A New Synthesis of 1,4-Dihydropyridines

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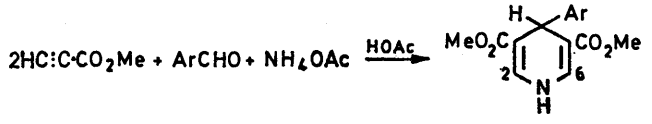
The synthesis of 1,4-dihydropyridines unsubstituted in the 1-, 2-, and 6-positions from methyl propiolate, aromatic aldehydes, and ammonium acetate in acetic acid is described. The products were oxidised to the corresponding pyridines. Certain features of their n.m.r. spectra are discussed.

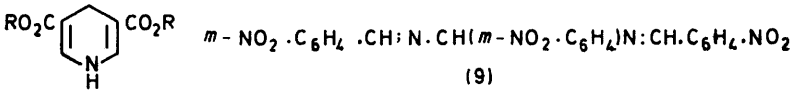
THE chemistry of dihydropyridines has assumed an increasing importance in recent years.[1] One of the most versatile [1] syntheses of 1,4-dihydropyridines is that due to Hantzsch [2] which uses a dicarbonyl compound or



(1) Ar = Ph
(2) Ar = *p*-MeC_6H_4
(3) Ar = *p*-$MeO{\cdot}C_6H_4$
(4) Ar = *o*-ClC_6H_4
(5) Ar = *p*-ClC_6H_4
(6) Ar = *p*-$HO{\cdot}C_6H_4$

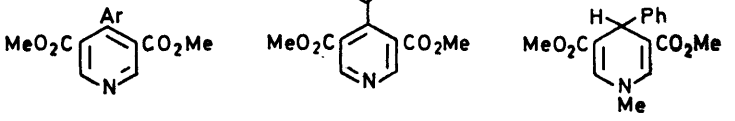
enamine, an aldehyde, and ammonia. However, owing to the lack of availability of suitable reagents, the 3-aminocrotonate,[6] whereas an abnormal reaction takes place with propiolaldehyde and with ethynyl ketones, leading eventually to pyridines.[6] Propiolic acid reacts with enamines in a highly complex fashion affording as the final product Hantzsch-type esters formally derived from acetaldehyde.[7]

Acetylenic esters react readily with ammonia or amines to form enamines,[8] and it might be expected that they could be used as enamine precursors in a modified Hantzsch synthesis. We have found that when methyl propiolate, an aromatic aldehyde, ammonium acetate and acetic acid are briefly warmed together, dihydropyridines [(1)—(6)] are formed readily in high yield. The products were characterised by elemental analysis and by their spectral properties, and



(9)

(7) R = Et
(8) R = Me



(10) Ar = Ph
(11) Ar = *p*-MeC_6H_4
(12) Ar = *p*-$MeO{\cdot}C_6H_4$
(13) Ar = *o*-ClC_6H_4
(14) Ar = *p*-ClC_6H_4

(15)

(16)

Hantzsch synthesis generally leads to 1,4-dihydropyridines with substituents in the 2- and 6-positions. Such substituents affect the properties of the dihydropyridines by their steric effect [3-5] and render them less suitable as model compounds for the coenzyme NADH. Few methods for the preparation of 1,2,6-unsubstituted 1,4-dihydropyridines exist [1,3] and their scope is limited.

Acetylenic compounds have hardly ever been used for the synthesis of dihydropyridines. The acetylenic aldehydes MeC:C·CHO and PhC:C·CHO are reported to react normally as the aldehyde components with methyl by oxidation to the corresponding pyridines (see later). The reaction probably proceeds *via* addition of ammonia to the triple bond of the methyl propiolate to give 3-aminoacrylate, which then reacts with the aldehyde in the usual manner.[1]

No dihydropyridines were formed when dimethyl acetylenedicarboxylate, phenylacetylene, or diphenylacetylene was used instead of methyl propiolate. When paraformaldehyde or hexamethylenetetramine was warmed with ethyl propiolate and ammonium acetate

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[4] U. Eisner, J. R. Williams, B. W. Matthews, and H. Ziffer, *Tetrahedron*, 1970, **26**, 899.
[5] U. Eisner, *Chem. Comm.*, 1969, 1348.
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[7] G. Schroll, S. P. Nygaard, S. O. Lawesson, A. M. Duffield and C. Djerassi, *Arkiv Kemi*, 1968, **29**, 525.
[8] L. W. Haynes in 'Enamines,' ed. A. G. Cook, Marcel Dekker, New York and London, 1969, p. 95.

