Pyridone–Pyridol Tautomerism in 2-Hydroxypyridines with [5,6]-Annelated Rings and Carbon Atoms at Positions [5] and [6]: 1,3-Dihydro-5-hydroxyfuro[3,4-*b*]pyridine, 1,3-Dihydro-5-hydroxythieno[3,4-*b*]pyridine, and 1,3-Dihydro-5-hydroxythieno[3,4-*b*]pyridine *S,S*-dioxide

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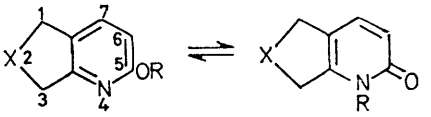
U.v. spectra, in a range of solvents, i.r. spectra, and ionization constants in water have been determined for the title compounds (I) to (VI), their *O*- and *N*-methylated derivatives (VII) to (XII), counterparts that correspond to *O*- and *S*-ring fission products (XIII) to (XVI), and their methylated derivatives (XVII) to (XIX). All the the title compounds exist to an appreciable extent in the pyridol form in solution in dioxan. By a comparison of the cyclic sulphide with, on the one hand the cyclic sulphone, and on the other the cyclic ether, the effects of electron withdrawal and of ring strain have been assessed almost independently of one another. Replacement of the sulphide ring by the (smaller) ether ring (*a*) increases the ratio [pyridol]/[pyridone] (K_T) in dioxan by a factor of 2·7, (*b*) lowers the base strength of the 2-methoxypyridine, (*c*) lowers the base strength of the 2-pyridone, but by a much smaller amount, (*d*) raises the acid strength of the 2-pyridone. Replacement of the sulphide by the sulphone ring (*a*) produces a 2·8-fold increase in K_T in dioxan, and (*b*), (*c*), and (*d*) reduces the base strengths and raises the acid strength, all by much greater amounts than in the above comparison. Analysis shows that no more than a third of the difference in K_T between the cyclic ether and the cyclic sulphide is attributable to greater electron withdrawal (inherent plus ring-strain-induced) by the oxygen ring; about two thirds of it is due to a Mills–Nixon–Brown type of ring strain in the pyridone (II), which is relieved by conversion into the pyridol (I) or by ionization. The effects of ' ring closure ' of the di-(methyl ether) to the cyclic ether, *e.g.* of [(XIII), (XIV)] to the [(I), (II)], show clear evidence of ring strain in the latter, whereas the effects of ' ring closure ' of the di-methylthio-compounds to the cyclic sulphides indicate only a small amount of ring strain in the last-named All the 2-hydroxypyridines listed are in the pyridone form in the solid state.

In the preceding study of 2,3-dihydro-6-hydroxy-4-methylfuro[2,3-*b*]pyridine [1] it was found that the five-membered ring annelated at the [5,6] position was of major importance in favouring the pyridol over the pyridone tautomer, and that this occurs by two distinct mechanisms: (*a*) a Mills–Nixon–Brown type of ring strain,[2] referred to as a ' direct ring-strain effect,' (*b*) by an electron-withdrawing effect which is an indirect

[1] E. Spinner and G. B. Yeoh, preceding paper.
[2] Refs. 17—20 of preceding paper.

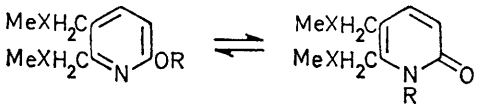
consequence of ring strain,[3] referred to as ' ring-strain-induced electron withdrawal.' It was deduced, but only indirectly, that (*a*) must be the more important of the two mechanisms.

In the compounds now studied the electron-withdrawing hetero-atom is separated from the pyridine ring by methylene groups; this greatly reduces the polar effect, but also eliminates any duality of polar effect; only the inductive + direct field effect operates. The effective size of the five-membered ring, and the strain in it, were varied by varying the size of the hetero-atom. Study of the open-chain counterparts (XVII) and (XVIII) has shown that the inherent polar effects of the oxygen and the sulphur atom, when separated from the pyridine ring by a methylene group, are very similar. Thus, the only major difference between cyclic sulphide and cyclic ether here is one of ring size.



(I) R = H, X = O
(III) R = H, X = S
(V) R = H, X = SO_2
(VII) R = Me, X = O
(IX) R = Me, X = S
(XI) R = Me, X = SO_2

(II) R = H, X = O
(IV) R = H, X = S
(VI) R = H, X = SO_2
(VIII) R = Me, X = O
(X) R = Me, X = S
(XII) R = Me, X = SO_2



(XIII) R = H, X = O
(XV) R = H, X = S
(XVII) R = Me, X = O
(XVIII) R = Me, X = S

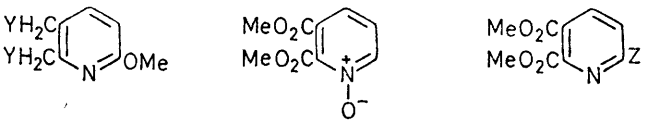
(XIV) R = H, X = O
(XVI) R = H, X = S
(XIX) R = Me, X = S

By contrast, the SO_2 group is much more electron withdrawing than S, but the effective ' size ' of the five-membered ring is about the same in the cyclic sulphide and in the cyclic sulphone (the C–S bond length is 1·80 Å in dimethyl sulphide [4] and close to 1·80 Å in dimethyl sulphone and other sulphones [5]; *cf.* 1·41 Å for the CO bond length in dimethyl ether [6]). Both 2,5-dihydrofuran [7] and 2,5-dihydrothiophen [8] are planar, and the five-membered ring in molecules (I) to (XII) must likewise be expected to be planar.

The compounds (I)—(XXI) are all both 5-substituted and 6-substituted pyridines (or pyridones). However, 5-substituents in 2-hydroxypyridines have far smaller effects on the pyridone–pyridol tautomerism than have 6-substituents. Whereas 6-chloro-2-hydroxypyridine is in the pyridol form in amounts variously estimated [9,10] as 97 and 86% in ethanol, 5-chloro-2-hydroxypyridine exists in the pyridol form to a considerable extent (30—40%) only in solvents of much lower polarity, such as dioxan and cyclohexane.[11] There is no unique correlation between pyridol content and electron-withdrawing effect of substituent either for 5- or for 6-substitution; *e.g.* a 6-amino-group, even though electron-donating, raises the pyridol content; [10] among the 5-halogeno-2-hydroxypyridines the pyridol content increases with increasing electron-withdrawing effect of the halogen, but 2-hydroxy-5-nitropyridine in dioxan shows no appreciable pyridol content.[11]

EXPERIMENTAL

Materials.—The compounds were obtained from 2,3-bis-(methoxycarbonyl)pyridine *N*-oxide (XXII) as detailed below.



