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Mass Spectrometry of Onium Compounds. XXVI.[1] Ionisation Potentials in Structure Analysis of Gaseous Aminopyridine 1-Oxides

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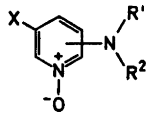
The isomeric aminopyridine 1-oxides, their methylamino and acetylamino analogues exist predominantly in the amine form in the gas phase in the mass spectrometer. The conclusion is based on ionisation potential data, and fragmentation characteristics, which have been compared with such data for *N*,*N*-dimethylamino and *N*,*N*-acetylmethylaminopyridine 1-oxides and 1-methoxypyridin-onimines.

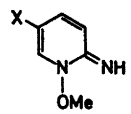
From ionisation potential measurements by electron impact in the mass spectrometer we have in recent reports [2,3] shown that the potentially tautomeric hydroxy-, mercapto-, and amino-pyridines in the gas phase exist predominantly in the enol and amine forms, respectively. The preference for the amino form in the gas phase has very recently been conclusively shown by a structural study of 2-aminopyridine by means of its microwave spectrum.[4] In this report we deal with the 1-oxides of the isomeric aminopyridines and their acylamino analogues. For comparative purposes in the interpretation of ionisation potential (IP) data corresponding *N*-methylamino analogues are included in the study. The IP data obtained are given in Table 1. The ionisation efficiency curves were recorded as previously described [5] and are interpreted by the semilog plot method.[6]

The influence of a substituent on the ease of ionisation depends on the nature of other substituents as well as on the ring system and relative position.[7] Generally an electron releasing substituent decreases the IP.[8] Thus the IP value for pyridine 1-oxide,[9] measured to 8.78

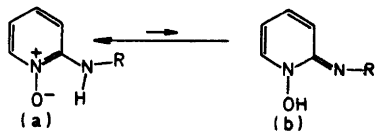
Table 1. Ionisation potentials for aminopyridine 1-oxides.



Comp.	Isomer	X	R^1	R^2	IP ± 0.05 eV
1	2	H	H	H	8.04
2	3	H	H	H	8.21
3	4	H	H	H	7.67
4	2	H	H	Me	7.67
5	3	H	H	Me	7.97
6	4	H	H	Me	7.45
7	2	H	Me	Me	7.62
8	3	H	Me	Me	7.85
9	4	H	Me	Me	7.32
10	2	H	H	Ac	8.05
11	3	H	H	Ac	8.40
12	4	H	H	Ac	7.76
13	2	H	Me	Ac	7.77
14	3	H	Me	Ac	8.18
15	4	H	Me	Ac	7.52
16	2	Cl	H	H	7.98
17	2	Cl	H	Me	7.61



(18) X = H, IP = 7.46 eV
(19) X = Cl, IP = 7.40 eV



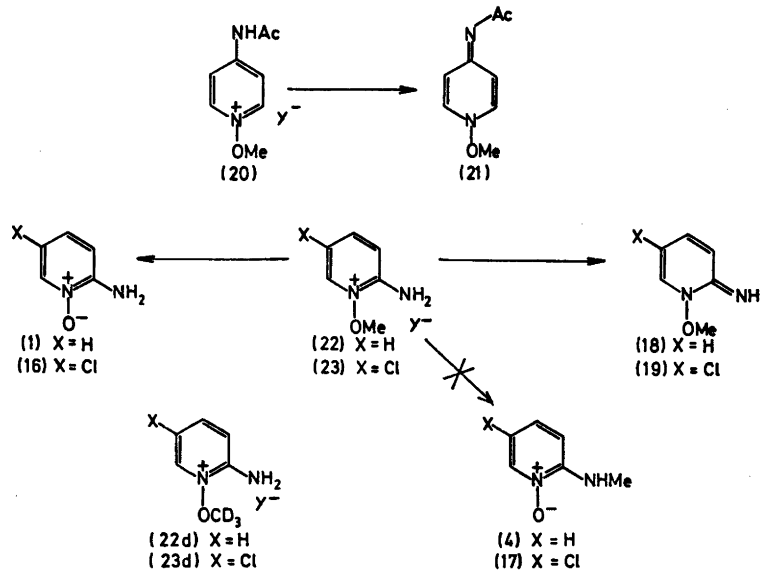
Scheme 1.

