the stability of a protonated aminopyridine. As this introduction of an oxygen atom



(XXXV) (XXXVI) (XXXVII) (XXXVIII)

lowers the stability of the pyridone imine form of an aminopyridine, but raises that of the amino-form, it should follow that (i) the intrinsic basicity of a hydroxy- or amino-pyridine 1-oxide (in the hydroxy- or amino-form) is much lower than that of the deoxygenated analogue, (ii) the difference between the basicities of a 1-hydroxypyridone or its imine and their deoxygenated analogues should be much less, and in either direction. Reference to the last column of Table 1 shows that all these predictions are borne out, except that 2-methoxypyridine 1-oxide is more strongly basic than expected, presumably because of hydrogen-bonding in (XIII).

Experimental

4-Aminopyridine 1-Oxide.—4-Nitropyridine 1-oxide (70 g.) was stirred under hydrogen with 2% palladium–strontium carbonate (14 g.) in ethanol (500 c.c.) at *ca.* 60°, until uptake of hydrogen (15—20 l./hr.) almost ceased. Evaporation and crystallisation of the residue from ethanol–ethyl acetate gave the amino-oxide (43 g., 78%) obtained on recrystallisation in tablets, m. p. 235—236° (lit.,[12] m. p. 229°) (Found: C, 54·6; H, 5·6. Calc. for $C_5H_6ON_2$: C, 54·6; H, 5·5%). Light absorption: max. at 270 mμ (ε 15,500) in 0·1N-hydrochloric acid; 276 mμ (ε 18,900) in 0·1N-sodium hydroxide.

The picrate (needles from ethanol) had m. p. 203—204° (lit.,[12] 201·5—202°,[13] 199—200°) (Found: C, 39·2; H, 2·9. Calc. for $C_{11}H_9O_8N_5$: C, 38·9; H, 2·7%); the *picrolonate* (beige laths from ethanol) had m. p. 241—244° (decomp.) (Found: C, 48·2; H, 3·9. $C_{15}H_{14}O_6N_6$ requires C, 48·2; H, 3·8%).

4-Amino-1-methoxypyridinium Salts.—The above amine, heated with one equivalent of methyl toluene-*p*-sulphonate for 12 hr. at 100°, gave the *toluene*-p-*sulphonate* (84%), deliquescent plates (from ethanol–ethyl acetate), m. p. 127—129° (Found: C, 53·0; H, 5·3. $C_{13}H_{16}O_4N_2S$ requires C. 52·7; H, 5·4%). This salt (0·6 g.) in ethanol (1·2 c.c.) and perchloric acid (0·32 c.c.) gave the *perchlorate* (36%) (plates from ethanol–ethyl acetate) m. p. 99—101°

(Found: C, 32·3; H, 4·1. $C_6H_9O_5N_2Cl$ requires C, 32·1; H, 4·0%). Light absorption: max. at 274 mμ (ε 19,300) in 0·1N-hydrochloric acid; 273 mμ (ε 19,900) in 0·1N-sodium hydroxide.

4-*Methylaminopyridine* 1-*Oxide*.—25% Aqueous methylamine (139 c.c.) and 4-chloropyridine 1-oxide (23·1 g.) were heated for 20 hr. at 140°. The product was evaporated with potassium carbonate (23 g.) at 100°/15 mm.; extraction of the residue with ethyl methyl ketone gave the *oxide* (17·4 g., 78%), which crystallised from the same solvent in highly deliquescent prisms, m. p. 192—194° (Found: C, 57·7; H, 6·6. $C_6H_8ON_2$ requires C, 58·0; H, 6·5%). Light absorption: max. at 279 mμ (ε 16,400) in 0·1N-hydrochloric acid; 285 mμ (ε 22,800) in 0·1N-sodium hydroxide.

The *picrate* (prisms from ethanol) had m. p. 193—194° (Found: C, 41·0; H, 3·3. $C_{12}H_{11}O_8N_5$ requires C, 40·8; H, 3·1%); the *picrolonate* (beige needles from ethanol) had m. p. 211—212° (decomp.) (Found: C, 49·9; H, 4·1; N, 21·1. $C_{16}H_{16}O_6N_6$ requires C, 49·5; H, 4·1; N, 21·6%).