under similar conditions, impure diethyl 1,4-dihydropyridine-3,5-dicarboxylate (7) was obtained in low and variable yield. Since the diester (7) is more readily available by other methods [3,9] this reaction was not investigated further. No dihydropyridines were produced when acetaldehyde, *o*-, *m*-, or *p*-nitrobenzaldehydes, salicylaldehyde, or 2-furaldehyde was used in the above reaction. *m*-Nitrobenzaldehyde reacted with methyl propiolate, ammonium acetate, and acetic acid to give the known [10] bis-imine (9), also formed by treating *m*-nitrobenzaldehyde with ammonium acetate in acetic acid.

Oxidation of the dihydropyridines with 20% nitric acid afforded the corresponding pyridines (10)—(14). In the case of the *p*-hydroxy-derivative (6) oxidation was accompanied by nitration of the benzene ring affording the pyridine (15), the hydroxy-proton of which had a chemical shift (δ 10·63) similar to that of *o*-nitrophenol (δ 10·35). No hydroxy-stretching band was detected in the i.r. region, presumably because it was very broad. The n.m.r. spectra of the pyridines (10)—(15) are given in Table 1. This method is a convenient route to the not otherwise readily accessible 4-arylpyridines.

TABLE 1

N.m.r. spectra of pyridines [a]

Compound	2- and 6-H	Aromatic H	CO_2Me	Other
(10)	9·03	7·07—7·53 (m)	3·57	
(11)	9·00	7·12 (q, *J* 8 Hz)	3·58	Me, 2·37
(12)	8·98	7·00 (q, *J* 9 Hz)	3·63	OMe, 3·80
(13)	9·20	6·92—7·50 (m)	3·62	
(14)	9·06	7·22 (q, *J* 9 Hz)	3·63	
(15)	9·22 [b]	7·10—8·27 (m)	3·60	OH, 10·63

[a] δ Values; solvent $CDCl_3$. Unless otherwise stated all signals are singlets. [b] Doublet (*J* 1 Hz).

The n.m.r. spectra of the dihydropyridines (1)—(6) in [$^2H_6$]acetone are listed in Table 2; only one point requires comment. The signal for the 2- and 6-protons in each case consisted of three sharp lines of more or less equal intensity, with almost, but not quite, equal spacings of 2—3 Hz between them. They collapsed to a singlet on addition of deuterium oxide. The NH signal was not detected, presumably because it is very broad, but the presence of NH was apparent from the i.r. absorption at *ca.* 3350 cm^{-1}.

The only previous report [3] of coupling of the 2- and 6-protons with the NH protons in 1,4-dihydropyridines suggested that the multiplicity of the signal for the 2- and 6-protons might be solvent dependent. We therefore examined the n.m.r. spectra of the *p*-chlorophenyl derivative (5) in a number of solvents; the results are summarised in Table 3. In [$^2H_5$]pyridine, [$^2H_6$]dimethyl sulphoxide, dimethylformamide, hexamethylphosphoric triamide, and deuteriochloroform the signal of the 2- and 6-protons appeared as a doublet, *J ca.* 5 Hz, although in the last case there was some overlap with the aromatic proton signal. The phenyl (1) and *p*-hydroxyphenyl (6) derivatives also gave a doublet, *J ca.* 5 Hz, in [$^2H_6$]dimethyl sulphoxide. In acetonitrile and in nitromethane the 2- and 6-protons in (5) resonated as a broad singlet.

The 4-unsubstituted dihydropyridine (8) [9] behaved analogously. In deuterioacetone the 2- and 6-protons gave rise to three lines, whereas in deuteriochloroform the signal appeared as a doublet, *J ca.* 5 Hz (see Tables 2 and 3). The signals for the 2-, 4-, and 6-protons in both solvents are slightly broadened, indicating mutual long-range coupling.

