Heterocycles in Organic Synthesis. Part 18.[1] The Replacement of an Amino-group by Hydrogen *via* Dihydropyridines [2]

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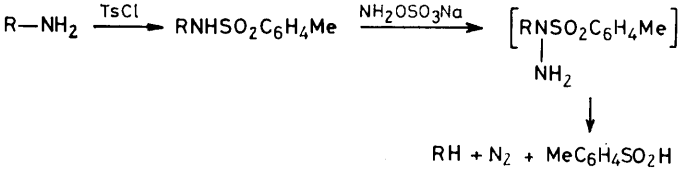
1-Substituted 2,4,6-triarylpyridinium cations are reduced by sodium borohydride to the corresponding 1,2-dihydropyridines. Whereas the 1-aryl derivatives are thermally stable, 1-benzyl-, 1-allyl-, and 1-heteroarylmethyl-2,4,6-triphenyl-1,2-dihydropyridines afford the corresponding hydrocarbons and triphenylpyridine.

THE conversion $R-NH_2 \longrightarrow R-H$ is a well studied important synthetic sequence for aromatic amines:[3] diazotisation yields the intermediates $R-N_2^+$ which are reduced with H_3PO_2 or with other reagents such as alcohols or formaldehyde. By contrast few general methods are available for this transformation in the aliphatic series: Nickon *et al.*[4] have shown that the sequence of the Scheme gives hydrocarbons from a wide



SCHEME

variety of amines, but in isolable yields which range from 2 to 80% and are typically 30—50% for aliphatic amines. Another general method [5] converts a variety of primary amines in 20—77% yield in a one-step treatment, but utilises the difficultly available reagent difluoroamine HNF_2. More recently, Hutchins *et al.*[6] have shown that *NN*-disulphonimides $RN(SO_2R')_2$ are reduced by sodium borohydride to the hydrocarbon RH.

Recent work from our laboratory has utilised the conversion of primary amines by pyrylium salts into pyridinium cations to effect transformations of the amino-group into other functionality.† We reasoned that, if these pyridinium cations were reduced to the dihydro-stage, it might be possible to effect transformations of the type $RNH_2 \longrightarrow RH$. This paper describes the results of these experiments.

Reduction of 1-*Aryl*-2,4,6-*triphenylpyridinium Salts.*—Aniline, 2- and 4-aminopyridine, and 2-amino-4,6-dimethylpyrimidine were converted to the perchlorates (1)—(4) (Table 1) which underwent smooth reduction to the corresponding 1,2-dihydropyridines (6)—(9), respectively on treatment with aqueous borohydride.[7] The structures of (6)—(8) were shown by elemental analysis (Table 2) and by spectral evidence: the n.m.r. pattern was particularly distinctive (Table 3) showing H-2 (δ *ca.* 5.5) coupled with H-3 (δ *ca.* 6.0) by *J* 6 Hz. H-5 of the dihydropyridine ring shows a signal with δ *ca.* 6.2.

The dihydropyridines (6)—(8) were very stable thermally:[8] prolonged heating of (7) at *ca.* 200 °C with or without Al_2O_3 gave a black resin still containing unchanged starting material; (7) was unaffected by refluxing in $POCl_3$ for 3 h or refluxing KOBu^t–Bu^{t}OH for 18 h,‡ but was decomposed completely by refluxing benzoyl chloride. With methyl iodide–silver perchlorate, (7) gave the quaternary derivative (10), but reaction of (10) with $NaBH_4$ led to intractable mixtures. The diperchlorate (10) reacted with aniline and *p*-toluidine to give the pyridinium salts (1) and (5) respectively. The hydrochloride of (7) did not thermolyse smoothly.