The product of heating this amine with methyl toluene-*p*-sulphonate did not crystallise; no solid perchlorate or tetrachloroferrate [29] could be prepared from this product.

4-*Dimethylaminopyridine* 1-*Oxide*.—After sublimation at 160°/0·05 mm., this compound [30] had m. p. 97—99° with resolidification and remelting at 214—216°. Light absorption max. at 288 mμ (ε 19,200) in 0·1N-hydrochloric acid, 289 mμ (ε 23,800) in 0·1N-sodium hydroxide.

4-*Dimethylamino*-1-*methoxypyridinium Salts*.—Prepared as the 4-amino-analogues, the *toluene*-p-*sulphonate*, deliquescent prisms (from ethanol–ethyl acetate) had m. p. 109—112° (Found: C, 55·4; H, 6·4. $C_{15}H_{20}O_4N_2S$ requires C, 55·6; H, 6·2%); the *perchlorate* (81%) (needles from ethanol) had m. p. 138—139° (Found: C, 38·1; H, 5·3; N, 10·8. $C_8H_{13}O_5N_2Cl$ requires C, 38·0; H, 5·2; N, 11·1%). Light absorption: max. at 290 mμ (ε 23,500) in 0·1N-hydrochloric acid; 291 mμ (ε 20,900) in 0·1N-sodium hydroxide.

1-*Methoxypyrid*-4-*one*.—4-Hydroxypyridine 1-oxide (2·22 g.), ethanolic sodium ethoxide (from 200 c.c. of ethanol and 0·46 g. of sodium), and methyl toluene-*p*-sulphonate (3·92 g.) were refluxed for 1 hr. (pH then 7). The cooled (solid carbon dioxide and ethanol) mixture was filtered and evaporated at 100°/20 mm. (during which two further filtrations were necessary). Extraction of the residue with chloroform (2 × 15 c.c.) and distillation of the extracts gave the *pyridone* (1·7 g., 68%), b. p. 190—195° (bath)/0·1 mm., highly deliquescent prisms, m. p. 60—65° after sublimation at 100°/0·1 mm. (Found: C, 57·6; H, 5·7. $C_6H_7O_2N$ requires C, 57·6; H, 5·6%). Light absorption: max. at 243 mμ (ε 11,200) in 5N-sulphuric acid; 262 mμ (ε 16,800) in water (Ochiai *et al.*[1,31] records b. p. 160°/0·01 mm. and states that it crystallised in a desiccator but that m. p. determination was difficult.)

The picrate (from ethanol) had m. p. 200—202° (lit.,[1] m. p. 200—201°).

1-*Benzyloxypyrid*-2-*one*.—2-Chloropyridine 1-oxide (20·9 g.) and charcoal (1 g.) were refluxed for 5 min. with sodium benzyloxide in benzyl alcohol (200 c.c. containing 3·72 g. of sodium), and the solution was filtered and concentrated at 140°/20 mm. Extraction with ethyl acetate (180 c.c.) (with 1 g. of charcoal), removal of solvent at 100°/20 mm., and recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) gave the pyridone (18·1 g., 56%), sufficiently pure for reduction. Sublimation at 120°/0·1 mm. and further recrystallisation raised the m. p. to 76—78°; the product was identical (mixed m. p. and infrared spectrum) with a sample (m. p. 77—79°) prepared by Shaw's method [2] (Found: C, 71·8; H, 5·3; N, 6·75. Calc. for $C_{12}H_{11}O_2N$: C, 71·6; H, 5·5; N, 7·0%) (lit.,[2] m. p. 85—86°). Light absorption max. at 297 mμ (ε 6200), infl. at 214 mμ (ε 11,400) in water; max. at 279 mμ (ε 6400), infl. at 207 mμ (ε 11,600) in 20N-sulphuric acid.

In our hands attempted preparation [2] of 2-benzyloxypyridine 1-oxide by perbenzoic acid oxidation of 2-benzyloxypyridine gave mainly 1-benzyloxypyrid-2-one (ultraviolet spectra).