(XX) Y = H
(XXI) Y = OH
(XXVI) Y = Cl

(XXII)

(XXIII) Z = OH
(XXIV) Z = Cl
(XXV) Z = OMe

N-Oxide.—Esterification of quinolinic acid (pyridine-2,3-dicarboxylic acid) with methanilic hydrogen chloride gave [12] dimethyl quinolinate, m.p. 57—57·5° (lit.,[12] (*a*) 53—54°, (*b*) 54—55°) (Found: C, 55·8; H, 4·6; N, 7·0. Calc. for $C_9H_9NO_4$: C, 55·4; H, 4·6; N, 7·2%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 1·25 (1H, q, *J* 5, 2, [6]CH?), 1·83 (1H, q, *J* 9, 2, [4]H?), 2·55 (1H, q, *J* 9, 5, [5]H), 6·06 (3H, s, CO_2Me), 6·12 (3H, s, CO_2Me). Dimethyl quinolinate (20·7 g.), glacial acetic acid (60 ml.), and 30% hydrogen peroxide (10 ml.) were heated at 83° for 2 hr.; further hydrogen peroxide (10) ml.) was added and heating was continued for 2 hr. The solvent was distilled off, the residue was made alkaline with aqueous sodium carbonate and extracted with chloroform. Evaporation of the latter left the N-*oxide* (11·7 g., 55%), m.p. 141—142° (from methanol) (Found: C, 51·4; H, 4·6; N, 6·7. $C_9H_9NO_5$ requires C, 51·2; H, 4·3; N, 6·6%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 1·67 (1H, q, *J* 5, 2, [6]CH?), 2·17 (1H, q, *J* 9, 2, [4]CH?), 2·72 (1H, q, *J* 9·5, [5]CH), 6·00 (3H, s, CO_2Me), 6·10 (3H, s, CO_2Me).

6-*Hydroxy*-2,3-*dimethoxycarbonylpyridine.*— Dimethyl quinoline *N*-oxide (0·400 g.) and acetic anhydride (4 ml.) were heated at 180° for 8 hr. The excess of the latter was distilled off, water (10 ml.) was added, and the mixture was warmed on a steam-bath for 30 min. The cooled solution was extracted with chloroform; evaporation of the extract gave the rearrangement product (XXIII) (0·200 g., 50%), m.p. 159—161° (from ethyl acetate) (lit.,[13] 158°) (Found: C, 51·1; H, 4·3; N, 6·6%), ^{1}H n.m.r. spectrum ($CDCl_3$); τ 2·20 (1H, d, *J* 10, [4]CH), 3·36 (1H, d, *J* 10, [5]CH), 6·03 (3H, s, CO_2Me), 6·17 (3H, s, CO_2Me). Unambiguous proof that the oxygen atom migrates to the 6- and not the 4-position in this rearrangement (and of the identity of our

[3] Ref. 35 of preceding paper.
[4] L. Pierce and M. Hayashi, *J. Chem. Phys.*, 1961, **35**, 479.
[5] *Chem. Soc. Special Publ.* 11, 1958, p. M 139; *cf.* pp. M 184, M 185.
[6] K. Kimura and M. Kubo, *J. Chem. Phys.*, 1959, **30**, 151; U. Blukis, P. H. Kasai, and R. J. Myers, *ibid.*, 1963, **38**, 2753.
[7] T. Ueda and T. Shimanouchi, *J. Chem. Phys.*, 1967, **47**, 4042, 5018.
[8] W. H. Green and A. B. Harvey, *J. Chem. Phys.*, 1968, **49**, 177.
[9] Ref. 9 of preceding paper.
[10] Ref. 10 of preceding paper.
[11] E. Spinner and G. B. Yeoh, unpublished results.
[12] (*a*) C. Engler, *Ber.*, 1894, **27**, 1789; (*b*) I. Heilbron, A. H. Cook, H. M. Bunbury, and D. H. Hey, ' Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, p. 2818.
[13] K. Gleu and K. Wackernagel, *J. prakt. Chem.*, 1937, **148**, 72.

product with Gleu and Wackernagel's [13] of known [14] constitution) will appear later.

6-*Chloro*-2,3-*bis*(*methoxycarbonyl*)*pyridine*.—This compound is obtainable both from the above hydroxy-compound, and directly from dimethyl quinolinate *N*-oxide. (*a*) The hydroxypyridine (XXIII) (0·102 g.) and phosphoryl chloride (4 ml.) were heated in a sealed tube at 180° for 4 hr. The excess of chloride was distilled off, water (10 ml.) was added, and the mixture was extracted with chloroform; the chloroform solution was dried, and the solvent was evaporated off to leave the *chloro-compound* (XXIV) (0·106 g., 95%), b.p. 110—112°/0·02 mm.

(*b*) The hydroxypyridine (XXIII) was heated under reflux for ½ hr. with an excess of thionyl chloride in methylene dichloride containing a few drops of dimethylformamide to give (XXIV) (80%).

(*c*) To dimethyl quinolinate *N*-oxide (42·9 g.) at 0° phosphoryl chloride (80 ml.) was added slowly and with stirring. The mixture was then immersed in an oil-bath at 90°. Soon effervescence started, and external heating was discontinued; when the mixture had ceased to reflux and effervescence had stopped the mixture was heated at 90° for 30 min. Work-up as under (*a*) above gave a chloro-compound (37·7 g., 80%) identical with the above (i.r. spectrum) (Found: C, 47·2; H, 3·9; Cl, 15·4; N, 6·4. $C_9H_8ClNO_4$ requires C, 47·1; H, 3·5; Cl, 15·5; N, 6·1%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 1·88 (1H, d, *J* 9, [4]CH), 2·55 (1H, d, *J* 9, [5]CH), 6·06 (3H, s, CO_2Me), 6·13 (3H, s, CO_2Me).

