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# **Stable Pyridine Anhydro-bases**

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Twelve 2- and 4-methylenedihydropyridines containing strongly electron-withdrawing groups on the methylene carbon atoms have been prepared. One anomalous reaction was encountered. The anhydro-bases are protonated in acid solution (in two cases also in water) on the exocyclic carbon atom forming pyridinium ions.

PYRIDINE anhydro-bases, which are formed by deprotonation of quaternary 2- and 4-alkylpyridinium salts, are too unstable to be isolated 1 unless they contain two phenyl groups (I and III;  $R^1 = R^2 = Ph$ )<sup>2</sup> or electron-

<sup>1</sup> E. N. Shaw, in "Pyridine and Its Derivatives, Part II," ed. E. Klingsberg, Interscience, London, 1961, p. 36. <sup>2</sup> A. E. Tschitschibabin and S. W. Benewolenskaja, *Ber.*,

1928, 61, 547.

<sup>3</sup> E. Koenigs, K. Köhler, and K. Blindow, Ber., 1925, 58, 933. 4 A. R. Katritzky, H. Z. Kucharska, and J. D. Rowe, J. Chem. Soc., 1965, 3093.

<sup>5</sup> S. Golding, A. R. Katritzky, and H. Z. Kucharska, J. Chem. Soc., 1965, 3090.

withdrawing substituents in the side-chain, e.g., the p-nitropenyl-,3 benzoyl-,4 and phenylsulphonyl-methylenedihydropyridines <sup>5</sup> (I and III;  $R^1 = H$ ,  $R^2 =$ p-NO<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>, COPh, SO<sub>2</sub>Ph, respectively). The nitrogen analogues 6-8 of sesquifulvalene, e.g., (V), represent

<sup>6</sup> (a) D. N. Kurzanov and N. K. Baranetskaya, Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk, 1958, 362; (b) ibid., 1961, 1703.

<sup>7</sup> (a) G. V. Boyd and L. M. Jackman, J. Chem. Soc., 1963, 548;
(b) G. V. Boyd and N. Singer, J. Chem. Soc. (B), 1966, 1017.
<sup>8</sup> J. A. Berson, E. M. Evleth, and Z. Hamlet, J. Amer. Chem. Soc., 1965, 87, 2887.

special types of stabilised anhydro-base. Carbanions derived from  $\alpha$ -methylene ketones, malononitrile, and cyclopentadiene react with 1-substituted pyridinium salts to yield anhydro-bases,<sup>9</sup> addition being followed by dehydrogenation. The products were assigned the 4-rather than the equally reasonable 2-methylenedihydropyridine structure; this orientation has been estab-

atives of reactive methylene compounds. We have used this method to prepare a number of anhydro-bases containing strongly electron-withdrawing groups.

Reactants and products are listed in Tables 1 and 2. Four pyridinium salts and four methylene compounds (malononitrile, ethyl cyanoacetate, cyanoacetamide, and ethyl malonate) were employed. Of the sixteen possible

TABLE 12-Methylene-1,2-dihydropyridines

	Methylene			Yield	$\mathbf{F}\mathbf{c}$	ound (S	%)		$\operatorname{Req}$	uired	(%)
Pyridinium salt	compound	Product	М. р.	(%)	С	н	N	Formula	С	н	N
1-Methyl-2-phenoxy-, iodide	Malonitrile	(Ia) <i>a</i>	203·5—204·5° b	66	<b>69</b> ∙0	4•4	26.71	$C_9H_7N_3$	<b>68</b> ·79	4.46	26.75
2-Bromo-1-methyl-, per- chlorate	Ethyl cyano- acetate	(Ib) °	127·5—128 <sup>d</sup>	24.5	64.66	5.86	13.82	$C_{11}H_{12}N_2O_2$	<b>64</b> ·70	5.88	13.73
2-Chloro-1,4,6-trimethyl-, perchlorate	, Malononitrile	(IIa) ª	201—202 °	34	71.13	5.96	<b>22·90</b>	$\mathrm{C}_{11}\mathrm{H}_{11}\mathrm{N}_{3}$	71.35	5.95	22.70
,, ,, ,,	Ethyl cyano- acetate	(IIb) ª	120—121 <sup>d</sup>	<b>4</b> 3·5	<b>67</b> ·01	6.78	11.88	$C_{13}H_{16}N_2O_2$	67.24	<b>6</b> ∙90	12.06
,, ,,	Cyanoacetamide	(VI) <sup>a</sup>	162-164 °	44	74.69	7.23	18.10	$C_{10}H_{12}N_2$	74.97	7.55	$17.48^{f}$
<sup>a</sup> Yellow needles. <sup>b</sup>	From ethanol. • 1	Reddish-br	own needles. d	From	water.	• Fro	m aque	ous ethanol.	f Mol.	. wt.:	found,