The 2-pyridyl (2) and 4-pyridyl (3) derivatives reacted with *m*-chloroperbenzoic acid to the oxides (11) and (13). Reduction of the *N*-oxide (11) with $NaBH_4$ gave, unexpectedly,[7] what we believe to be the 1,4-dihydro-

TABLE 1

1-Substituted -2,4,6-triphenylpyridinium perchlorates

Compound	*N*-Substituent	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.	Crystal form	Crystallisation solvent	Formula	Found (%) C	H	N	Required (%) C	H	N
(1)	Phenyl	90	255—258	260	*a*	Prisms								
(2)	2-Pyridyl	95	272—275	300—301	*b*	Prisms	EtOH	$C_{28}H_{21}ClN_2O_4$	69.3	4.5	5.6	69.4	4.3	5.8
(3)	4-Pyridyl	91	>300	230—231	*b*	Prisms	MeCN	$C_{28}H_{21}ClN_2O_4$	68.9	4.3	6.0	69.4	4.3	5.8
(4)	4,6-Dimethyl-pyrimidin-2-yl	53	223—225			Prisms	Me_2CO–H_2O	$C_{29}H_{24}ClN_3O_4$	67.3	4.9	8.3	67.8	4.7	8.2
(14)	Allyl	85	146—148			Prisms	EtOH	$C_{26}H_{22}ClNO_4$	69.6	4.8	3.1	69.7	4.9	3.1
(14)	Benzyl	87	196—198	196—198	*c*	Prisms	EtOH	$C_{30}H_{24}ClNO_4$	72.3	4.5	2.4	72.4	4.8	2.8
(14)	2-Furylmethyl	45	118 (decomp.)	122 (decomp.)	*d*	Prisms	EtOH–Et_2O	$C_{28}H_{22}ClNO_5$	68.9	4.6	2.6	68.9	4.5	2.8
(14)	2-Pyridylmethyl	77	226—227	226—227	*c*	Prisms	EtOH–Et_2O	$C_{29}H_{23}ClN_2O_4$	69.1	4.8	5.6	69.8	4.6	5.6
(14)	4-Pyridylmethyl	80	178 (decomp.)	178 (decomp.)	*c*	Prisms	EtOH–Et_2O	$C_{29}H_{23}ClN_2O_4$	69.6	4.6	5.8	69.8	4.6	5.6

[a] See ref. 11. [b] E. A. Zvezdina, M. P. Zhdanova, V. A. Bren, and G. N. Dorofeenko, *Khim. Geterotsikl. Soedinenci*, 1974, 1461. [c] A. R. Katritzky, J. B. Bapat, R. J. Blade, B. P. Leddy, P. L. Nie, C. A. Ramsden, and S. S. Thind, *J.C.S. Perkin I*, 1979, 418. [d] A. R. Katritzky, M. F. Abdel-Megeed, G. Lhommet, and C. A. Ramsden, *J.C.S. Perkin I*, 1979, 426.

† See ref. 1 and earlier papers in this series.

‡ For a recent report of the resistance of dihydropyridine to proton loss see R. R. Schmidt and G. Berger, *Chem. Ber.*, 1976, **109**, 2936.

derivative (12): it showed a 2H singlet at δ 6.20; presumably the dihedral angle between these protons and the 4-position hydrogen causes a low coupling. The H-4 signal apparently occurs at *ca.* 6.8, overlapped by some of the aromatic protons.

