Reduction of Some 1-Substituted Pyridinium Salts

By **R. Morrin Acheson** * and **Giuseppe Paglietti,** Department of Biochemistry, South Parks Road, Oxford OX1 3QU

Reductions by sodium borohydride and dithionite of four 1-substituted pyridinium salts gave in all cases mixtures of mainly 1,2- and 1,4-dihydropyridines which were analysed by n.m.r. spectroscopy. Palladium–charcoal hydrogenation catalyst isomerised certain reduced pyridines.

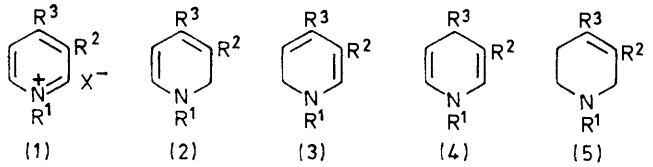
DIHYDROPYRIDINES continue to attract interest,[1] and in connection with other work [2] we have prepared a number of these compounds by reduction of pyridinium salts. Reduction with sodium borohydride and dithionite usually gives 1,2- and 1,4-dihydropyridines, respectively, although mixtures are formed in some cases.[1] The structures and purity of our dihydropyridines have been determined from their n.m.r. spectra. This is the most sensitive method of analysing mixtures of reduced pyridines, and as our experiments have shown that several literature preparations for single compounds in fact give mixtures, our results are presented.

Reduction by sodium borohydride of the 1-phenylnicotinamide derivative (1a) in methanolic sodium hydroxide gives a 2.5 : 1 mixture of the 1,2- (2a) and 1,6- (3a) dihydro-compounds. When water is used as solvent these dihydropyridines are formed in 1 : 1 ratio along with traces of the 1,4-dihydro-derivative (4a), and

[1] U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1; R. E. Lyle and P. S. Anderson, *Adv. Heterocyclic Chem.*, 1966, **6**, 46.

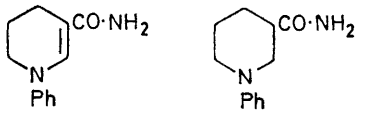
[2] R. M. Acheson, G. Paglietti, *J.C.S. Chem. Comm.*, 1973, 665; R. M. Acheson, G. Paglietti, and P. A. Tasker, *J.C.S. Perkin I*, 1974, 2496.

adding more borohydride to the filtrate from these gave the tetrahydropyridine (5a), presumably formed by further reduction of the 1,2-dihydropyridine (2a). Use of aqueous sodium hydroxide as reaction medium gave compounds (2a), (3a), (5a), and also (4a) in almost



(1) (2) (3) (4) (5)

	R^1	R^2	R^3	X
a;	Ph	$CO{\cdot}NH_2$	H	Cl
b;	Me	CN	H	I
c;	Me	$CO{\cdot}NH_2$	H	$MeSO_4$
d;	$PhCH_2$	H	Me	Br



(6) (7)

equal proportions. These mixtures could not be separated owing to the instability of their constituents, and it is noteworthy that the m.p.s of the 1,2-, 1,4-, and 1,6-dihydropyridines and these mixtures are very similar. Reduction of the 3-cyano-1-methylpyridinium iodide (1b) with sodium borohydride under similar conditions to those of Schenker and Druey [3] and Kinoshito and Kawasaki [4] gave a mixture which contained the 1,2-dihydropyridine (3b) and the tetrahydropyridine (5b), as reported, but also the 1,4-dihydropyridine (4b). These compounds were separated moderately well by high vacuum distillation. Reduction by sodium borohydride of the pyridinium methyl sulphate (1c) gave a substance of the same m.p. (76—77°) and u.v. spectrum as reported [5] for a pure dihydropyridine. The n.m.r. spectrum showed that the substance was in fact a mixture of the dihydropyridines (3c) and (4c) in a 2.5 : 1 ratio. A reinterpretation of their u.v. spectrum confirms this conclusion and it has not been possible to isolate (3c) in a pure state. The proportions of the isomers formed in this reduction are solvent-dependent, as has been noted [1] in other cases. The 1,2-dihydropyridine (2d) from the reduction of (1d) with borohydride is very reactive but can be handled at 0 °C under nitrogen and has been converted into a dihydroazocine.[2] The presence of an electron-attracting group at position 3 greatly stabilises this type of compound, presumably by resonance interaction with the lone electron pair on the nitrogen atom.

