Synthesis of 1,2-Dihydropyridines

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Summary Hydrogenation of 3,5-disubstituted pyridines yields 1,2-dihydropyridines.

IN connection with another study[1] the 1,2-dihydropyridine (IIa) was required. No general method for the preparation of *N*-unsubstituted 1,2-dihydropyridines is available, although the corresponding *N*-alkyl compounds may be prepared by borohydride reduction of pyridinium salts.[2] We describe the preparation of (II) as well as of (V) by catalytic hydrogenation of the corresponding pyridines.

Nucleophilic addition to 3,5-disubstituted pyridines by hydride ion[3,4] generally yields mixtures of 1,2- and 1,4-dihydropyridines. Borohydride reduction[5,6] of (Ia) gave a mixture of (IIa) and (IIIa) from which the unstable (IIa) could be separated only with considerable loss.

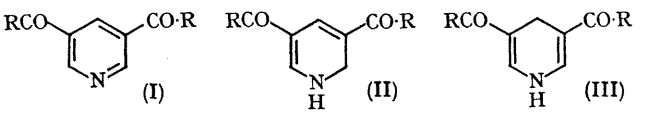
Wenkert[7] has recently described the catalytic hydrogenation of nicotinic acid derivatives to the corresponding 1,4,5,6-tetrahydropyridines. Reduction presumably stops

at this stage owing to the resistance of the N·C:C·C:O grouping to hydrogenation. The presence of acyl substituents in both the 3- and 5-positions might therefore be expected to result in the isolation of a dihydropyridine[8] and this was borne out by experiment.

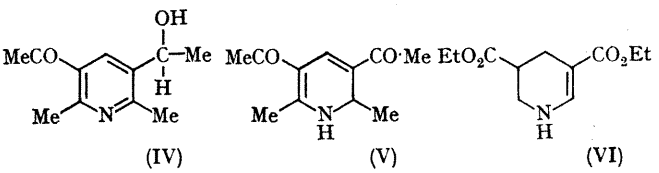
Hydrogenation of (Ia) (ethanol, palladium on charcoal) was stopped after 1 mole of hydrogen had been taken up, and afforded (IIa)[5] (54%), [$\delta(CDCl_3)$ 7·58 (q, $J_{6,1}$ *ca.* 7 Hz., $J_{6,4}$ 1·5 Hz., 6-H), 7·48 (m, 4-H), *ca.* 6·0 (broad, NH), *ca.* 4·36 (m, 2-H), 4·20, 4·18 (q, ester CH_2), 1·28 (t, ester CH_3)], containing only traces of the 1,4-isomer (IIIa). Similarly, (Ib) gave (IIb)[5] (54%), [$\delta(CDCl_3)$ 7·61 (q, $J_{6,1}$ 7·0 Hz., $J_{6,4}$ 1·5 Hz., 6-H), 7·49 (m, 4-H), *ca.* 6·0 (broad, NH), 4·36 (q, $J_{2,4}$ 0·75Hz, $J_{2,1}$ *ca.* 1·7 Hz, 2-H), 3·77, 3·73 (s, ester CH_3)], and (Ic) yielded (IIc)† (70%), m.p. 198—200°, $\lambda_{max.}$ 217, 281, and 386 nm. (ϵ 12,000, 16,200, and 5900), $\nu_{max.}$ (KBr) 3420 (NH) 1682 and 1642 (C=O) cm.$^{-1}$; $\delta(CD_3OD)$ 7·89 (d, $J_{6,4}$ 1·5 Hz, 6-H), 7·67 (m, 4-H), 4·30 (s, broad, 2-H), 2·30 (s, 5-CO·CH_3), 2·18 (s, 3-CO·CH_3). 3,5-Diacetyl-2,6-lutidine gave a mixture of (IV)[1] and (V), m.p. 158—160°, $\lambda_{max.}$ 223, 314, and 394 nm. (ϵ 9900, 21,900, and 8900); $\nu_{max.}$ ($CHCl_3$) 3390 (NH), 1655, 1645 (C=O) cm.$^{-1}$; $\delta(CDCl_3)$ 7·51 (s, broad, 4-H), *ca.* 6·5 (broad, NH), 4·75 (q, 2-H), 2·43 (s, 5-CO·Me), 2·32 (s, 3-CO·Me), 2·30 (s, 6-Me), and 1·12 (d, J 6·0 Hz, 2-Me), which was separated chromatographically after acetylation of (IV).