	TABLE 2
4-]	Methylene-1,4-dihydropyridines

	Methylene			Yield	Fc	und (	%)		Req	uired	(%)
Pyridinium salt	compound	Product	М. р.	(%)	С	н	Ν	Formula	С	н	Ν
1-Methyl-4-phenoxy-,	Malononitrile	(IIIa) ª	237—239° b	63	68.59	4.43	26.99	$C_9H_7N_3$	<b>68</b> ·79	<b>4·46</b>	26.75
10 II II	Ethyl cyano- acetate	(IIIb) <i>ª</i>	179—179·5 °	37	64.79	5.96	13.92	$\mathrm{C_{11}H_{12}N_2O_2}$	<b>64</b> ·70	5.88	13.73
,, ,,	Cyanoacetamide	(IIIc) ª	222—223 (decomp.) <sup>d</sup>	<b>56</b>	61.69	5.05	23.79	$\mathrm{C_9H_9N_3O}$	61.71	5.14	24.00
	Ethyl malonate	(IIId) ª	96·5-97 °	<b>24</b>	62.24	6.76	5.84	C <sub>13</sub> H <sub>17</sub> NO	62.14	6.82	5.57
4-Methoxy-1,2,6-tri- methyl-, perchlorate	Malononitrile	(IVa) <sup>a</sup>	320—324 <sup>f</sup>	71	71.26	6.03	22.79	$C_{11}^{13}H_{11}^{1}N_{3}$	71.35	5.95	22.70
,, ,, ,,	Ethyl cyano- acetate	(IVb) a	215—217 °	76	67.54	6.85	12.09	$\mathrm{C_{13}H_{16}N_2O_2}$	67.24	<b>6</b> ∙90	12.06
,.	Cyanoacetamide	(IVc) <sup><i>a</i></sup>	277—278 (decomp.) <sup>f</sup>	39.5	<b>64</b> ·98	6.66	20.60	$C_{11}H_{13}N_{3}O$	65.02	<b>6</b> ∙40	20.69

<sup>a</sup> Yellow needles. <sup>b</sup> From ethanol. <sup>c</sup> From aqueous ethanol. <sup>d</sup> From water. <sup>e</sup> From ethanol-light petroleum (b. p. 60-80°). <sup>f</sup> From aqueous acetic acid.

lished  ${}^{6b,8}$  only in the case of the 4-cyclopentadienylidenedihydropyridines (V; R = Me or  $CH_2Ph$ ). Such com-



pounds can be synthesised unambiguously <sup>7,8</sup> by condensing quaternary pyridinium salts carrying suitable substituents in the 2- or the 4-position with metal deriv-

products, four (Ic), (Id), (IId), and (IVd) could not be obtained. The condensation of 2-chloro-1,4,6-trimethylpyridinium perchlorate with cyanoacetamide took an unexpected course, yielding instead of (IIc) a bright yellow base with composition and spectroscopic properties  $[v_{max}, 2180 \text{ cm}.^{-1} (CN), \text{ lack of absorption in the}$ primary amide region] corresponding to the cyanomethylene compound (VI). Its p.m.r. spectrum (deuteriochloroform) exhibited six singlets at  $\tau$  3.23, 4.29, 6.57, 6.85, 7.74, and 7.95 of relative areas 1:1:1:3:3:3:3. The peaks at  $\tau$  3.23 and 4.29 are assigned to the 3- and 5-ring protons respectively. The signal at  $\tau$  6.57 arises from  $H_{\alpha}$  which is shielded, being near the axis of the nitrile triple bond. One of the ring protons resonates at considerably lower field (3.23) than the other. This is very probably H(3) which is deshielded by the magnetic anisotropy of the nitrile bond as it is rigidly held perpendicular to that bond. The signal of this proton incidentally provides evidence for the geometrical configuration <sup>9</sup> F. Kröhnke, K. Ellegast, and E. Bertram, Annalen, 1956, 600, 176.

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shown in (VI), in which the nitrile group is away from the N-methyl group, since for the alternative (CN and H interchanged) one would expect to find two shielded protons  $[H_{\alpha} \text{ and } H(3)]$  and one olefinic proton, H(5). The three methyl signals at  $\tau$  6.85, 7.74, and 7.95 are assigned to the N-, 6-, and 4-methyl groups respectively, the order of increasing field being that of increasing distance from the nitrogen atom. The loss of the carbamoyl moiety is surprising in view of the formation of the normal amides in the 4-series; we intend to ininvestigate this reaction further.