2-*Hydroxypyridine* 1-*Oxide*.—The above pyridone (15 g.) in ethanol (60 c.c.), shaken over 5% palladium–charcoal (0·75 g.), absorbed 1700 c.c. of hydrogen (at 1 atm.) in 85 min. Filtration hot, and evaporation, gave the oxide (6·85 g., 83%), m. p. 148—149° after recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) (Found: C, 54·2; H, 4·5; N, 12·6. Calc. for $C_5H_5O_2N$: C, 54·1; H, 4·5; N, 12·6%) (lit.,[2] m. p. 149—150°). Light absorption: max. at 209, 276 mμ (ε 4300, 5600) in 20N-sulphuric acid; 225, 296 mμ (ε 6400, 5200) in 0·001N-sulphuric acid; 210, 313 mμ (ε 26,700, 6200), infl. at 237 mμ (ε 6200) in 0·1N-sodium hydroxide.

[29] Blatt and Gross, *J. Amer. Chem. Soc.*, 1955, **77**, 5424.
[30] Katritzky, Randall, and Sutton, *J.*, 1957, 1769.
[31] Ochiai, Teshigawara, Oda, and Naito, *J. Pharm. Soc. Japan*, 1945, **65**, 516A, 1; *Chem. Abs.*, 1951, **45**, 8527.

2-Ethoxypyridine 1-Oxide.—2-Chloropyridine 1-oxide (2·6 g.) was refluxed for 30 min. with ethanolic sodium ethoxide (20 c.c. containing 0·46 g. of sodium) (pH then 7—8). Evaporation at 100°/20 mm., extraction with chloroform (2 × 15 c.c.), removal of solvent, and recrystallisation from ethanol–ethyl acetate gave the oxide (2·24 g., 80%), m. p. (after further recrystallisation) 71—73° (softens from 67°) (lit.,[32] m. p. 71—73°). Light absorption: max. at 280 mμ (ε 7000) infl. at 209 mμ (ε 6200) in 10N-sulphuric acid; max. at 214, 249, 293 mμ (ε 27,200, 7400, 4500) in water. The picrate had m. p. 110—111° (lit.,[32] m. p. 111—113°).

2-Methoxypyridine 1-Oxide.—Prepared as the last compound, the *oxide* (68%) formed hygroscopic needles, m. p. 78—79°, from ethyl acetate (Found: C, 57·8; H, 5·7. $C_6H_7O_2N$ requires C, 57·6; H, 5·6%). Light absorption: max. at 280 mμ (ε 6300), infl. at 210 mμ (ε 5200) in 20N-sulphuric acid; max. at 213, 249, 293 mμ (ε 25,000, 7600, 4500) in water.

It formed a *hydrate* in air, as prisms, m. p. 66·5—67·5° (Found: C, 48·0; H, 6·7; N, 8·9. $C_6H_7O_2N,1{\cdot}5H_2O$ requires C, 47·4; H, 6·6; N, 9·2%). The *picrate* (needles from ethanol) had m. p. 140—143° (Found: C, 41·0; H, 2·8; N, 15·6. $C_{12}H_{10}O_9N_4$ requires C, 40·7; H, 2·8; N, 15·8%).

1-Methoxypyrid-2-one.—Prepared as for the 4-analogue the *pyrid-2-one* (77%) had b. p. 130° (bath)/0·05 mm.; it partially solidified (Found: C, 57·8; H, 5·9. $C_6H_7O_2N$ requires C, 57·6; H, 5·6%). Light absorption: max. at 276 mμ (ε 5200), infl. at 207 mμ (ε 3800) in 20N-sulphuric acid; max. at 224, 296 mμ (ε 5300, 4100) in water. This compound did not readily form a picrate in ethanol.

4-Methoxypyridine 1-Oxide.[13]—Light absorption: max. at 244 mμ (ε 12,000) in 5N-sulphuric acid; 261 mμ (ε 16,300) in water.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 15th*, 1957.]

[32] Newbold and Spring, *J.*, 1948, 1864.