eV in the present work, is lowered on amine substitution (Table 1). Methylation of the amino group in aniline decreases the IP.[10] This effect was found to be very similar in all three aminopyridine isomers.[3]

The primary and secondary 2- and 4-aminopyridine 1-oxides can partially exist as the tautomeric 1-hydroxypyridin-2- and -4-onimines (Scheme 1). The *N*,*N*-dimethylaminopyridine 1-oxides, however, cannot tautomerise and must evaporate as such. The IP values (*7*–*9*) are increased by 0.2 eV from the 2- to the 3-isomer but decreased by 0.5 eV from the 3- to the 4-isomer. The same changes are seen for the primary amines (*1*–*3*) and for the secondary amines (*4*–*6*). The same pattern is evident also by comparison of the data for the 2-analogue series (*1*,*4*,*7*) with the 3- and 4-series; monomethylation has decreased IP with 0.2–0.3 eV relative to the parent amine and dimethylation has further reduced this value by 0.1 eV.

On prototropic shifts the 3-amines (*2*, *5*) can form the corresponding zwitterionic 1-hydroxy derivatives. The charge separation introduced will reduce the volatility compared to that of the non-charged amine form. On energetic grounds structures with charge separation should be disfavoured in the gas phase because at 10^{-6} Torr the charges cannot be dispersed by solvation or other intermolecular interactions. The 3-amines (*2*, *5*) must therefore be assumed present in the gas phase in the amine form. Consequently it follows from the systematic IP differences discussed above that the 2- and 4-isomers exist in the amine form in the gas phase. Furthermore the same IP pattern is seen for the acetyl derivatives (*10*–*12*) on comparison with the *N*-methyl analogues (*13*–*15*), and hence the same conclusion is reached. The amino form has also been found to be preferred by 2- and 4-aminopyridine 1-oxides and acylamino analogues in solid state and solution.[11,12]

Support for the above conclusion was to be sought in IP measurements of analogues locked in the onimine form by *O*-methylation. The 1-methoxy analogues, however, were only available as pyridinium salts with weak nucleophilic anions as *p*-toluenesulfonate or perchlorate anion. In the mass spectrometer these reactive molecules were largely decomposed, transmethylated on the nitrogen or demethylated. The cation from 4-acetamido-1-methoxypyridinium perchlorate (*20*, Scheme 2), however, appeared



Scheme 2.

to evaporate after proton loss as 1-methoxypyridin-4-*N*-acetylonimine (*21*). Unfortunately the relative molecular ion peak intensity was only of the order 1 % which with our present technique is too weak for obtaining reproducible IP data.

Similar studies for the *ortho* isomers also proved difficult. Thus the spectra from 1-methoxy-2-aminopyridinium toluene-*p*-sulfonate contain a signal for the mass number (*m/e* 124) of 1-methoxypyridin-2-onimine (*18*). Demethylation, however, is a competitive reaction to proton abstraction and evaporation of the onimine. Pyrolytic demethylation (*m/e* 110) was suggested by variable signal intensities. This deduction was confirmed by the appearance potential (AP) (8.02 eV) which was the same as IP for (*1*). The relative intensities for the signals corresponding to deprotonation and demethylation were increased from 1:8 to 1:2 on changing the anion from toluene-*p*-sulfonate to perchlorate. AP for the *m/e* 124 species was determined to 7.46 eV as compared to 7.67 eV for the isomeric *N*-methylpyridine 1-oxide (*4*). The experimental difficulties encountered and the closeness of these values made any conclusion uncertain. Support was sought in other derivatives. For this purpose the 5-chloro analogues (*17*) and (*23*) were prepared. A chlorine atom has little effect on the IP of an aromatic system.[8,9] This is also seen in the present work by comparison of the data (Table 1) for (*1*) and the 5-chloro analogue (*16*). IP for the *N*-oxide (*17*) was 7.61 eV as compared to 7.40 eV for the gaseous species from the 1-methoxy analogue (*23*). The difference is the same as between (*4*) and (*22*).