* For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[3] K. Schenker and J. Druey, *Helv. Chim. Acta*, 1959, **42**, 1960.
[4] N. Kinoshito and T. Kawasaki, *J. Pharm. Soc. Japan*, 1963, **83**, 123.

Hydrogenation of both compounds (3a) and (4a) afforded the tetrahydropyridine (6), the resonance-stabilised enamine system being unaffected. However, (2a) with 1 mol. equiv. of hydrogen gave compounds (5a), (6), and (7) in the ratio 1 : 1.45 : 1.6; more vigorous conditions yielded only (6) and (7). Attempted hydrogenation of the tetrahydropyridine (5a) caused partial isomerisation to the more conjugated isomer (6), a type of reaction noted before,[6] and the formation of the piperidine (7) (ratio 1 : 1.3). In the hydrogenation of (2a) it is not clear if the 3,4-double bond moves into the 2,3-position before or after reduction of the other double bond. Thermal isomerisations of 1,2- to 1,4-dihydropyridine do not appear to have been observed, but trimethyl 4*H*- and 2*H*-quinolizine-1,2,3-tricarboxylates can be regarded as examples of these types of pyridines and do exist in thermal equilibrium.[7]

Reduction by alkaline sodium dithionite of the 1-methylpyridinium salt (1c) gave a substance with the properties described by Karrer and Blumer [8] and confirmed by Hutton and Westheimer,[9] who identified the compound as the 1,4-dihydropyridine (4c). Our n.m.r. spectra show that 10% of the isomer (3c) is present. This would not have been detected in the earlier n.m.r. studies, but its presence accounts for the variability of the u.v. spectra of the sample of the '1,4-dihydro' compound, as the 1,2-isomers are relatively unstable. Similar reductions of the salts (1a and b) gave relatively pure samples of the 1,4-dihydropyridines (4a and b).

EXPERIMENTAL

The instruments employed have been described.[2] N.m.r. spectra were recorded at 60 MHz. All analyses for new compounds were within accepted limits for C, H, and N and are available in Supplementary Publication No. SUP 21590 (5 pp.),* which also contains the u.v., i.r., and mass spectral data. Solvents were removed *in vacuo* by use of rotatory evaporators. Borohydride reductions were effected under nitrogen with vigorous stirring. Mixtures were analysed by n.m.r. spectroscopy (see Table).

3-Carbamoyl-1-phenylpyridinium Chloride (1a).[10]—Nicotinamide (48.8 g) and 2,4-dinitrochlorobenzene (80.8 g) were heated on a steam-bath for 2 h; the product was dissolved in hot methanol (200 ml) and aniline (44 ml) was added. After refluxing for 45 min the solvent was removed and the residue treated with water (200 ml), filtered, and extracted with chloroform. The aqueous phase was evaporated to dryness, and the residue was dissolved in the minimum amount of methanol; the solution at 0 °C deposited the salt (1a), further quantities being precipitated by ether [total 52.9 g, m.p. 242—243.5° (lit.,[10] 236—238°)].