6-*Methoxy*-2,3-*bis*(*methoxycarbonyl*)*pyridine*.—The chloro-compound (XXIV) (47 g.) in methanol (100 ml.) and sodium methoxide solution (from 6·1 g. sodium and 300 ml. anhydrous methanol) were stirred and heated under reflux for 1 hr. The cooled solution was filtered and the sodium chloride filtered off was washed with methanol; an excess of solid carbon dioxide was added to the combined filtrate and washings. Methanol was removed from the filtrate and the residue was poured into water (100 ml.) to give the methoxy-compound (XXV) (41·5 g., 90%); it had m.p. 63—64° (from methanol) (Found: C, 53·5; H, 5·3; N, 6·1. $C_{10}H_{11}NO_5$ requires C, 53·3; H, 4·9; N, 6·2%), ^{1}H n.m.r. spectrum (CCl_4): τ 1·96 (1H, d, *J* 9, [4]CH), 3·26 (1H, d, *J* 9, [5]CH), 6·04 (6H, s, CO_2Me and OMe), and 6·14 (3H, s, CO_2Me).

The methoxy-compound was heated under reflux with concentrated hydrobromic acid (25 vol.) for 15 hr.; the product was then heated to 250° to give 6-hydroxypyridine-3-carboxylic acid; this had the same i.r. spectrum as an authentic specimen (kindly supplied by Professor A. Albert). This shows that in the compounds (XXIII)—(XXV) Z is in the α-position.

2,3-*Di*(*hydroxymethyl*)-6-*methoxypyridine*.—Lithium aluminium hydride (0·299 g.) was added to 2,3-dimethoxycarbonyl-6-methoxypyridine (0·903 g.) in anhydrous ether (25 ml.) and the mixture was stirred at room temperature for 45 min. It was cooled to 0°, and treated dropwise with saturated aqueous sodium sulphate until no further effervescence took place; the mixture was stirred for 1 hr. and then filtered. The solid obtained was washed with methanol–ether (1 : 1), and the combined washings and filtrate were evaporated. Water (3 ml.) was added to the residue, and the solution was extracted continuously with chloroform. Evaporation of the extract gave the crude *dimethylol* (XXI) (0·438 g., 65%), b.p. 132—134°/0·3 mm.; ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·40 (1H, d, *J* 9, [4]CH), 3·35 (1H, d, *J* 9, [5]CH), 5·24 (2H, s, 2-CH_2), 5·38 (2H, s, 3-CH_2), 6·04 (3H, s, OMe), 6·47 (1H, s, OH). It gave a *hydrochloride*, m.p. 116—117° (Found: C, 46·6; H, 6·1; Cl, 17·4; N, 6·8. $C_8H_{12}ClNO_3$ requires C, 46·7; H, 5·8; N, 6·8; Cl, 17·4%).

2,3-*Di*(*chloromethyl*)-6-*methoxypyridine*.—The dimethylol (XXI) (4·35 g.) was treated with thionyl chloride (10 ml.) at room temperature for 15 min. Excess of thionyl chloride was evaporated off, water (25 ml.) was added, and the solution was extracted with light petroleum (b.p. 60—80°). The dried extracts, on evaporation, gave the *di*(*chloromethyl*) *compound* (XXVI) (3·9 g., 74%), b.p. 88°/0·15 mm. (Found: C, 46·8; H, 4·3; Cl, 33·5; N, 6·8. $C_8H_9Cl_2NO$ requires C, 46·6; H, 4·4; Cl, 34·4; N, 6·8%). ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·43 (1H, d, *J* 9, [4]CH), 3·28 (1H, d, *J* 9, [5]CH), 5·32 (4H, s, 2-CH_2 and 3-CH_2), 6·08 (3H, s, OMe). Addition of an excess of concentrated hydrochloric acid to the compound followed by evaporation to dryness gave a quantitative yield of the *hydrochloride*.

1,3-*Dihydro*-5-*methoxyfuro*[3,4-b]*pyridine*—The di-(chloromethyl) compound (XXVI) (1·3 g.) was stirred with potassium hydroxide (0·6 g.) in water (50 ml.) at 75° for 10 hr. The reaction mixture was steam distilled and the distillate was extracted with chloroform. Evaporation of the latter gave the *cyclic ether* (VII) (0·11 g., 13%) subliming at 0·3 mm./22°, m.p. 36—38° (from ethyl acetate) (Found: C, 63·3; H, 6·1; N, 9·2. $C_8H_9NO_2$ requires C, 63·6; H, 6·0; N, 9·3%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·59 (1H, d, *J* 9, [7]CH), 3·39 (1H, d, *J* 9, [6]CH), 4·95 (2H, s, [3]CH_2), 4·99 (2H, s, [1]CH_2). With picric acid it gave an adduct $C_8H_9NO_2,1{\cdot}5C_6H_3N_3O_7$, m.p. 126—127° (from ethanol).

From the steam distillation mother liquor the dimethylol (XXI) (0·26 g., 24%) was isolated.

1,3-*Dihydro*-5-*hydroxy*[3,4-b]*pyridine*.—The methoxypyridine (VII) (0·312 g.) was demethylated with sodium iodide (0·6 g.) in glacial acetic acid (8 ml.) on a steam-bath for 2 hr. The acetic acid was evaporated off, dilute aqueous sodium thiosulphate was added, and the solution was extracted first with ether (to remove the by-product 2,3-di(acetoxymethyl)-6-hydroxypyridine, m.p. 115—116°), and then with chloroform. Evaporation of the latter gave the *hydroxypyridine* [(I), (II)] (0·042 g., 14%), m.p. 230—232° (from ethanol) (Found: C, 61·1; H, 5·2; N, 10·1. $C_7H_7NO_2$ requires C, 61·3; H, 5·2; N, 10·2%).

1,3,4,5-*Tetrahydro*-4-*methyl*-5-*oxofuro*[3,4-b]*pyridine*.—The methoxy-compound (VII) (0·15 g.) rearranged to the *N*-methylpyridone when heated with methyl iodide (2 ml.) at 110° for 10 hr. The mixture was evaporated to dryness, and picric acid (0·15 g.) in ethanol was added to the residue. Concentration of the solution gave the *picrate* of the *N*-methylpyridone (VIII) (0·050 g., 13%), m.p. 156—158° (from ethanol) (Found: C, 44·2; H, 3·17; N, 14·5. $C_{14}H_{12}N_4O_9$ requires C, 44·2; H, 3·18; N, 14·7%). The base regenerated from the picrate was not crystalline; ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·76 (1H, d, *J* 10, [7]CH), 3·53 (1H, d, *J* 10, [6]CH), 5·00 (4H, s, [1]CH and [3]CH), 6·59 (3H, s, NMe).