TABLE 2

1-Substituted 2,4,6-triphenyl-1,2-dihydropyridines

Compound	*N*-Substituent	Yield (%)	M.p. (°C)	Crystal form	Crystallisation solvent	Formula	Found (%) C	Found (%) H	Found (%) N	Calc. (%) C	Calc. (%) H	Calc. (%) N
(6)	Phenyl	75	134	Prisms	MeCN	$C_{29}H_{23}N$	89.9	6.0	4.0	90.4	5.9	3.6
(7)	2-Pyridyl	75	155—157	Prisms	EtOH	$C_{28}H_{22}N_2$	86.7	5.8	7.4	87.0	5.7	7.2
(8)	4-Pyridyl	56	202—205	Prisms	MeCN	$C_{28}H_{22}N_2$	86.7	5.6	7.3	87.0	5.7	7.2
(9)	4,6-Dimethylpyrimidin-2-yl	78	197—200	Micro-crystals	MeCN	$C_{29}H_{25}N_3$	83.3	6.2	9.9	83.8	6.0	10.1
(15)	Allyl	85	Oil [a]									
(15)	Benzyl	86	97—100	Prisms	EtOH	$C_{30}H_{25}N$	89.7	6.1	3.2	90.1	6.3	3.5
(15)	2-Furylmethyl	85	Oil [a]									
(15)	2-Pyridylmethyl	75	127—129	Prisms	EtOH	$C_{29}H_{24}N_2$	86.4	6.1	6.9	86.9	6.0	6.9
(15)	4-Pyridylmethyl	85	Oil [a]									

[a] Unstable, further characterisation by the n.m.r. only, see Table 3.

Reduction of 1-*Allyl-*, 1-*Benzyl-*, *and* 1-*Picolyl*-2,4,6-*triphenylpyridinium Salts.*—The thermal stability of dihydropyridine (7) and its analogues presumably arises from the forbidden nature of a 1,2-elimination involving a 1,3-hydrogen shift. It seemed that systems of type (15) might undergo an allowed electrocyclic reaction to yield 2,4,6-triphenylpyridine (16) and the deaminated product (17). Where the double bond in (15) had been incorporated in an aromatic ring system, it was expected that (17) would spontaneously tautomerise and re-aromatise to (18).

A series of pyridinium salts of type (14) (prepared by standard methods, Table 1) underwent smooth reduction by $NaBH_4$ into the 1,2-dihydropyridines (15) (Table 2). The above speculations were justified when these dihydropyridines (15) underwent smooth thermal fission with the deaminated products (17) [or (18)] distilling off in high yield (Table 4).*,†

The sequence of reactions (14) ⟶ (18) thus represents a three-step method for the conversion of allylic, benzylic, and heterobenzylic amines to the corresponding hydrocarbons in 50% overall yield. Such reactions have not been previously reported, the nearest analogy is perhaps the conversion of the allyldihydroquinoline (19) into the n-propylquinoline (20).[9]

TABLE 3

N.m.r. spectra (δ) of dihydropyridines

Compound	*N*-Substituent	Aryl protons	1,2-Dihydropyridine ring protons 2	3	5	N–CH_2 (AB quartet) Proton A	Proton B	*J* Hz
(6)	Phenyl	7.9—6.7 (20 H, m)	5.55 (1 H, d) [a]	5.9 (1 H, m)	6.33 (1 H, s)			
(7)	2-Pyridyl	8.35 (1 H, d) 7.8—7.0 (16 H, m) 6.9—6.6 (2 H, m)	[b]	[b]	[b]			
(8)	4-Pyridyl	8.25 (2 H, d) 7.8—7.0 (15 H, m) 6.9—6.6 (2 H, m)	5.65 (1 H, d) [a]	6.3—6.0 (1 H, m)	6.35 (1 H, s)			
(9)	4,6-Dimethyl-2-pyridyl	8.0—7.1 (15 H, m) 7.1—6.9 (1 H, m)	6.3 (1 H, d) [a]	6.4 (1 H, m)	6.35 (1 H, s)		[c]	
(15)	Benzyl	8.2—7.5 (20 H, m)	5.50 (1 H, d, *J* 6 Hz)	6.05—5.95 (1 H, m)	6.1 (1 H, s)	4.98	4.42	15
(15)	2-Furylmethyl	8.2—7.5 (15 H, m) 6.6—6.5 (2 H, m)	5.50 (1 H, d, *J* 6 Hz)	6.05—5.85 (1 H, m)	6.2—6.1 (1 H, s) [d]	4.67	4.30	15
(15)	2-Pyridylmethyl	9.0—8.85 (1 H, d, *J* 6 Hz) 8.3—7.5 (18 H, m)	5.62 (1 H, *d*, *J* 6 Hz)	6.0 (1 H, m)	6.2—6.1 (1 H, s) [d]	5.12	4.62	15
(15)	4-Pyridylmethyl	8.8—8.7 (2 H, m) 8.2—7.5 (~17 H, m)	5.35 (1H, d, *J* 6 Hz)	5.89 (1 H, m)	6.0 (1 H, s)	4.87	4.29	15