TABLE 2

N.m.r. spectra of dihydropyridines [a]

Compound	2- and 6-H	Aromatic H	4-H	CO_2Me	Other
(1)	7·40, 7·45, 7·48 (444, 447, 449)	7·07—7·38 (m)	4·90	3·55	
(2)	7·39, 7·46, 7·48 (443·5, 446·5, 449)	7·12 (q, *J* 8 Hz)	4·87	3·57	Me, 2·23
(3)	7·41, 7·45, 7·49 (444·5, 447, 449·5)	7·02 (q, *J* 9 Hz)	4·85	3·59	OMe, 3·75
(4)	7·42, 7·47, 7·50 (445, 448, 450)	7·12—7·40 (m)	5·37	3·53	
(5)	7·47, 7·50, 7·53 (457·5, 460, 463)	7·33 (t, *J* 10 Hz)	4·90	3·58	
(6)	7·35, 7·40, 7·45 (441, 444, 447)	6·91 (q, *J* 9 Hz)	4·82	3·57	
(8)	7·16, 7·20, 7·25 (429·5, 432, 435)		3·23	3·68	
(16)	7·32 (439·5)	7·00—7·42 (m)	4·90	3·59	NMe, 3·39

[a] Solvent [$^2H_6$]acetone; δ values (values in Hz in parentheses). Unless otherwise stated all signals are singlets.

TABLE 3

Solvent effects on the n.m.r. spectra of dihydropyridines [a]

Compound	Solvent	2- and 6-H	Aromatic H
(5)	C_5D_5N	7·68, 7·77 (461, 466·5)	7·48 (q, *J* 9 Hz)
(5)	$(CD_3)_2SO$	7·37, 7·46 (442·5, 447·5)	7·27
(5)	$Me_2N{\cdot}CHO$	7·49, 7·58 (449·5, 455)	7·32
(5)	$(Me_2N)_3PO$	7·30,[b] 7·39 (438, 443·5)	7·27 (t, *J* 12 Hz)
(5)	$CDCl_3$	7·30,[b] 7·38 (438, 443)	7·27 (t, *J* 10 Hz)
(5)	$MeNO_2$	7·38 [c] (443)	7·28 (t, *J* 9 Hz)
(5)	MeCN	7·36 [c] (441·5)	7·27
(1)	$(CD_3)_2SO$	7·37, 7·45 (442·5, 447)	7·23
(6)	$(CD_3)_2SO$	7·32, 7·41 (439·5, 444·5)	6·83 (q, *J* 8·5 Hz)
(8)	$CDCl_3$	7·08, 7·17 (425, 430)	

[a] δ Values (values in Hz in parentheses). Unless otherwise stated all signals are singlets. [b] Partly obscured by aromatic protons. [c] Broad.

The *N*-methyl derivative (16) was prepared [3] in order to determine whether the observed effect was due to slow inversion of the *N*-substituent. However, the *N*-methyl signal was a sharp singlet, indicating rapid inversion.

[9] E. Booker and U. Eisner, following paper.
[10] A. Fürth, *Monatsh.*, 1906, **27**, 844.

The effect in [$^2H_6$]acetone apparently is due to the presence of traces of deuterium oxide in the solvent, leading to a mixture of the deuteriated compound (which gives a singlet) and the protonated compound (which gives a doublet). Thus, addition of water to a solution of (5) in [$^2H_6$]acetone caused a change from a three-line pattern to a doublet. Progressive dilution of the solution of (5) caused the relative intensity of the centre line due to the deuteriated form slightly to increase as the deuterium oxide content was increased. A solution of (3) in acetone showed a doublet for the 2- and 6-protons; addition of deuterium oxide (5 μl) converted this into a singlet. Progressive addition to this of water (2—3 μl portions) caused a change to three lines with the centre line gradually diminishing in intensity. The separations between the lines were 2·50 and 2·65 Hz, giving an isotope effect of 0·075 Hz. Finally, when the [$^2H_6$]acetone was dried over molecular sieves a broad singlet was observed for the 2- and 6-protons, and when a different batch of [$^2H_6$]acetone was used the expected doublet was seen for compounds (2) and (8).

A similar observation was made by Becker [11] in the case of 1,7-dimethylcytosine, and was attributed to deuterium oxide in the [$^2H_6$]dimethyl sulphoxide solvent.

EXPERIMENTAL

M.p.s were determined with a Thomas-Hoover capillary apparatus. T.l.c. was carried out on pre-coated silica gel F-254 plates (Brinkmann Instruments, Inc.) with ethyl acetate–light petroleum (1 : 1) as eluant. N.m.r. spectra ($CDCl_3$ solutions unless otherwise stated) were measured with a Varian A-60 instrument. I.r. spectra (Nujol mulls) were recorded on a Beckman 33 instrument; only strong absorptions are noted. U.v. spectra were determined for solutions in methanol on a Beckman Acta III instrument. The deuterioacetone was purchased from Diaprep (Aldrich).