In the u.v. spectral determinations the picrate was used.

1,3-*Dihydro*-5-*methoxythieno*[3,4-b]*pyridine*.—The hydrochloride of the di(chloromethyl) compound (XXVI) (6·4 g.), placed in the thimble of a Soxhlet extractor, was slowly (during *ca.* 1 hr.) introduced into a refluxing solution of ethanolic sodium sulphide (obtained by dissolving 3·3 g. of

[14] W. Koenigs and G. Koerner, *Ber.*, 1883, **16**, 2152; J. Diamant, *Monatsch.*, 1895, **16**, 760.

sodium in 100 ml. of ethanol, saturating one half of this solution with hydrogen sulphide at 0°, then combining the two halves and adding 200 ml. of ethanol). After a further brief period under reflux, the solution was cooled, filtered, and the filtrate was evaporated to dryness. The residue was steam-distilled, and the distillate was extracted with chloroform; evaporation of the latter gave the *cyclic sulphide* (IX) (2·1 g., 50%), m.p. 76—77° (from ethyl acetate–light petroleum) (Found: C, 57·7; H, 5·7; N, 8·2. C_8H_9NOS requires C, 57·5; H, 5·4; N, 8·4%). This compound slowly decomposes on storage, especially when damp; ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·62 (1H, d, *J* 9, [7]CH), 3·47 (1H, d, *J* 9, [6]CH), 5·87 (4H, s, [1]CH_2 and [3]CH_2), 6·13 (3H, s, OMe).

Extraction of the steam distillation mother liquor with ethyl acetate gave the 'dimeric' *cyclic disulphide* with a ten-membered ring (0·1 g., 3%), m.p. 240—241° (from ethyl acetate) [Found: C, 57·6; H, 5·4; N, 8·5%; *M* (mass spectrum), 334. Required C, H, and N as above; *M* for $(C_8H_9NOS)_2$, 334].

1,3-*Dihydro*-5-*hydroxythieno*[3,4-b]*pyridine*.— The methoxy-compound (IX) (0·20 g.) was heated with sodium iodide (0·405 g.) in acetic acid (5 ml.) on a steam-bath for 4 hr. The acid was evaporated off and the residue was treated with dilute aqueous sodium thiosulphate; the *hydroxypyridine* (III, IV) (0·174 g., 94%) was filtered off, m.p. 235—236° (decomp.) (from ethanol) (Found: C, 55·1; H, 4·7; N, 9·1. C_7H_7NOS requires C, 54·9; H, 4·6; N, 9·2%), ^{1}H n.m.r. spectrum: τ 2·62 (1H, d, *J* 10, [7]CH), 3·80 (1H, d, *J* 10, [6]CH), 6·03 (4H, s, [1]CH_2 and [3]CH_2).

1,3,4,5-*Tetrahydro*-4-*methyl*-5-*oxo*-*thieno*[3,4-b]*pyridine*.— The hydroxy-compound [(III), (IV)] (0·12 g.) in methanol (5 ml.) and an excess of ethereal diazomethane [15] were stirred at room temperature for 1 hr. The ether was evaporated off; by t.l.c. of the residue (on Kieselgel G, with ethyl acetate) the N-*methylpyridone* (X) (0·40 g., 30%) was separated, m.p. 100—102° (from ethyl acetate) (Found: C, 57·9; H, 5·5; N, 8·2. C_8H_9NOS requires C, 57·5; H, 5·4; N, 8·4%).

This compound was not obtained by the action of methyl iodide on the methoxy-compound (IX); under mild conditions *S*-methylation occurred, under more drastic ones the five-membered ring in the methylsulphonium ion was cleaved. The methoxy-compound (IX) (0·124 g.) when kept in a sealed tube with methyl iodide (2 ml.) at room temperature for 3 days gave 1,3-*dihydro*-5-*methoxy*-2-*methyl*-2H$^+$-*thieno*[3,4-b]*pyridinium iodide* (0·17 g., 50%), m.p. 128—130° (from methanol–light petroleum) (Found: C, 34·9; H, 4·1; N, 4·55. $C_9H_{12}INOS$ requires C, 35·0; H, 3·9; N, 4·3%).

1,3-*Dihydro*-5-*methoxythienol*[3,4-b]*pyridine* SS-*Dioxide*.—1,3-Dihydro-5-methoxythieno[3,4-b]pyridine (IX) (0·15 g.) in glacial acetic acid (9 ml.) was added slowly to stirred aqueous hydrogen peroxide (30%, 9 ml.), the temperature being kept below 10°. The mixture was stirred for 9 hr. at room temperature. Most of the solvent was evaporated off and saturated aqueous sodium carbonate was added to the residue; the solution was extracted with chloroform. Evaporation of the extract left the *cyclic sulphone* (XI) (0·15 g., 84%), m.p. 174—176° (decomp.) (from ethanol) [Found: C, 48·5; H, 4·3; N, 6·8%; *M* (mass spectrum), 199. $C_8H_9NO_3S$ requires C, 48·2; H, 4·5; N, 7·0%; *M*, 199], ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·51 (1H, d, *J* 9, [7]CH), 3·24 (1H, d, *J* 9, [6]CH), 5·64 (4H, s, [1]CH_2 and [3]CH_2), 6·09 (3H, s, OMe).

1,3-*Dihydro*-5-*hydroxythieno*[3,4-b]*pyridine* SS-*Dioxide*.— The methoxy-compound (XI) (0·90 g.) and 50% (w/v) hydrogen bromide in glacial acetic acid (1 ml.) were heated on a steam-bath for 3 hr. The solvent was evaporated off under reduced pressure and the residue was diluted with a little water; the mixture was evaporated to dryness in a vacuum desiccator. A little ethanol was added to the residue which upon trituration gave the *hydroxy-pyridine* [(V), (VI)] (0·54 g., 60%), m.p. <310° (from methanol) (Found: C, 45·9; H, 3·9; N, 7·6. $C_7H_7NO_3S$ requires C, 45·4; H, 3·8; N, 7·6%), ^{1}H n.m.r. spectrum [$(CD_3)_2SO$–D_2O]: τ 2·38 (1H, d, *J* 10, [7]CH), 3·39 (1H, d, [6]CH), 5·48 (2H, s, [3]CH_2), 5·58 (2H, s, [1]CH_2).