[a] Weak coupling with H-5. [b] Overlapping multiplet (3 H) at δ 6.5—6.1. [c] CH_3 groups found at δ 2.2 (6 H, s). [d] Weak coupling with H-3.

EXPERIMENTAL

Preparation of the Pyridinium Perchlorates (*Table* 1).—2,4,6-Triphenylpyrylium perchlorate (0.07 mol) and the amine (0.09 mol) were stirred in ethanol (100 ml) for 4 h at 20 °C. The salt was filtered off, and recrystallised from ethanol.

Reduction of Pyridinium Perchlorates to Dihydropyridines (*Table* 2).—Sodium borohydride (0.13 g, 0.003 6 mol) was added slowly with stirring at 0—5 °C to the 1-substituted 2,4,6-triphenylpyridinium perchlorate (0.003 6 mol) in acetonitrile–methanol (1 : 1). The mixture was kept for 1 h, solvent removed at 40 °C and 12 mmHg, and water

* We emphasise that there is yet no evidence for the postulated electrocyclic reaction. Labelling experiments to elucidate the reaction mechanism are proposed.

† These labelling experiments (with Dr. B. Plau) indicate that, at least for the *N*-benzyl compound, the major pathway is free-radical rather than electrocyclic.

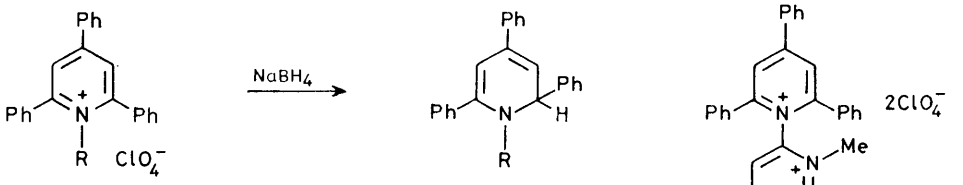
TABLE 4

Pyrolyses of 1-substituted 2,4,6-triphenyl-1,2-dihydropyridines

1-Substituent	Temp. (°C)	Pressure (mmHg)	Time (h)	Product isolated	Yield (%)	Characterisation of products
Allyl	200	~760	3	1,2-Dibromopropane	81	b.p. 140—143 (lit,[c] 141.6—141.90) [b,d]
Benzyl	220	12—15 [a]	2	Toluene	75	b,e
2-Furylmethyl	200	a	1	2-Methylfuran	82	b.p. 62.50 (lit.,[f] 65.0) [b,d]
2-Pyridylmethyl	220	a	2	2-Picoline	75	b,e
4-Pyridylmethyl	220	a	2	4-Picoline	77	b,e

[a] Usually water pump was used. [b] Characterised by ^{1}H n.m.r. spectra. [c] 'Beilstein's Handbuch der Organischen Chemie', eds. B. Prager and P. Jacobson, Verlag von Julius Springer, Berlin, vol. I, 1918, p. 109. [d] I.r. spectrum compared with published spectrum. [e] Direct comparison of i.r. and n.m.r. spectra with those of authentic sample. [f] 'Beilstein's Handbuch der Organischen Chemie,' eds. B. Prager, P. Jacobson, and F. Richter, Verlag von Julius Springer, Berlin, vol. XVII, 1933, p. 36.