Preparation of 1,4-*Dihydropyridines*.—Methyl propiolate (1 ml), the aromatic aldehyde (1 g), ammonium acetate (1 g), and acetic acid (1 ml) were warmed together on a steam-bath for 10—15 min. The product crystallised on cooling; it was filtered off and crystallised from methanol. *Dimethyl* 1,4-*dihydro*-4-*phenylpyridine*-3,5-*dicarboxylate* (1) was obtained as yellow crystals (79%), m.p. 211—213°; $\lambda_{max.}$ 208, 222s, 264s, 275s, and 360 nm (ε 13,000, 11,800, 1800, 1700, and 7800); $\nu_{max.}$ 3360, 1715, 1680, 1210, and 1090 cm^{-1} (Found: C, 65·7; H, 5·3; N, 5·0. $C_{15}H_{15}NO_4$ requires C, 65·9; H, 5·5; N, 5·1%). *Dimethyl* 1,4-*dihydro*-4-p-*tolylpyridine*-3,5-*dicarboxylate* (2) was obtained as yellow crystals (76%), m.p. 213—215°; $\lambda_{max.}$ 211, 246s, 281, and 360 nm (ε 14,600, 6400, 5700, and 6200); $\nu_{max.}$ 3350, 1715, 1685, 1300, 1220, and 1095 cm^{-1} (Found: C, 66·7; H, 6·0; N, 4·8. $C_{16}H_{17}NO_4$ requires C, 66·9; H, 6·0; N, 4·9%). *Dimethyl* 1,4-*dihydro*-4-p-*methoxyphenylpyridine*-3,5-*dicarboxylate* (3) was obtained as yellow crystals (68%), m.p. 197—198·5°, $\lambda_{max.}$ 216, 247s, 283, and 359 nm (ε 17,000, 5800, 5900, and 7400); $\nu_{max.}$ 3350, 1715, 1680, 1220, and 1090 cm^{-1} (Found: C, 63·3; H, 5·8; N, 4·6. $C_{16}H_{17}NO_5$ requires C, 63·4; H, 5·6; N, 4·6%). *Dimethyl* 4-o-*chlorophenyl*-1,4-*dihydropyridine*-3,5-*dicarboxylate* (4) was obtained as crystalline material (56%), m.p. 240—242°, $\lambda_{max.}$ 211, 221s, and 364 nm (ε 11,500, 9600, and 5900), $\nu_{max.}$ 3330, 1715, 1690, 1515, 1215, and 1090 cm^{-1} (Found: C, 58·7; H, 4·6; Cl, 11·2; N, 4·4. $C_{15}H_{14}ClNO_4$ requires C, 58·55; H, 4·6; Cl, 11·5; N, 4·55%). *Dimethyl* 4-p-*chlorophenyl*-1,4-*dihydropyridine*-3,5-*dicarboxylate* (5) was obtained as yellow crystals (72%), m.p. 219—221°, $\lambda_{max.}$ 222s, 242s, 279s, and 364 nm (ε 13,900, 9200, 1800, and 6700), $\nu_{max.}$ 3315, 1700, 1670, 1490, 1290, 1210, and 1080 cm^{-1} (Found: C, 58·4; H, 4·7; Cl, 11·4; N, 4·4. $C_{15}H_{14}ClNO_4$ requires C, 58·55; H, 4·6; Cl, 11·5; N, 4·55%). *Dimethyl* 1,4-*dihydro*-4-p-*hydroxyphenylpyridine*-3,5-*dicarboxylate* (6) was obtained as pale yellow crystals (52%), m.p. 267·5—270·5°; $\lambda_{max.}$ 223s, 247s, 282, and 358 nm (ε 16,900, 6700, 4100, and 8000), $\nu_{max.}$ 3410, 3350, 1695, 1620, 1300, 1200, and 990 cm^{-1} (Found: C, 62·3; H, 5·4; N, 4·7. $C_{15}H_{15}NO_5$ requires C, 62·3; H, 5·2; N, 4·8%).