This compound was also obtained in *ca.* 50% yield by the oxidation of 1,3-dihydro-5-hydroxythieno[3,4-*b*]pyridine [(III), (IV)] with peracetic acid.

1,3,4,5-*Tetrahydro*-4-*methyl*-5-*oxo*-*thieno*[3,4-b]*pyridine* SS-*Dioxide*.—The methoxy-compound (XI) (0·300 g.) was treated with methyl iodide (1 ml.) at 110° for 6 hr. Ethyl acetate was added to the cool mixture which was then filtered; recrystallization of the precipitate gave the rearrangement product, the N-*methylpyridone* (XII) (0·10 g., 33%), which decomposed at 280° (Found: C, 48·1; H, 4·5; N, 6·9. $C_8H_9NO_3S$ requires C, 48·2; H, 4·5; N, 7·0%). From the filtrate starting material (0·15 g.) was recovered.

2,3-*Di*(*methoxymethyl*)-6-*methoxypyridine*.—The di(chloromethyl) compound (XXVI) (1·6 g.) was heated under reflux with sodium methoxide solution (from 0·5 g. sodium and 50 ml. of methanol) for 30 min. The solvent was evaporated off and water was added to the residue; the mixture was then extracted with chloroform. Evaporation of the extract gave the *di*(*methoxymethyl*) *compound* (XVII) (1·23 g., 80%), b.p. 60°/4 mm. (Found: C, 60·6; H, 7·9; N, 7·3. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·32 (1H, d, *J* 10, [4]CH, 3·27 (1H, d, [5]CH), 5·46 (2H, s, 2-CH_2), 5·51 (2H, s, 3-CH_2), 6·08 (3H, s, 6-OMe), 6·60 (3H, s, aliph. OMe), 6·62 (3H, s, aliph. OMe).

2,3-*Di*(*methoxymethyl*)-6-*hydroxypyridine*.—The methoxy-compound (XVII) (0·108 g.) was heated with sodium iodide (0·20 g.) in acetic acid (2 ml.) on a steam-bath for 2 hr. The acid was evaporated off and the residue was diluted with dilute aqueous sodium thiosulphate; the mixture was extracted with chloroform. The extract was evaporated to dryness and the residue was sublimed; the sublimate was warmed with aqueous sodium carbonate and then extracted with chloroform. Evaporation of the extract gave the hydroxy-pyridine [(XIII), (XIV)] (0·050 g., 25%), m.p. 89—91° (from benzene–light petroleum) (Found: C, 59·2; H, 7·0; N, 7·6. $C_9H_{13}NO_3$ requires C, 59·0; H, 7·15; N, 7·6%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·63 (1H, d, *J* 10, [4]CH), 3·56 (1H, d, [5]CH), 5·56 (2H, s, 6-CH_2), 5·81 (2H, s, 5-CH_2), 6·53 (3H, s, OMe), 6·68 (3H, s, OMe).

When heating on the steam-bath was continued for 4 hr. 2,3-di(acetoxymethyl)-6-hydroxypyridine, m.p. 115—116°, was isolated. Attempts to prepare the *N*-methylpyridone (XIV; NMe in place of NH) failed.

2,3-*Di*(*methylthiomethyl*)-6-*methoxypyridine*.—A solution of sodium methoxide (from 0·5 g. of sodium and 20 ml. of anhydrous methanol) was saturated with methanethiol, and, at room temperature, the di(chloromethyl) compound (XXVI) (0·104 g.) was added to it. The reaction set in at once, and the mixture was left for 30 min. and then filtered. The precipitate was washed with chloroform, and the

[15] Ref. 40 of preceding paper.

combined filtrate and washings were evaporated to dryness. Water (5 ml.) was added to the residue and the solution was extracted with chloroform. Evaporation of the latter gave the *di(methylthiomethyl) compound* (XVIII) (0·98 g., 86%), b.p. 80°/0·5 mm. (Found: C, 52·2; H, 6·9; N, 6·1. $C_{10}H_{15}NOS_2$ requires C, 52·4; H, 6·6; N, 6·1%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·48 (1H, d, *J* 9, [4]CH), 3·36 (1H, d, [5]CH), 6·05 (3H, s, OMe), 6·11 (2H, s, 6-CH_2), 6·22 (2H, s, 5-CH_2), 7·81 (3H, s, SMe), 7·94 (3H, s, SMe).

2,3-*Di(methylthiomethyl)*-6-*hydroxypyridine*.— The methoxy-pyridine (XVIII) (0·20 g.) was demethylated when heated with sodium iodide (0·40 g.) in glacial acetic acid (3 ml.) at 60° for 4 hr. Work-up as for the cyclic sulphide (III, IV) gave the *hydroxy-pyridine* [(XV), (XVI)] (0·12 g., 64%), m.p. 152—153° (from ethyl acetate) (Found: C, 50·5; H, 6·3; N, 6·4. $C_9H_{13}NOS_2$ requires C, 50·2; H, 6·1; N, 6·5%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·57 (1H, d, *J* 10, [4]CH), 3·53 (1H, d, [5]CH), 5·85 (1H, s, labile H), 6·25 (2H, s, 2-CH_2), 6·42 (2H, s, 3-CH_2), 7·85 (3H, s, SMe), 7·94 (3H, s, SMe).

1,6-*Dihydro*-1-*methyl*-2,3-*di(methylthiomethyl)*-6-*oxo-pyridine*.—The hydroxy-pyridine [(XV), (XVI)] (0·10 g.) was treated with ethereal diazomethane by the method used above for the *N*-methylation of the cyclic sulphide [(III), (IV)], followed by the same working-up procedure, the *N*-methylpyridone (XIX) (0·040 g., 39%) being obtained, m.p. 75—77° (from ethyl acetate–light petroleum) (Found: C, 52·8; H, 6·5; N, 6·0. $C_{10}H_{15}NOS_2$ requires C, 52·4; H, 6·6; N, 6·1%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·75 (1H, d, *J* 10, [4]CH), 3·50 (1H, d, [5]CH), 6·22 (2H, s, 2-CH_2), 6·32 (3H, s, NMe), 6·45 (2H, s, 3-CH_2), 7·83 (3H, s, SMe), 7·93 (3H, s, SMe).