Any pyrolytic transmethylation in the salt (*22*) before evaporation (*22*→*4*) would affect AP for the *m/e* 124 species. Formation of (*4*) could occur by intra- or intermolecular reactions from (*22*). The latter possibility was investigated by deuteriation. The methyl group in (*22*) was perdeuteriated (*22d*) and mixed with equimolar quantities of the non-deuteriated 5-chloro analogue (*23*). The chlorine atom in (*23*) serves to mark the pyridine nucleus in the non-deuterated compound for identification after any transmethylation reaction. The chlorine atom is assumed not to significantly affect the activity. This assumption is supported by the very similar nature of the spectra from (*22*) and (*23*). A homogeneous mixture was strived at by evaporation in the instrument of a common methanol solution. In the case of intermolecular transmethylation four isotopically different molecular ion signals should be obtained.[18] The spectra, however, contained two such signals which exclude an intermolecular process. The conclusion was experimentally confirmed by mixing the deuteriated 5-chloro compound (*23d*) with (*22*). Comparative examination of the fragmentation spectra from the isomeric 2-methylaminopyridine 1-oxide (*4*) and 1-methoxypyrid-2-onimine (*18*) also excludes any significant intramolecular transmethylation. Thus $[M-OH]^+$ is the base peak in the spectrum of (*4*), other characteristic peaks being $[M-O]^+$ 18 % and $[M]^{+\cdot}$ 23 %. In the spectrum from (*22*) the molecular ion $[M]^{+\cdot}$ is the most intense peak, the relative intensities of the $[M-O]^+$ and $[M-OH]^+$ being 10 – 15 %. Similar differences were found in the spectra of the chlorine analogues (*16*, *23*). The gaseous molecules from (*22*) and (*23*) after proton loss are therefore assigned the respective onimine structures (*18*, *19*).

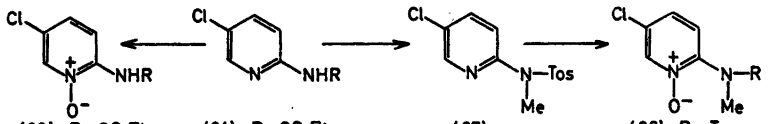
The IP effect of a methyl group relative to that of a hydrogen atom on a phenolic oxygen in simple systems is of the order 0.2 – 0.3 eV.[2,8] Using this value in conjunction with the IP's for (*18*) and (*19*) the IP's for the onimine forms of (*1*) and (*16*) are estimated to about 7.7 eV. The observed values are about 8.0 eV. The results are thus in agreement with the above concluded amino formulation.

From the larger dipole moments it is known that pyridine *N*-oxides are much more strongly polarised than corresponding pyridines.[14,15] High polarisation in the ground state and mesomeric stabilisation from the *N*-oxide group after electron removal are expected to be important factors in the observed decrease in IP for *N*-oxides relative to the corresponding pyridines.[3]

Characteristic primary fragments for the *N*-oxides and base peaks are recorded in Table 3. The mass spectra of heteroaromatic *N*-oxides are characterised by either the $[M-O]^+$ or $[M-OH]^+$ fragment, the latter being the more important when a hydrogen is readily extractable from an α-substituent.[16,17] All *N*-oxides show the $[M-O]^+$ fragment. The 2-isomers are of special interest for the study of the $[M-OH]^+$ fragment. In the 2-amino (*1*) the molecular ion is the base peak. The 2-

Table 2. Characteristic fragment intensities in the spectra of pyridine 1-oxides.

