Reduction of 3,5-Disubstituted Pyridines to Dihydropyridines†

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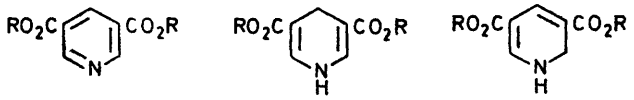
The reduction of pyridine-3,5-dicarboxylates by sodium borohydride to give the corresponding 1,2- and 1,4-dihydropyridines has been investigated, and the compositions of the isomer mixtures produced in various solvents have been determined. New syntheses have been developed for 3,5-disubstituted 1,4-dihydropyridines involving reduction with sodium cyanoborohydride, and for 1,2-dihydropyridine-3,5-dicarboxylates involving reduction with diborane. Details of the previously reported catalytic hydrogenation of pyridines are given.

ALTHOUGH a number of methods for the synthesis of dihydropyridines have been described,[1] many of these suffer from disadvantages, particularly lack of generality and formation of mixtures. 3,5-Diacyldihydropyridines lacking substituents in the 1-, 2-, and 6-positions are especially difficult to prepare. We have reported [2] a synthesis of dimethyl 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates. The isomeric 1,2-dihydropyridines are even more difficult to synthesise and very few examples are known. In a preliminary communication [3] we have described the synthesis of several 3,5-diacyl-1,2-dihydropyridines by catalytic hydrogenation, and now give details of this work.

Although reduction of pyridines with sodium borohydride generally gives mixtures of the 1,2- and 1,4-dihydropyridines,[1] treatment of diethyl pyridine-3,5-dicarboxylate (1) with sodium borohydride in ethanol for 4 days [4] afforded the pure 1,4-isomer (3) in 25—40%



(1) R = Et (2) R = Me (3) R = Et (4) R = Me (5) R = Et (6) R = Me

yield. Kuthan *et al.*[5] have claimed that although the diethyl ester (3) was obtained 98% pure in this manner, reduction of dimethyl pyridine-3,5-dicarboxylate, (2), under the same conditions, gave a 55 : 45 mixture of the isomers (4) and (6). This was ascribed to the greater steric requirements of the ethyl than of the methyl group. We have repeated this work but used a reaction period of only 5 min instead of 4 days. Under these conditions the composition of the mixture of the ethyl esters (3) and (5) was virtually identical with that of the mixture of methyl esters (4) and (6), with a content of about 40% of the 1,2-dihydro-isomer (see Table). The discrepancy between our results and those of Kuthan *et al.* may be explained by the lower stability of the ethyl ester (5) than of the methyl ester (6): the former decomposes in alcoholic solution; the latter does not. The products of the decomposition of (5) have not been investigated. The difference in stabilities of the ethyl (5) and methyl (6) esters is puzzling; it is paralleled by the relative rates of dehydrogenation of the *N*-methyl derivatives of (5) and (6) by free radicals.[6]

Reduction of pyridines with sodium borohydride

Compound	Solvent	% Yield	% 1,2-Isomer
(1)	Acetonitrile	58	63
(1)	Dioxan	57	56
(1)	Tetrahydrofuran	40	50
(1)	Dimethylformamide	45	47
(1)	Dimethyl sulphoxide	63	43
(1)	2,5,8-Trioxanonane	69	40
(1)	Ethanol	55	39
(2)	Methanol	45	37
(1)	Acetic acid	76	38
(2)	Acetic acid	57	40
(1)	Formamide	17	36
(1)	Pyridine–water (2 : 1)	64	15
(1)	Pyridine	74	13
(1)	Tetrahydrofuran–water (1 : 3)	Incomplete reduction	
(1)	Triethylamine	Incomplete reduction	

It was decided to study the isomer ratio [(3) : (5)] in the product of borohydride reduction under standard conditions, in the hope of finding a synthetically useful method. The results are listed in the Table. Both total yield and isomer ratio vary widely although there is no obvious correlation with factors such as solvent

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[1] U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

[2] T. Chennat and U. Eisner, preceding paper.

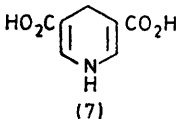
[3] U. Eisner, *Chem. Comm.*, 1969, 1348.

[4] P. J. Brignell, U. Eisner, and P. G. Farrell, *J. Chem. Soc.* (*B*), 1966, 1083.

[5] J. Paleček, L. Ptáčková, and J. Kuthan, *Coll. Czech Chem. Comm.*, 1969, **34**, 427.

[6] U. Eisner, W. P. Hambright, A. Lewis, and M. Sadeghi, unpublished results.

polarity. None of the solvents shows much promise of synthetic utility, with the exception of pyridine which gives a high yield with a low ratio of 1,2-isomer. The latter may be readily removed either by spontaneous decomposition or by preferential oxidation with silver oxide.[7] However, this method has now been superseded by another route (see later).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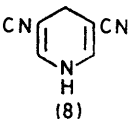
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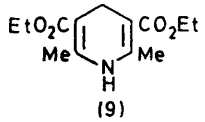
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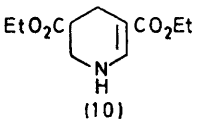
(10)

We next investigated the reaction of the pyridine (1) with other complex metal hydrides. Neither sodium trimethoxyborohydride nor Redal [$NaAlH_2(O{\cdot}CH_2{\cdot}CH_2{\cdot}OMe)_2$] [8] gave useful results, but sodium cyanoborohydride was highly satisfactory, affording the essentially pure 1,4-dihydropyridine (3) in 77% yield. Similarly, the dimethyl ester (2) gave the 1,4-dihydropyridine (4) in 77% yield. The content of the corresponding 1,2-isomer was 1—5%. The previously unknown 1,4-dihydropyridine-3,5-dicarboxylic acid (7) was prepared analogously; it could also be made, less efficiently, by borohydride reduction in formamide. The 1,4-dihydropyridines (8) and (9) were synthesised by the same route in good yield. Clearly, reduction with cyanoborohydride is a very good method for the preparation of 1,4-dihydropyridines and is superior to reductions with other complex hydrides.