6-*Methoxy*-2,3-*dimethylpyridine*.—The di(chloromethyl) compound (XXVI) (1·7 g.) was stirred with zinc (4·4 g.) and glacial acetic acid (30 ml.) for 6 hr. The solution was filtered and the filtrate was made alkaline with aqueous potassium hydroxide and extracted with chloroform. After evaporation of the extract the liquid mixture was subjected to preparative t.l.c. with ethyl acetate–light petroleum (3 : 1) and Kieselgel G. This gave 6-methoxy-2,3-dimethylpyridine (XX) (0·344 g., 33%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·78 (1H, d, *J* 9, [4]CH), 3·57 (1H, d, *J* 9, [5]CH), 6·14 (3H, s, OMe), 7·64 (3H, s, 2-Me), 7·85 (3H, s, 3-Me). With picric acid it formed a *picrate*, m.p. 139—140° (from ethanol) (Found: C, 45·9; H, 4·0; N, 15·2. $C_{14}H_{14}N_4O_8$ requires C, 45·9; H, 3·8; N, 15·3%).

Also isolated were an acetoxymethyl derivative (0·186 g., 12%), b.p. 55°/0·5 mm., and a hydroxymethyl derivative (0·91 g., 7%), b.p. 145°/0·3 mm., m.p. 39—40°; presumably 3-*acetoxymethyl*-6-*methoxy*-2-*methylpyridine* (Found: C, 61·9; H, 7·1; N, 7·4. $C_{10}H_{13}NO_3$ requires C, 61·5; H, 6·7; N, 7·2%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·57 (1H, d, *J* 9, [4]CH), 3·52 (1H, d, [5]CH), 5·00 (2H, s, 3-CH_2), 6·15 (3H, s, OMe), 7·58 (3H, s, 2-Me), 7·95 (3H, s, ester Me); and 3-*hydroxymethyl*-6-*methoxy*-2-*methylpyridine* (Found: C, 62·3; H, 7·4; N, 8·7. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%), ^{1}H n.m.r. spectrum ($CDCl_3$): τ 2·53 (1H, d, *J* 9, [4]CH), 3·49 (1H, d, [5]CH), 5·40 (2H, s, 3-CH_2), 6·09 (3H, s, OMe), 7·55 (3H, s, 2-Me), 8·14 (1H, s, OH).

Spectra and Ionization Constants.—These were determined as in the preceding paper.[1] In u.v. spectroscopy, where a picrate was used as the specimen for measurement there was always an aliquot of picric acid in the solution in the reference beam.

Tautomeric Equilibrium Constants.—These were estimated from the u.v. absorption curves as in the preceding paper. However, many of the curves obtained in this work show some vibrational structure, especially for dioxan solutions, and *N*-methylation sometimes changes the relative intensity distribution among the sub-bands. In such cases, weighted mean absorption wavelengths, rather than $\lambda_{max.}$ values, were used to assess the *N*-methylation shift in the pyridone absorption (this is taken into account in the selection of '$\lambda_{far\ side}$').

In one case, compounds (II) and (VIII), the asymmetry of the band near 310 mμ was not the same for pyridone and *N*-methylpyridone (picrate) in water, there being a significant absorption 'deficit' for (II) at $\lambda_{max.,\ ol}$. A correction was made to the results obtained in ethanol and dioxan, assuming the relative absorption 'deficit' (*i.e.* the deviation from equal band asymmetry) to be the same as in water.

The K_T values near unity reported in this work are expected to be correct to well within a factor of 1·2, but as the pyridol content decreases the margin of uncertainty increases (and more so than in the preceding [1] work, because the *N*-methylpyridone spectra here have slight inflexions near $\lambda_{max.,\ ol}$, in addition to the more pronounced ones near '$\lambda_{far\ side}$').

RESULTS AND DISCUSSION

U.v. Spectra, Tautomeric Equilibrium Constants, and Ionization Constants.—The u.v. spectra of compounds (I)—(XIX) are given in Table 1, and the tautomeric equilibrium constants [pyridol]/[pyridone] (K_T) estimated from them are in Table 2.

The variation in K_T is comparatively small among the cyclic compounds (I)—(VI), but in dioxan K_T occurs in a conveniently measurable range. The cyclic ether [(I), (II)] and the cyclic sulphone [(V), (VI)] have almost equal K_T values; in dioxan this is only 2·7 times the K_T of the cyclic sulphide [(III), (IV)], but in ethanol the increase in K_T on going from cyclic sulphide to cyclic ether or sulphone is greater. Cyclization has a considerable effect in raising the pyridol content, as is shown by comparison of the cyclic sulphide with the dimethylthio-compound [(XV), (XVI)], and, even more so, by that between cyclic ether [(I), (II)] and dimethoxy-compound [(XIII), (XIV)].

These results are explained by the same effects as were observed in the preceding work.[1] An assessment of the relative contributions of the various effects is possible by analysis of the ionization constants listed in Table 3.

The basic ionizations of the methoxypyridines are uncomplicated, entailing no major change in bond structure, and their base strengths afford quite a sensitive measure of the electron-withdrawing effects of the substituents. The base strengths of the dimethylthio-compound (XVIII) and the dimethoxy-compound (XVII) are almost the same, showing that the electron-withdrawing effect of SMe here is almost as great as that of OMe. [Rather remarkably, the difference in p*K* between the dihydroxy-compound (XXI) and the dimethoxy-compound (XVII) is greater than that between (XVIII) and (XVII).]

TABLE 1

U.v. spectra [a]