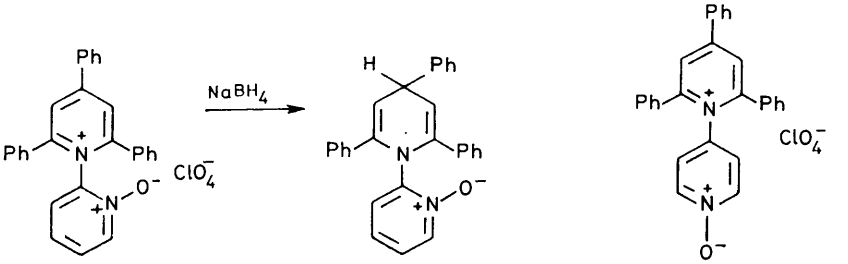
(50 ml) and diethyl ether (100 ml) added. The ether layer was separated, dried ($MgSO_4$), and evaporated to give the dihydropyridine.



(1) R = Ph
(2) R = 2-pyridyl
(3) R = 4-pyridyl
(4) R = 4,6-dimethylpyrimidin-2-yl
(5) R = *p*-tolyl

(6) R = Ph
(7) R = 2-pyridyl
(8) R = 4-pyridyl
(9) R = 4,6-dimethylpyrimidin-2-yl

(10)



(11) (12) (13)

Dihydropyridine (7) formed a *hydrochloride* (100%) with dry hydrogen chloride in ether, m.p. 100—103 °C (from acetone) (Found: N, 6.9. $C_{28}H_{23}ClN_2$ requires N, 6.6%); $\nu_{max.}$ (Nujol) 1 640, 1 625, 1 590, 1 515—1 555, 1 490, 1 270—1 260, 1 225, 1 155, 1 035, 965, 885, 850, 760, 750, 715, and 685 cm^{-1}.

1-(2-*Pyridyl*)-2,4,6-*triphenylpyridinium chlorate* (10).—Silver perchlorate–acetonitrile complex ($AgClO_4$,4CH_3CN [10]) (20 g) and methyl iodide (45 g) were added to 1-(2-pyridyl)-2,4,6-triphenylpyridinium perchlorate in dichloroethane (100 ml). The mixture was stirred for

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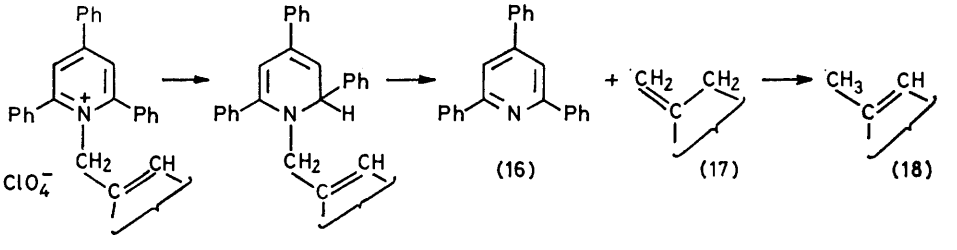
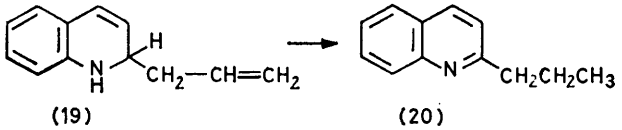


(14) (15) (16) (17) (18)



(19) (20)