Reduction of 3-Carbamoyl-1-phenylpyridinium Chloride (1a).—(i) Sodium borohydride (2.4 g) was added in small portions to the salt (1a) (14.1 g) in methanol (50 ml) with

[5] W. Trauber and P. Karrer, *Helv. Chim. Acta*, 1958, **41**, 2066.
[6] R. E. Lyle and S. E. Mallett, *Ann. New York Acad. Sci.*, 1967, **145**, 83.
[7] R. M. Acheson, S. J. Hodgson, and R. G. M. Wright, unpublished observation.
[8] P. Karrer and F. Blumer, *Helv. Chim. Acta*, 1947, **30**, 1157.
[9] R. F. Hutton and F. H. Westheimer, *Tetrahedron*, 1958, **3**, 73.
[10] *Cf.* H. Lettre, W. Haede, and E. Ruhbaum, *Annalen*, 1953, **579**, 123.

aqueous 2N-sodium hydroxide (20 ml) at 0—5 °C. After 10 min *3-carbamoyl-1,2-dihydro-1-phenylpyridine* (2a) (85 g) was filtered off; yellow plates (from MeOH), m.p. 138—140°. The mother liquors from (2a) gave the 1,6-isomer (3a) as yellow prisms (from MeOH) (3.4 g), m.p. 133—135°.

(ii) Sodium borohydride (0.5 g) in water (50 ml) at 0 °C was added to the salt (1a) (5.0 g) in water (100 ml), cooled with ice, during 10 min. After stirring for 1 h the precipitate (2.55 g) was collected, and gave yellow prismatic needles (from MeOH), m.p. 136—138°, containing (2a) and (3a) (1 : 1 ratio) with traces of (4a). The reaction mixture filtrate was stirred with sodium borohydride (0.5 g) near pyridine (4b) was also prepared as described [4] and had the same n.m.r. spectrum as in the Table.

Reduction of 3-Carbamoyl-1-methylpyridinium Salts.—These reactions were effected as for the 1-phenyl analogue (1a). Procedure (i) with (1c) gave a 2.3 : 1 ratio of (3c) to (4c); use of the corresponding chloride or iodide at 0—10 °C and −10 to 0 °C gave a ratio of *ca.* 1.4 : 1. Procedure (ii) (*cf.* ref. 5) gave a 38% yield of a 1 : 1 mixture of (3c) and (4c), having the u.v. spectrum reported [5] which was considered [5] to be due to (3c) alone; when 2-ethoxyethanol or propan-1-ol was used as partial solvent [*cf.* (i)] the product ratio was *ca.* 1 : 1.6. Reduction of (1c) with dithionite as