Substituents	$[M]^{+\cdot}$	% I	$[M-O]^{+}$	% I	$[M-OH]^{+}$	% I	$[M-Me]^{+}$	% I	$[M-CH_2CO]^{+\cdot}$	% I	$[M-Ac]^{+}$	% I	Base peak *m/e*
2-NH_2	110	*100*	94	26	93	11	–	–	–	–	–	–	
3-NH_2	»	88	»	27	»	10	–	–	–	–	–	–	54
4-NH_2	»	*100*	»	23	»	10	–	–	–	–	–	–	
2-NHMe	124	23	108	18	107	*100*	108	2	–	–	–	–	
3-NHMe	»	*100*	»	26	»	38	»	2	–	–	–	–	
4-NHMe	»	*100*	»	15	»	30	»	9	–	–	–	–	
2-NMe_2	138	8	122	20	121	*100*	123	7	–	–	–	–	
3-NMe_2	»	98	»	16	»	*100*	»	2	–	–	–	–	
4-NMe_2	»	*100*	»	33	»	38	»	5	–	–	–	–	
2-NHAc	152	25	136	9	135	–	137	5	110	*100*	109	–	110
3-NHAc	»	38	»	4	»	–	»	2	»	46	»	1	43
4-NHAc	»	9	»	45	»	–	»	4	»	24	»	2	94
2-NMeAc	166	7	150	5	149	–	151	–	124	33	123	1	107
3-NMeAc	»	*100*	»	16	»	–	»	2	»	36	»	61	
4-NMeAc	»	31	»	21	»	–	»	2	»	90	»	21	43
2-NH_2-5-Cl	144	*100*	128	69	127	7	–	–					
2-NHMe-5-Cl	158	30	142	45	141	*100*	143	3					



Scheme 3.

methylamino and 2-dimethylamino derivatives (*4,7*), however, have $[M-OH]^+$ as base peak, and the molecular ion has relatively low intensity. This suggests that $[M-OH]^+$ is preferentially formed by hydrogen abstraction from the carbon of the *N*-methyl group rather than from the electronegative amino nitrogen atom.

The primary fragmentation of the acetyl derivatives are characterised by the ready cleavage of the acetyl group as such or by expulsion as ketene preceeded or followed by *N*-oxide fragmentations.

The new compounds used in these studies were synthesised by modifications of established routes. The flow sheet for the 5-chloro derivatives is shown in Scheme 3. Amino groups must be deactivated by an acyl group for selective peroxide oxidation of the pyridine nitrogen atom such as in the carbamate (*24*). The acyl group is hydrolytically removed after oxidation. Methylation of the amino group in the carbamate (*24*) was unsatisfactory but proceeded readily in the sulfonamide (*25*) to form (*27*) which was oxidised and hydrolysed to (*17*).

EXPERIMENTAL

The mass spectra were recorded on an AEI MS902 mass spectrometer attached to an AEI DS30 data system. The electron energy was 70 eV and the ionising current 100 μA. During recording of the ionisation efficiency curves, repeller was at cage potential and the ionising current was 20 μA. Xenon was the reference compound. The IE-curves were interpreted by the semilog-plot method. The recorded IP values are the average of three determinations, the deviation being ± 0.05 eV. The compounds were introduced by the heated direct insertion probe at a source temperature of 220 °C.

Syntheses

2-Amino- (1) [18] and *3-aminopyridine 1-oxide (2)* [12,19] were synthesised according to literature.

4-Aminopyridine 1-oxide (3). 4-Nitropyridine 1-oxide (7.0 g, 0.05 mol) in ethanol (150 ml) was hydrogenated at 0.38 MPa* over 10 % palladium on charcoal for 1 – 2 h (until the uptake of hydrogen had almost ceased). The catalyst was then removed, the solution evaporated and the residual amine acetylated by refluxing for 1 h in a solution of acetic anhydride (3 ml) and ethyl methyl ketone (15 ml). The solid which crystallised from the cold solution was recrystallised from ethyl acetate-ethanol (1:1). 4-Acetamidopyridine 1-oxide (*12*) was thus obtained as needles, m.p. 264 – 265 °C (Lit. 260 – 261 °C).[12]

(*12*) thus obtained (1.5 g, 0.01 mol) was heated in 3 M HCl (12 ml) for 3 h, the reaction mixture evaporated and the residual title compound as HCl-salt crystallised from ethanol; yield 0.9 g (84 %), m.p. 181 – 183 °C.[20]

2-Methylamino- (4) [18] and *4-methylamino-pyridine 1-oxide (6)* [11] were synthesised according to literature.