1 week at 20 °C. The filtered solution was evaporated and the *diperchlorate* (19.0 g, 66%) isolated by fractional crystallisation from acetonitrile from which it separated as prisms, m.p. 293—296 °C (decomp.) (Found: C, 58.2; H, 4.3; N, 4.9. $C_{29}H_{24}Cl_2N_2O_8$ requires C, 58.1; H, 4.0; N, 4.7%); $\nu_{max.}$ (Nujol) 1 620, 1 595, 1 570, 1 540, 1 510, 1 490, 1 415, 1 350, 1 290, 1 250, 1 165, 1 100—1 050, 925, 880, 770, 760, 725, and 690 cm^{-1}; $\delta(CF_3CO_2H$; 60 MHz) 8.9—8.4 (4 H, m), 8.3—7.9 (2 H, m), 7.75—7.4 (15 H, m), and 4.35 (3 H, s). The diperchlorate (10) (2.9 g, 0.005 mol), *p*-toluidine (5.3 g, 0.05 mol), and ether (50 ml) were stirred 4 h at 20 °C. 1-(*p*-Tolyl)-2,4,6-triphenylpyridinium perchlorate (5) (2.4 g, 96%) separated, m.p. 248—250 °C (lit.,[11] 243—244 °C). The conversion (7) ⟶ (1) was achieved similarly: (95%), m.p. 262—264 °C (lit.,[11] 260 °C).

1-(1-*Oxido*-2-*pyridyl*)-2,4,6-*triphenylpyridinium Perchlorate* (11).—*m*-Chloroperbenzoic acid (1.8 g) was added at 0 °C with stirring to 1-(2-pyridyl)-2,4,6-triphenylpyridinium perchlorate (4.85 g). The whole was refluxed for 48 h: addition of ether to the cooled solution gave the *oxide* (4.55 g, 91%) which separated from ethanol as prisms, m.p. 285—287 °C (Found: C, 66.9; H, 4.3; N, 5.5. $C_{28}H_{21}ClN_2O_5$ requires C, 67.1; H, 4.2; N, 5.6%); $\nu_{max.}$ (Nujol) 1 625, 1 610, 1 560—1 540, 1 480, 1 440, 1 415, 1 360, 1 270, 1 250, 1 110—1 070, 845, 855, 775, 765, 725, and 695 cm^{-1}; $\delta(CDCl_3$; 60 MHz) 8.1 (2 H, s) and 8.05—6.9 (19 H, m).

The N-*oxido*-4-*pyridyl derivative* (13) (90%) was similarly prepared as prisms (from EtOH), m.p. 229—232 °C (Found: C, 67.1; H, 4.2; N, 5.5%); $\nu_{max.}$ (Nujol) 1 620, 1 600, 1 580, 1 560, 1 550—1 540, 1 485, 1 410, 1 360, 1 275, 1 260, 1 245, 1 175, 1 110, 1 090—1 070, 840, 780, 775, and 695 cm^{-1}; $\delta(CF_3CO_2H$; 60 MHz) 8.84—8.5 (1 H, m), 8.35 (2 H, s), and 8.3—7.4 (18 H, m).

1-(1-*Oxido*-2-*pyridyl*)-2,4,6-*triphenyl*-1,4-*dihydropyridine* (12).—Sodium borohydride (0.302 g) was added with stirring at 0—5 °C to the *N*-oxide (11) (4.0 g) in acetonitrile (5 ml) and methanol (20 ml). After filtration and evaporation, acetone gave the solid 1,4-*dihydropyridine* (3.0 g, 93%), m.p. 176—179 °C (from ethanol) (Found: C, 83.5; H, 5.5; N, 6.9. $C_{28}H_{22}N_2O$ requires C, 83.6; H, 5.5; N, 7.0%); $\nu_{max.}$ (Nujol) 1 625, 1 600, 1 590, 1 575, 1 545, 1 480, 1 450, 1 430, 1 350, 1 310, 1 275, 1 250, 1 235, 1 205, 1 130, 850, 800, 780, 765, 740, 730, 715, 705, 680, and 685 cm^{-1}.

Thermolysis of Dihydropyridines (*Table* 3).—The dihydropyridine (0.02 mol) was dried at 50 °C and 0.5 mmHg, or 20 °C and 0.5 mmHg, for solid and oily liquid dihydropyridine respectively. The dihydropyridine was then heated at 12—15 mmHg and 200—220 °C.

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