Solvent	Water		99% Ethanol		Dioxan	
Compd.	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
[(I), (II)]	311, 227	7240, 6980	315, 230; *284*	5550, 6440; *2420*	*348*, *332*, *325*, 318, *240*, 226; 288	*1160*, *2630*, *2820*, 3000, *2860*, 4550; 4420
(VIII) [b]	312, 229	6950, 5970	319, 233	6480, 6800	*344*, 326+320	*3350*, 5910
(VII)	*c*		283, 221	6000, 7700	285, 224	6250, 6370
[(III), (IV)]	311, 229	7340, 6320	*334*, 318+313, 232	*3490*, 6080, 6530	*346*, 329, *324*, 317, 234; *286*	*1960*, 4120, *4320*, 4540, 5650; *2940*
(X)	314, 232	7070, 6070	*338*, 318, 233	*2800*, 5950, 6360	*343*, 328, 318, 237	*4040*, 6910, 6840, 7560
(IX)	284, 220	5470, 5500	284, 223	5420, 5600	285, 226	5680, 5370
[(V), (VI)]	306, 231	6660, 6730	*338*, *323*, 310, 232; *284*	*1720*, *4180*, 4860, 5610; *2850*	*345*, *329*, *322*, 315, 234; 287	*910*, *2130*, *2300*, 2600, 3100; 3630
(XII)	309, 232	6760, 6760	*336*, 316+311, 234	*2770*, 6020, 6870	*343*, 325, 316, 236	*2960*, 5780, 5880, 6840
(XI)	282, 221	6500, 6740	281, 222	5770, 7570	282, 226	5950, 5640
[(XIII), (XIV)]	303, 233	6540, 3030	*c*		313, 238	5040, 9000
(XVII)	*c*		*c*		277, 227	4950, 8490
[(XV), (XVI)]	*c*		317, 240	7100, 11,200	*344*, 322, 242; *285*	*2600*, 5010, 10,600, *2330*
(XIX)	*c*		320, 242	7110, 11,000	326, 245	5290, 9140
(XVIII)	*c*		284, 228	6340, 10,500	285, 228	6150, 11,200

[a] Inflexions in italics; very weak inflexions not recorded unless of special importance. [b] Picrate used (see Experimental section). In dioxan the peak near 240 mμ was not accessible. [c] Not measured.

TABLE 2

K_T = [Pyridol]/[Pyridone] for compounds [(I), (II)], [(III), (IV)], [(V), (VI)], [(XIII), (XIV)], and [(XV), (XVI)] in various solvents, estimated by u.v. spectroscopy [a]

Compound	Str. [b]	Dioxan	EtOH	H_2O
[(I), (II)]	O	1·08	0·16	<0·05
[(III), (IV)]	S	0·43	<0·05	<0·05
[(V), (VI)]	SO_2	1·09	0·20	<0·05
[(XIII), (XIV)]	$(MeO-)_2$	<0·1 [c]	*d*	<0·05
[(XV), (XVI)]	$(MeS-)_2$	0·1	<0·05	*d*

[a] For approximations made, see Experimental section in this and the preceding paper. <0·05 means no detectable amount of pyridol. [b] Distinguishing structural feature. [c] See text. [d] No measurement (amount of pyridol expected to be undetectable).

'Cyclization' of (XVIII) to (IX), and of (XVII) to (VII), is base-weakening, even though one of the electron-withdrawing atoms is lost. This is clearly due to ring-strain-induced electron withdrawal. There is little strain in the five-membered sulphide ring, and the drop in the pK_a value is only 0·38, but the strain in the oxygen ring is more substantial, and is reflected by a lowering of the basicity on cyclization by 1 pK unit.

The difference in K_T between the cyclic sulphide [(III), (IV)] and the cyclic sulphone [(V), (VI)] must be due to the stronger electron withdrawal by the SO_2 group. A quantitative measure of the difference in electron-withdrawal between the sulphide and the sulphone ring is given by the difference in the basicities of the corresponding methoxy-compounds (IX) and (XI), 2·15 pK units. The corresponding difference between cyclic sulphide (IX) and cyclic ether (VII) is only one third of this value (0·7); *i.e.* the difference in

TABLE 3

Ionization constants of compounds (I) to (XXI) in water at 20° (pK_a and average deviation [a])

		2-Hydroxypyridines		*N*-Methyl-2-pyridones		2-Methoxypyridines	
Str. [b]	Compd. [c]	Acidic	Basic	Compd.	Basic	Compd.	Basic
O	[(I), (II)]	9·85 ± 0·05	0·50 ± 0·03	(VIII)	0·01 ± 0·02	(VII)	1·56 ± 0·02
S	[(III), (IV)]	10·68 ± 0·03	0·69 ± 0·06	(X)	0·26 ± 0·04	(IX)	2·26 ± 0·04
SO_2	[(V), (VI)]	8·99 ± 0·03	−0·40 ± 0·04	(XII)	−0·94 ± 0·04	(XI)	0·09 ± 0·04
$(MeO-)_2$	[(XIII), (XIV)]	11·06 ± 0·04	0·55 ± 0·03			(XVII)	2·55 ± 0·05
$(MeS-)_2$	[(XV), XVI)]	11·19 ± 0·04	0·76 ± 0·05	(XIX)	0·24 ± 0·04	(XVIII)	2·64 ± 0·04
$(HO-)_2$						(XXI)	2·98 ± 0·04
$(H-)_2$						(XX)	4·86 ± 0·03
Parent Compd. [d]		11·70 ± 0·03	0·77 ± 0·02		0·32 ± 0·02		3·28 ± 0·06

[a] In 9 determinations. [b] Distinguishing structural feature. [c] The pK_a values are, in effect, those of the (predominant) pyridone tautomers. [d] Data for unsubstituted 2-hydroxy-[16] and 2-methoxy-[17] pyridine, and 1-methyl-2-pyridone [17] are included for reference.

electron withdrawal between five-membered SO_2 and S ring is about three times as great as that between O and S ring. Thus, insofar as electron-withdrawal by the O ring causes K_T to be higher for the hydroxy-pyridine [(I), (II)] than for [(III), (IV)], K_T for the cyclic ether [(I), (II)] should be *ca.* one third of the way between K_T for the cyclic sulphide [(III), (IV)] and that of the cyclic sulphone [(V), (VI)] (and closer to the former).

Actually [(I), (II)] and [(V), (VI)] have roughly equal K_T values. Thus about two thirds of the difference in K_T between cyclic ether [(I), (II)] and cyclic sulphide [(III), (IV)] must be due to something other than greater electron withdrawal by the O ring. This other (and more important) effect is clearly the relief of ring strain that results from the conversion of the pyridone (II) into the pyridol (I). [It is true that this argument is based on pK values in aqueous solution, whereas the observed K_T values are those for ethanolic and dioxan solutions. However, neither ring-strain-induced electron withdrawal nor the inductive effect of the SO_2 group, which arises mainly from the double positive charge on the (well sheltered) S atom, are expected to be influenced by the solvent in a major way.]