60 MHz ^{1}H N.m.r. spectra (τ values; J in Hz; Me_4Si as internal standard)

Compound	Solvent	Proton assignments
(1d)	D_2O	1-C_6H_5·CH_2, 2.3—2.6m; 1-C_6H_5·CH_2, 4.13s; 2,6-H_2, 1.08d; 3,5-H_2, 2.00d; 4-Me, 7.23; $J_{2,3}$ 6
(2a)	$(CD_3)_2SO$	Ar-H, 6-H, and $CONH_2$, 2.5—3.2m; 2-H_2, 5.50s; 4-H, 3.10d;[a] 5-H, 4.85dd;[a] $J_{4,5}$ 8.3, $J_{5,6}$ 6
(2d)	$CDCl_3$	1-C_6H_5·CH_2, 2.72s; 1-C_6H_5·CH_2, 6.07s; 2-H_2, 6.30m; 3-H, 5.22br, m; 4-Me, 8.36br; 5-H, 5.37dd (J 7 and 1.5); 6-H, 3.92d
(3a)	$(CD_3)_2SO$	Ar-H, 2.6—3.0m; 2-H, 2.41s; 3-$CONH_2$, 3.17s, br; 4-H; 3.60dt,[b,c] 5-H, 4.68dt,[b] 6-H_2, 5.65dd,[c] $J_{4,5}$ 9, $J_{4,6}$ 1.8, $J_{5,6}$ 4.8
(3b)	$CDCl_3$	1-Me, 7.22; 2-H, 3.36; 4-H, 4.28dq; 5-H, 5.1dt; 6-H_2, 5.96q; $J_{4,5}$ 9, $J_{5,6}$ 4, $J_{2,4} \simeq J_{4,6} \simeq 2$
(3c)[d]	$CDCl_3$	1-Me, 7.21; 2-H, 2.85d; 3-$CONH_2$, 4.4br; 4-H, 3.93m; 5-H, 5.05dt; 6-H_2, 5.97dd; $J_{4,5}$ 9, $J_{5,6}$ 4, $J_{2,4} \simeq J_{4,6} \simeq 2$
(4a)	$CDCl_3$	Ar-H, 2.7—3.1m; 2-H, 2.55d; 3-$CONH_2$, 4.26s, br; 4-H_2, 6.87dd; 5-H, 5.13dt; 6-H, 3.75m; $J_{4,5}$ 3, $J_{5,6}$ 9, 1,3-couplings, J *ca.* 1—2
(4b)	$CDCl_3$	1-Me, 7.12; 2-H, 3.58, 4-H_2, 6.96m; 5-H, 5.39dt; 6-H, 4.37dt; $J_{4,5}$ 4, $J_{4,6}$ 1—2, $J_{5,6}$ 8
(4c)	$CDCl_3$	1-Me, 7.12; 2-H, 3.10d; 3-$CONH_2$, 3.75br; 4-H_2, 6.96m; 5-H, 5.33dt; 6-H, 4.33dd; $J_{4,5}$ 4, $J_{4,6}$ *ca.* 1.5, $J_{5,6}$ 8
(5a)	$(CD_3)_2SO$	Ar-H and $CONH_2$, 2.6—3.4m; 2-H_2, 6.18d[e] (J *ca.* 2); 4-H, 3.3m;[e] 5-H_2, 7.5—8.0m;[f] 6-H_2, 6.72t (J 6)
(5b)	$CDCl_3$	1-Me, 7.70; 2-H_2, 7.03m;[g] 4-H, 3.50m;[g] 5,6-H_4, 7.5—7.9m
(6)	$CDCl_3$	Ar-H, 2.4—3.1m; 2-H, 2.24; 3-$CONH_2$, 3.6br; 4-H_2 and 5-H_2, 7.4—8.3m; 6-H_2, 6.3—6.8m[h]
(7)	$CDCl_3$	Ar-H, 2.5—3.5m; 3-$CONH_2$, 4.0br;[i] other protons 6.8—7m

[a] Irradiation at these points simplifies the resonances at 3.10 and 4.85 in confirmation of these assignments. [b] Simplify to doublet on irradiation at 5.65. [c] Collapses to broad singlet on irradiation at 4.70. [d] Deduced from the spectrum of its mixture with (4c). [e] Collapses to apparent singlet on irradiation at 7.80. [f] Simplified by irradiation at 6.70. [g] Collapses to apparent singlet on irradiation at 7.70. [h] Collapses to singlet on irradiation at 8.17. [i] Collapses after 24 h with D_2O.

0 °C for 1 h and the precipitate (from EtOH) gave *3-carbamoyl-1,2,5,6-tetrahydro-1-phenylpyridine* (5a) (0.9 g), m.p. 170—173°.

(iii) Sodium borohydride (3 g) in ice–water (20 ml) was added over 5 min to the salt (1a) (3.76 g) in water (20 ml) containing sodium hydroxide (0.8 g) and stirring was continued for 1 h. The precipitate (1.9 g), yellow and green needles (from methanol), m.p. 130—136°, contained (2a), (3a), (4a), and (5a) (ratio 1 : 1 : 1 : 0.8).

(iv) Sodium dithionite (27 g) was added in small portions with vigorous stirring to the salt (1a) (10 g) and sodium carbonate (13.7 g) in water (200 ml). After heating to 50 °C for 0.5 h the precipitate was collected and gave 3-carbamoyl-1,4-dihydro-1-phenylpyridine (4a) (6.33 g), yellow needles (from ethanol), m.p. 145—147°.