Uninterrupted hydrogenation of (Ia) resulted in a total uptake of two moles of hydrogen affording, in high yield, the unstable tetrahydropyridine (VI), m.p. 51—53°, $\lambda_{max.}$ 281 nm. (ϵ 20,300); $\nu_{max.}$ 3450 (NH), 1720, 1765 (CO_2Et) cm.$^{-1}$; $\delta(CDCl_3)$ 7·49 (d, broad, $J_{2,1}$ 5·5 Hz, 2-H), *ca.* 4·95 (broad, NH), 4·20, 4·18 (q, ester CH_2), 3·23—3·33 (m, 6-H), 2·50—2·72 (m, 4H + 5H), 1·27 (t, ester CH_3), accompanied by some 1,4-dihydropyridine (IIIa). The tetrahydropyridine (VI), together with the pyridine (Ia), was also produced by disproportionation of (IIa) with palladium–charcoal in ethanol. The same reaction occurred with the 1,4-isomer (IIIa) but at a much slower (*ca.* 25 times) rate.

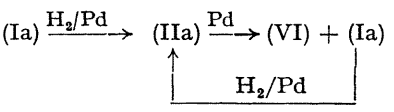
When hydrogenation of (Ia) with 1 mole of hydrogen was carried out using a less active catalyst, with a corresponding increase in the reaction period, (VI) was formed along with (IIa) and some (IIIa), *i.e.* disproportionation of (IIa) competed with hydrogenation of (Ia). This fact, together



(a)R=OEt, (b)R=OMe, (c)R=Me



with the observation that (VI) is resistant to hydrogenation under the conditions used, suggests that it is produced by disproportionation of (IIa) rather than by hydrogenation according to the scheme:



Competition between hydrogenation and disproportionation evidently takes place during the hydrogenation of diethyl 2,6-lutidine-3,5-dicarboxylate and of 3,5-diacetyl-4-methylpyridine, which were reduced very slowly and yielded inseparable mixtures of di- and tetra-hydropyridines. The fully substituted diethyl 2,4,6-collidine-3,5-dicarboxylate and 3,5-dicyano-2,4,6-collidine were resistant to hydrogenation under the conditions used, probably because of steric factors.

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† Satisfactory elemental analyses were obtained for all new compounds.

[1] U. Eisner, J. R. Williams, B. Matthews, and H. Ziffer, *Tetrahedron*, in the press.
[2] *e.g.* W. Traber and P. Karrer, *Helv. Chim. Acta*, 1958, **41**, 2066.
[3] J. Kuthan and E. Janečková, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1654.
[4] J. Kuthan, J. Procházková, and E. Janečková, *Coll. Czech. Chem. Comm.*, 1968, **33**, 3558.
[5] After the completion of this work a paper by J. Paleček, L. Ptáčková and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1969, **34**, 427, appeared describing essentially the same results for the borohydride reduction.
[6] On immediate work-up the mixture of (IIa) and (IIIa) is obtained in 67% yield. Prolonged reaction periods result in the decomposition of (IIa) and recovery of pure (IIIa) in 30—40% yield, *cf.* P. J. Brignell, U. Eisner, and P. G. Farrell, *J. Chem. Soc.* (*B*), 1966, 1083.
[7] E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, 1968, **33**, 747.
[8] The only recorded instance of such a reaction is the formation of 3,5-dicyano-1,2-dihydro-4-methylpyridine on hydrogenation of 2,6-dichloro-3,5-dicyano-4-methylpyridine, *cf.* R. Lukeš and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2173.