The ionization constants of the pyridones with annelated rings also provide evidence of the operation of a second (here less conspicuous) effect, in addition to ring-strain-induced electron withdrawal. In uncomplicated comparisons the base strengths of pyridones are *ca.* half as sensitive to polar effects as are those of the methoxypyridines. *E.g.* comparing cyclic sulphide and cyclic sulphone, which do not differ in ring strain, ΔpK among the *N*-methylpyridones (X) and (XII) (1·2) is 55% of that among the methoxypyridines (IX) and (XI) (2·15). Comparing cyclic sulphone with unsubstituted parent compound, the difference among the *N*-methyl-2-pyridones (1·26) is 40% of that among the 2-methoxypyridines (3·19).

When compounds differing in ring strain are compared this correlation breaks down. Among the sulphides, ' cyclization ' of the methoxypyridine (XVIII) to (IX) lowers the pK_a by 0·38 units, but ' cyclization ' of the pyridones (XVI) and (XIX) to (IV) and (X) scarcely changes the base strength. Among the ethers, ' cyclization ' of the 2-methoxy-pyridine (XVII) to (VII) lowers the base strength by 1 pK unit, but ' cyclization ' of the pyridone (XIV) to (II) leaves it unchanged. Thus the base-weakening ring-strain-induced electron withdrawal is counterbalanced in the bicyclic pyridones by a base-strengthening effect, *i.e.* by the reduction in ring strain on cation formation.

For the pyridones the base strength differences between cyclic ether and cyclic sulphide {0·19 for the pair [(I), (II)]—[(III), (IV)], 0·25 for the pair (VIII)—(X)}, are only 17—21% of the differences between cyclic sulphide and cyclic sulphone {1·09 for the pair [(III), (IV)]—[(V), (VI)], 1·20 for the pair (X)—(XII)}. These percentages are lower than the corresponding one for the ΔpK values among the corresponding methoxy-compounds (VII), (IX), and (XI), which is 33%. This shows that cation formation by the pyridonoid cyclic ethers (II) and (VIII) occurs more readily than expected, *i.e.* it is accompanied by a greater reduction in ring strain than cation formation by the pyridonoid cyclic sulphides (IV) and (X). (The ring strain in cyclic sulphide and cyclic sulphone being the same, the difference in their pK values affords a yard-stick against which to compare other differences.)

The *acidic* ionization constants of the pyridones in uncomplicated comparisons show *ca.* 85% of the sensitivity to polar effects exhibited by the base strengths of the corresponding methoxy-compounds. Comparing cyclic sulphone and cyclic sulphide, *i.e.* [(III), (IV)]—[(V), (VI)] with (IX)—(XI), the ratio is 80%; comparing sulphone [(V), (VI)] with unsubstituted 2-hydroxypyridine,[16] and (XI) with 2-methoxypyridine,[17] it is 85%.

By contrast, ' cyclization ' of the hydroxypyridines, [(XIII), (XIV)] to [(I), (II)], and [(XV), (XVI)] to [(III), (IV)], raises the acid strengths by *greater* amounts than the corresponding ' cyclizations ' [(XVII) to (VII), and (XVIII) to (IX)] lower the base strengths of the corresponding methoxypyridines (the proportionality factors being 1·2—1·3, instead of *ca.* 0·85). Thus a special acid strengthening effect is operative in the bicyclic 2-pyridones, in addition to ring-strain-induced electron withdrawal (which is already operative in the methoxypyridines). This effect is clearly the reduction in ring strain on anion formation by the bicyclic 2-pyridones (II) and (IV).

Similarly, the difference in acid strength between cyclic ether [(I), (II)] and cyclic sulphide [(III), (IV)] is greater than the difference in base strength between the corresponding methoxy-pyridines (VII) and (IX) (proportionality factor 1·2). In fact, the acidic pK of [(I), (II)] is half-way between those of cyclic sulphide [(III), (IV)] and cyclic sulphone [(V), (VI)], whereas among the methoxypyridines the cyclic ether (VII) shows only a third of the base-weakening effect found for the cyclic sulphone (XI), when both are compared with the cyclic sulphide (IX). (See above, concerning the ' yard-stick ' for comparisons.) This shows that anion formation by the (pyridonoid) cyclic ether (II) occurs more readily than expected: it is accompanied by a greater reduction in ring strain than is that by the sulphide (IV).

In summary, in the ionization constants examined in this work exactly the same effects are found to be operative as are manifest for 2,3-dihydro-6-hydroxy-4-methylfuro[2,3-*b*]pyridine and 3,4-dihydro-7-hydroxy-5-methylpyrano[2,3-*b*]pyridine, and their derivatives,[1] though the relative prominence of the effects differs somewhat for the two sets of compounds (for both acidic and basic ionization constants.)

The 5,6-dimethylthio-compound [(XV), (XVI)] has a greater tendency to exist in the pyridol form than has

[16] Ref. 46 of preceding paper.
[17] Ref. 4 of preceding paper.

the dimethoxy-compound [(XIII), (XIV)] even though SMe here is slightly less electron-withdrawing than OMe; this is contrary to the fairly general rule that electron withdrawal by substituents favours the pyridol form (see, however, introduction and following paper). This may be due to some steric hindrance in the pyridone (XVI), or may be connected with the high inductomeric polarizability of the S atom. The ionization constants are uninformative on this point. [As far as the electrostatic effect of the substituent is concerned the dimethylthio-compounds (XV), (XVI), (XVIII), and (XIX), and the dimethoxy-compounds (XIII), (XIV), and (XVII), are the best 'open-chain' counterparts for the cyclic sulphides (III), (IV), (IX), and (X), and for the cyclic ethers (I), (II), and (VII), respectively, that can be devised, but insofar as other effects are important there are no compounds that even approach being ideal open-chain counterparts.]

The Solid-state I.r. Spectra.—All the hydroxypyridines examined in this work show very intense carbonyl stretching bands in the i.r. region, ranging in frequency from 1650 cm.$^{-1}$ for the dimethoxy-compound (XIV) to 1688 cm.$^{-1}$ for the cyclic ether (II). Like those examined in the preceding work,[1] they are all in the pyridone form in the solid state. 1-Methyl-2-pyridone has a much higher dipole moment than 2-methoxypyridine,[17] and strong dipole–dipole forces can generally be expected to favour the pyridone over the pyridol form in the solid state. (Intermolecular hydrogen-bonding is expected to be strong, normally, in both solid 2-pyridones and solid 2-pyridols.)

All the 2-methoxypyridines examined here show an intense i.r. band in the range 1608—1600 cm.$^{-1}$; it is due to the aromatic skeletal stretching vibration numbered 8a.[18]

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[18] Refs. 54 and 55 of preceding paper.