3-Methylaminopyridine 1-oxides (5). 3-Acetylmethylaminopyridine 1-oxide (1.7 g, 0.01 mol) was dissolved in 3 M HCl (15 ml) and the solution refluxed for 4 h. Evaporation left the title compound as HCl-salt which was recrystallised twice from ethanol/ether; yield 1.2 g (74 %), m.p. 165 °C (Found: C 44.92; H 5.68. Calc. for $C_8H_{10}N_2O_2$: C 45.00; H 5.62).

2-Dimethylamino- (7) [18] and *4-dimethylaminopyridine 1-oxide (9)* [11] were prepared according to literature.

3-Dimethylaminopyridine 1-oxide (8). 3-Bromopyridine 1-oxide[21] (1.8 g, 0.01 mol) and 30 % aqueous dimethylamine (15 ml) were heated together at 155 °C for 48 h in a sealed glass tube. Potassium carbonate (1 g) was added to the solution before evaporation; the dried residue was extracted with ethanol, the ethanol solution heated with charcoal before evaporation of the filtrate. The residual material (1.1 g, 80 %) was crystallised from ethanol/ether in needles, m.p. 41 °C. (Found: C 60.85; H 7.51. Calc. for $C_7H_{10}N_2O$; C 60.86; H 7.24).

2-Acetamido- (10) [12] *3-acetamidopyridine 1-oxide (11)* [4,19] were prepared according to literature; the synthesis of *4-acetamidopyridine 1-oxide (12)* is described under (*3*) above.

2-Acetylmethylamino- (13) [18] and *4-acetylmethylaminopyridine 1-oxide (15)* [12] were prepared according to literature.

3-Acetylmethylaminopyridine 1-oxide (14). 3-Acetylmethylaminopyridine[22] (1.5 g, 0.01 mol) and 35 % hydrogen peroxide (1.8 ml) in acetic acid (6 ml) were heated at 70 – 80 °C for 24 h. The solution was then evaporated at reduced pressure, the residue dissolved in chloroform (20 ml) and treated with anhydrous potassium carbonate. After filtration and evaporation the

* 1 MPa ≈ 10.2 kg/cm².

residual material (1.5 g, 90 %) was recrystallised from ethanol/ethyl acetate, m.p. 163 – 165 °C. (Found: C 58.15; H 5.85. Calc for $C_8H_{10}N_2O_2$: C 57.83; H 6.02).

2-Amino-1-methoxypyridinium perchlorate (22) was prepared from its toluene-*p*-sulfonate.[18]

2-Amino-5-chloro-1-methoxypyridinium perchlorate (23). 2-Amino-5-chloropyridine 1-oxide (7.2 g, 0.05 mol) and methyl toluene-*p*-sulfonate (9.3 g, 0.05 mol) were heated together at 100 °C overnight to produce 1-methoxy-pyridinium toluene-*p*-sulfonate which after crystallisation from ethanol/ethyl acetate or ethanol/ether had m.p. 137 °C; yield 14.2 g (86 %).

The tosylate thus prepared (1.7 g, 0.005 mol) in ethanol (3 ml) was mixed with 60 % perchloric acid (0.8 ml) when the desired perchlorate was precipitated (1.1 g, 85 %); needles from ethanol, m.p. 100 °C (Found: C 28.12; H 3.10. Calc. for $C_6H_8Cl_2N_2O_6$: C 27.80; H 3.12). The 1-trideuteriomethoxypyridinium analogues (*22d*) and (*23d*) were prepared as above by *O*-methylation of the respective *N*-oxides using trideuteriomethyl toluene-*p*-sulfonate as the alkylating agent. Exchange of anion was again carried out in ethanolic solution by addition of perchloric acid.

4-Acetylamino-1-methoxypyridinium perchlorate (20) [12] was prepared by the above procedures.

2-Ethoxycarbonylamino-5-chloropyridine 1-oxide (24). Ethyl chloroformate (14 ml) was added dropwise to a stirred and cooled (0 °C) solution of 2-amino-5-chloropyridine (15.5 g) in pyridine (60 ml) and the solution left at room temperature. Water was added after 18 h and the precipitated material (68 %) crystallised from ethanol, m.p. 178 °C.