Reduction of 3-Cyano-1-methylpyridinium Iodide (1b).—Sodium borohydride (2.0 g) in water (2.5 ml) and methanol (10 ml) was added at 0 °C to the iodide (1b) (12.3 g) in water (30 ml) and methanol (40 ml). After 30 min the mixture was filtered, diluted with water (100 ml), and extracted with dichloromethane. Evaporation of the washed, dried (Na_2SO_4) extract gave an air-sensitive yellow-orange oil (5.86 g). Distillation gave 3-cyano-1,2,5,6-tetrahydro-1-methylpyridine (5b) (2.1 g), b.p. 104° at 15 Torr, and mixtures of (3b) and (4b) (1.4 g in 1 : 2 ratio, b.p. 78—80° at 0.25 Torr; and 0.7 g in 1 : 1 ratio, b.p. 90—100° at 0.2 Torr). Refractionation of this last distillate gave mainly 1,4-dihydropyridine (4b), b.p. 82—84° at 0.25 Torr, and a fraction, b.p. 94—96° at 0.1 Torr, mainly the 1,6-dihydropyridine (3b). The 1,4-dihydro- described [8,9] gave (4c) with the properties described but containing *ca.* 10% of (3c).

3-Carbamoyl-1,4,5,6-tetrahydro-1-phenylpyridine (6).—(i) The 1,4-dihydropyridine (4a) (0.4 g) in methanol (30 ml) over 10% palladised charcoal (0.4 g) was hydrogenated to give the *tetrahydropyridine* (6) (0.25 g) as plates (from MeOH–H_2O), m.p. 182—184°.

(ii) A similar hydrogenation of the 1,6-dihydropyridine (3a) gave the tetrahydropyridine (6), identical (m.p. and spectra) with the above specimen.

3-Carbamoyl-1,2,3,4,5,6-hexahydro-1-phenylpyridine (7).—(i) The 1,2,5,6-tetrahydropyridine (5a) (0.2 g) in ethanol (20 ml) was hydrogenated over 10% palladised charcoal (0.11 g), previously saturated with hydrogen, at 19 °C until no further hydrogenation occurred. The product, transferred to chloroform, was extracted with N-hydrochloric acid, the chloroform layer (A) being retained. The aqueous solution was basified and re-extracted ($CHCl_3$). Evaporation of the dried (Na_2SO_4) extract gave the *hexahydropyridine* (7) (100 mg), m.p. 145—146° (from $CHCl_3$–Et_2O–petroleum). Extract A yielded compound (6) (75 mg), identical with the specimen described above.

(ii) The dihydropyridine (2a) (1.0 g) was hydrogenated as in (i) until 1 mol. equiv. had been taken up. Filtration and evaporation gave a yellow solid which was extracted with N-hydrochloric acid. The insoluble fraction was compound (6) (0.29 g, 36%), and the acid-soluble material, after recovery by basification and solvent extraction, was chromatographed over deactivated alumina. The hexahydropyridine (7) (0.32 g, 40%) was eluted by chloroform,

and the tetrahydropyridine (5a) (0.2 g, 24%) by chloroform containing ethanol (10%), all products being identified by mixed m.p. and u.v. and n.m.r. spectral comparisons. If the hydrogenation of (2a) was continued to completion, the only products were (6) and (7) (1.4 : 1 ratio).

1-*Benzyl*-1,2-*dihydro*-4-*methylpyridine*.—Benzyl bromide (12 ml) was added to 4-methylpyridine (9.6 g) in ethanol (55 ml), and after refluxing for 2½ h and removal of solvent addition of ether precipitated 1-*benzyl*-4-*methylpyridinium bromide* (1d) (29.4 g), crystals (from methanol–ether), m.p. 161—162°.

This salt (7.8 g) was reduced with sodium borohydride (0.57 g) in methanol–2N-sodium hydroxide in the usual way, and after diluting the mixture with water 1-benzyl-1,2-dihydro-4-methylpyridine (5.44 g) (2d) was obtained as an oil by extraction with dichloromethane. It rapidly darkened in air but was stable at 0 °C under nitrogen.

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