Formation of NN′-*Bis*-(m-*nitrobenzylidene*)-m-*nitrobenzylidenediamine* (9).—Treatment of *m*-nitrobenzaldehyde under these conditions gave the product (9), m.p. 160—161° (lit.,[10] 160°) (from acetonitrile) (Found: C, 58·2; H, 3·5; N, 16·2%. Calc. for $C_{21}H_{15}N_5O_6$: C, 57·8; H, 3·4; N, 16·25%), δ 7·47—8·78 (complex m, aromatic and olefinic) and 6·18br (1H, s, aliphatic).

Oxidation of Dihydropyridines.—The dihydropyridine (0·5 g) and 20% nitric acid (10 ml) were warmed on a steam-bath with occasional shaking for 15 min. The hot solution was filtered, if necessary, and the filtrate was cooled and basified with sodium hydrogen carbonate solution. The resulting pyridine was filtered off [or extracted with ether in the case of (13)], crystallised from light petroleum, and sublimed at 0·01 mmHg. *Dimethyl* 4-*phenylpyridine*-3,5-*dicarboxylate* (10) was obtained as a crystalline solid, m.p. 93—94·5°, $\nu_{max.}$ 1730, 1590, 1570, 1125, and 1015 cm^{-1} (Found: C, 66·1; H, 4·9; N, 5·0. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%). *Dimethyl* 4-p-*tolylpyridine*-3,5-*dicarboxylate* (11) had m.p. 133—135°, $\nu_{max.}$ 1725, 1590, 1195, and 1105 cm^{-1} (Found: C, 67·2; H, 5·2; N, 4·8. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%). *Dimethyl* 4-p-*methoxyphenylpyridine*-3,5-*dicarboxylate* (12) had m.p. 74—75°, $\nu_{max.}$ 1725, 1525, 1265, 1110, and 1050 cm^{-1} (Found: C, 63·9; H, 5·0; N, 4·6%. $C_{16}H_{15}NO_5$ requires C, 63·8; H, 5·0; N, 4·65%). *Dimethyl* 4-o-*chlorophenylpyridine*-3,5-*dicarboxylate* (13) had m.p. 71—72°, $\nu_{max.}$ 1730, 1285, and 1200 cm^{-1} (Found: C, 58·7; H, 4·1; Cl, 11·5; N, 4·4. $C_{15}H_{12}ClNO_4$ requires C, 58·9; H, 3·95; Cl, 11·6; N, 4·6%). *Dimethyl* 4-p-*chlorophenylpyridine*-3,5-*dicarboxylate* (14) had m.p. 118—120°, $\nu_{max.}$ 1750, 1730, 1285, 1240, 1210, and 1000 cm^{-1} (Found: C, 59·0; H, 4·0; Cl, 11·5; N, 4·7%. $C_{15}H_{12}ClNO_4$ requires C, 58·9; H, 3·95; Cl, 11·6; N, 4·6%). *Dimethyl* 4-(4-*hydroxy*-3-*nitrophenyl*)*pyridine*-3,5-*dicarboxylate* (15) could not be crystallised from light petroleum. It was chromatographed on a column of silica gel 60 with chloroform and chloroform–acetone (9 : 1) as eluants. The product was obtained as a bright yellow solid, m.p. 142—144° (from methanol), $\nu_{max.}$ 1750, 1725, and 1280 cm^{-1} (Found: C, 54·0; H, 3·8; N, 8·3. $C_{15}H_{12}N_2O_7$ requires C, 54·2; H, 3·6; N, 8·4%).

Dimethyl 1,4-*Dihydro*-1-*methyl*-4-*phenylpyridine*-3,5-*dicarboxylate* (16).—The dihydropyridine (1) (250 mg) in dry dimethoxyethane (15 ml) was treated with sodium hydride (250 mg; 57% dispersion in oil, washed with dry ether several times) and the mixture was stirred for 1 h. Methyl iodide (2·4 ml) was added and stirring was continued for 1 h. The solution was filtered through Celite and the filtrate was evaporated to dryness. The oily residue was

[11] E. D. Becker, private communication.

treated with dry ether and the crystalline solid obtained was filtered off and recrystallised from methanol; m.p. 192·5—194°, $\lambda_{max.}$ 225, 248s, and 368 nm (ε 11,900, 9600, and 6700), $\nu_{max.}$ 1710, 1590, 1285, 1225, and 1075 cm^{-1} (Found: C, 66·7; H, 6·1; N, 4·7. $C_{16}H_{17}NO_4$ requires C, 66·9; H, 6·0; N, 4·9%).

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