### TABLE 3

Electronic spectra of 2-methylene-1,2-dihydropyridines

	$\lambda_{\max}$ (m $\mu$ ) (log $\varepsilon$	in parentheses)
Cpd.	In water	In 50% sulphuric acid
(Ia)	294 (4.09), 368 (4.05)	262 (3.80), 270 * (3.66)
(Ib)	294 (3.56), 368 (4.09)	268 * (3.96), 274 (3.98)
(IIa)	<b>290</b> (3·96), 365 (4·20)	267 (3.83)
(IIb)	<b>294</b> (3.56), 368 (4.09)	268 * (3.96), 274 (3.98)
(VI)	268 (3·96), 272 * (3·94)	268 (3·96), 272 * (3·95)
	<ul> <li>Inflexion.</li> </ul>	

### TABLE 4

Electronic spectra of 4-methylene-1,4-dihydropyridines

	$\lambda_{max.}$ (m $\mu$ ) (log	$\varepsilon$ in parentheses)				
Cpd.	In water	In 50% sulphuric acid				
(IIIa)	231 * (3.94), 354 (4.57)	258 (3.85)				
(IIIb)	227 (4.24), 357 (4.65)	262 - 268 (3.65)				
(IIIc)	229 (4·22), 360 (4·61)	262 (3.65), 270 * (3.59)				
(IIId)	226(3.86), 262(3.74),	224 - 226 (3.90), 261 (3.74),				
. ,	268 * (3.70), 370 (3.82)	268 * (3.68)				
(IVa)	$242 - 246 (3 \cdot 80), 357 (4 \cdot 59)$	277-282 (3.84)				
(IVb)	231 (4.30), 352 (4.67)	275-283 (3.90)				
(IVc)	235(4.20), 355(4.64)	275 - 283 (3.88)				
* Inflexion						

The electronic absorption spectra of the yellow anhydrobases and their conjugate acids are summarised in Tables 3 and 4. The 2-methylenedihydropyridines absorb maximally at 290—294 and 365—368 mµ; these bands appear at *ca.* 230 and 352—360 mµ (with enhanced extinction coefficients) in the spectra of the 4-methylene compounds. The slight hypsochromic shift in the position of the long-wave absorption band in passing from an  $\alpha$ -anhydro-base to the corresponding  $\gamma$ -compound is generally observed in methylenedihydropyridines.<sup>4,5,10</sup> The spectra of the colourless conjugate acids show only one strong absorption band near 270 mµ owing to protonation on the exocyclic carbon atom to yield pyridinium salts (cf. VII). The structures of the protonated

<sup>10</sup> E. M. Evleth, J. A. Berson, and S. L. Manatt, J. Amer. Chem. Soc., 1965, 87, 2908.

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species were substantiated by comparing their spectra with those of equimolecular mixture of pyridinium salts and the appropriate methylene compounds, in each case virtual identity being observed; thus the ethoxycarbonylcyanomethylene-bases (IIb) and (IVb) in acid solution and a mixture of 1,2,4,6-tetramethylpyridinium perchlorate and ethyl cyanoacetate all absorb maximally at 274 m $\mu$ . Further evidence for the position of protonation was obtained from the p.m.r. spectrum of compound (VI) in trifluoroacetic acid solution, which shows the presence of a methylene group (VII;  $X = CF_3 \cdot CO_2$ ). The spectrum contains six singlets in the ratio 1:1:2:3:3:3. The methyl signals appear at  $\tau$ 5.67, 7.10, and 7.29, which are close to the chemical shifts of 1-, 2-, and 4-methyl protons in alkylpyridinium salts.<sup>11</sup> The 3- and 5-protons are in the aromatic region ( $\tau 2.03$ and 2.18) and the methylene signal appears at  $\tau$  5.48.

2-Benzylidene-1,2-dihydro-1-methylpyridine (I;  $R^1 =$ H,  $R^2 = Ph$ ) exists in aqueous solution in equilibrium with 2-benzyl-1-methylpyridinium hydroxide; as the solution becomes more dilute the hydroxide form predominates.<sup>12</sup> We found evidence for the existence of pyridinium hydroxides in only two cases. The mononitrile (VI) appears to exist solely as the hydroxide (VII; X = OH) in dilute aqueous solution since it dissolves in water to give a colourless solution the spectrum of which is identical with that of a solution of the base in dilute sulphuric acid. The diethoxycarbonyl compound (IIId) is partly protonated in aqueous solution since absorption bands at 262 and 268 m $\mu$ , characteristic of the pyridinium ion, as well as the anhydro-base band at  $370 \text{ m}\mu$  are observed. The spectra of aqueous solutions of the remaining ten compounds gave no evidence of the presence of pyridinium hydroxides; two strongly electron-withdrawing groups evidently stabilise the anhydro-bases to such an extent that the formation of hydroxides is completely suppressed.

### EXPERIMENTAL

The anhydro-bases were prepared by adding a pyridinium salt (0.01M) to an ethanolic solution (35 ml.) of sodium ethoxide (1 mol.) and a methylene compound (1 mol.) and refluxing the mixture for 30 min.—1 hr. The product separated on cooling or on concentrating the solution. When the pyridinium salt contained a halogen substituent 2 mol. of sodium ethoxide were employed.

We thank Mr. A. W. Ellis for the n.m.r. spectra.

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<sup>11</sup> J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 1961, 859. <sup>12</sup> H. Decker, *Ber.*, 1905, **38**, 2493; see also J. G. Aston and P. A. Lasselle, *J. Amer. Chem. Soc.*, 1934, **56**, 426.