A solution of 2-ethoxycarbonylamino-5-chloropyridine thus obtained (20.1 g, 0.1 mol) and 30 % hydrogen peroxide (15 ml) in acetic acid (32 ml) was heated at 70 – 80 °C for 24 h. The solution was then evaporated at reduced pressure, the residue dissolved in chloroform (150 ml) and the solution heated and shaken with anhydrous potassium carbonate (10 g) for 10 min. Filtration and evaporation of the filtrate left the crude 1-oxide which crystallised in needles from ethanol; yield 21 g (97 %). (Found: C 44.48; H 4.18. Calc. for $C_8H_9ClN_2O_3$: C 44.34; H 4.15).

2-Amino-5-chloropyridine 1-oxide (16). 2-Ethoxycarbonylamino-5-chloropyridine 1-oxide (10.0 g, 0.05 mol) was heated under reflux in conc. HCl (20 ml) for 24 h. Evaporation and crystallisation of the residual material from ethanol furnished the title compound as HCl salt; yield 5.7 g (71 %), m.p. 163 °C. (Found: C 33.15; H 3.31. Calc. for $C_5H_5ClN_2O.HCl$: C 33.21; H 3.63).

The title compound was generated from its salt by addition of one equivalent of sodium ethoxide solution to a solution of the HCl-salt as above prepared. Removal of the salt, evaporation of the ethanol solution and recrystallisation of the residue from ethyl acetate/ethanol furnished the title compound, m.p. 193 °C. (Found: C 41.68; H 3.67. Calc. for $C_5H_5ClN_2O$: C 41.52; H 3.46).

5-Chloro-2-p-toluenesulfonamidopyridine (25). A solution of 2-amino-5-chloropyridine (12.9 g, 0.1 mol) and *p*-toluenesulfonyl chloride (22.5 g, 0.15 mol) in pyridine (25 ml) was heated on a steam-bath for 5 h. The precipitate formed on pouring the solution into water was recrystallised from benzene; m.p. 174 – 175 °C, yield 28.1 g (quantitative). (Found: C 51.07; H 4.29. Calc. for $C_{12}H_{11}ClN_2O_2S$: C 50.95; H 3.89).

5-Chloro-2-N-methyl-p-toluenesulfonamidopyridine (27). A solution of dimethyl sulfate (12.6 g, 0.1 mol) in acetone (50 ml) was added dropwise over 30 min to a refluxing mixture of 5-chloro-2-*p*-toluenesulfonamidopyridine (28.2 g, 0.1 mol) and anhydrous potassium carbonate (28.0 g, 0.2 mol) in acetone (500 ml). The heating was continued for another 3 h. The cold reaction mixture was then filtered and the filtrate evaporated. The oily product was next dissolved in chloroform (150 ml), the solution extracted with 10 % NaOH solution to remove any material not alkylated, and the organic solution washed and dried. Evaporation and recrystallisation from ethanol gave colourless prisms; m.p. 68 – 70 °C, yield 26.0 g (88 %). (Found: C 52.82; H 4.84. Calc. for $C_{13}H_{13}ClN_2O_2S$: C 52.61; H 4.38).

5-Chloro-2-methylaminopyridine 1-oxide (17). 5-Chloro-2-*N*-methyl-*p*-sulfonamidopyridine (14.8 g, 0.05 mol) and 30 % hydrogen peroxide (8 ml) in acetic acid (30 ml) were heated at 70 – 80 °C for 24 h. The solution was then evaporated and the residual oxide (*28*) subjected to hydrolysis by heating on a steam bath for 3 h in 80 % sulfuric acid (25 ml). The cold solution was diluted with water (20 ml) and made alkaline with 0.91 M ammonia before extraction with chloroform. The chloroform solution was washed, dried and evaporated and the residue crystallised from ethanol/ether; yield 6.4 g (81 %), m.p. 153 °C. (Found: C 45.64; H 4.47. Calc. for $C_6H_7ClN_2O$: C 45.42; H 4.41).

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