The next reducing agent investigated was diborane. When the diethyl ester (1) was reduced in tetrahydrofuran an isomer mixture (35% yield) was obtained which contained 79% of the 1,2-dihydropyridine (5). The dimethyl ester (2) similarly afforded the crude 1,2-dihydropyridine (6) in about 50% yield. This method is so far the best route to the 1,2-isomers (5) and (6), being simpler than the catalytic hydrogenation previously described,[3] which gave a product (54%) containing 78% of the 1,2-dihydropyridine (5). Separation of the pure 1,2-dihydropyridines (5) and (6) from their 1,4-isomers is rather laboriously achieved by column chromatography on silica gel G of small particle size.* Pure (6), but not (5), may be isolated on a small scale by thick-layer chromatography. Kuthan *et al.*[5] separated the isomers by chromatography on alumina, but we could not repeat this procedure and found considerable isomerisation to take place on the column.

* This separation was carried out by M. Sadeghi.

[7] J. Kuthan and E. Janečková, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1654.

[8] J. Kuthan, J. Procházková, and E. Janečková, *Coll. Czech. Chem. Comm.*, 1968, **33**, 3558.

Reduction of (1) with diborane is highly solvent dependent. In the presence of pyridine the yield of mixture was 77%, containing only 9% of the 1,2-isomer (5). Pyridine–borane [9] in tetrahydrofuran gave a mixture (91%) containing 13% of (5). In pyridine the total yield was 88% of a product containing 16% of (5). These results are closely analogous to those of reduction by borohydride in pyridine (see Table) and the same species may be involved.

Mumm *et al.*[10] have described the reduction of pyridines to 1,4-dihydropyridines by aluminium amalgam. Application of this technique to the pyridine (1) yielded essentially the known [3] tetrahydropyridine (10), accompanied by small amounts of the 1,2-dihydropyridine (5).

EXPERIMENTAL

M.p.s were determined with a Thomas-Hoover capillary apparatus. U.v. spectra were measured on a Cary 14 instrument for solutions in methanol. T.l.c. was carried out on precoated silica gel F-254 plates (Brinkmann Instruments, Inc.) with ethyl acetate–light petroleum (b.p. 60—80°) (1 : 1) as eluant.

Determination of Composition of Isomer Mixtures.—The method of Kuthan [11] was used. The absorbance of the mixture was measured at 283 nm for the ethyl ester (5) and at 281 nm for the methyl ester (6). A calibration curve was constructed by using known mixtures of the 1,4- and 1,2-dihydropyridines (3) and (5). The u.v. spectra of the carefully purified 1,2-dihydropyridines were redetermined since there were some discrepancies with the results of Kuthan,[5] especially for the dimethyl ester (6). They are as follows: for (5): $\lambda_{max.}$ 217, 283, and 392 nm (ε 12,300, 19,000, and 5600); for (6): $\lambda_{max.}$ 213, 281, and 386 nm (ε 13,100, 19,400, and 5600).

Diethyl (1) and dimethyl (2) pyridine-3,5-dicarboxylates were prepared by esterifying the acid (Aldrich) with the alcohol (10 vol) and sulphuric acid (1 vol) or thionyl chloride (0·5 vol).

Reduction of Diethyl Pyridine-3,5-dicarboxylate (1) *with Sodium Borohydride.*—Sodium borohydride (191 mg) was added in one portion to a solution of (1) (500 mg) in the appropriate solvent (5 ml) cooled in ice–salt. After 5 min 10% acetic acid (70 ml) was added and the solution was kept at 0° until precipitation was complete. The product was filtered off and dried and the u.v. spectrum determined.

Reductions with Sodium Cyanoborohydride.—(a) *Dimethyl pyridine-3,5-dicarboxylate* (2). The ester (2) (5 g) in acetic acid (20—33 ml) was cooled in ice and sodium cyanoborohydride (3·75 g) was added. After 5 min water (200 ml) was added and the mixture was kept at 0° overnight and filtered. The product (3·72 g, 74%) was shown to consist essentially of the 1,4-dihydropyridine (4) by t.l.c. It was sufficiently pure for most purposes. A further crop (123 mg) was isolated from the filtrate by treatment with sodium hydrogen carbonate. For rigorous purification it was dissolved in methanol (150 ml) and stirred with silver oxide (500 mg) for 4 h. The solution was filtered and

[9] M. D. Taylor, L. R. Grant, and C. A. Sands, *J. Amer. Chem. Soc.*, 1955, **77**, 1506; R. P. Barnes, J. H. Graham, and M. D. Taylor, *J. Org. Chem.*, 1958, **23**, 1561.

[10] O. Mumm and W. Beth, *Ber.*, 1921, **54**, 1591; O. Mumm and J. Diederichsen, *Annalen*, 1939, **538**, 195.

[11] E. Janečková and J. Kuthan, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1495.

evaporated to dryness under reduced pressure. The residue was filtered through a column of silica gel (40 g) (chloroform as eluant) in order to remove traces of silver salts. It was crystallised from aqueous methanol and sublimed at 130° and 0·01 mmHg; m.p. 157—159° (lit.,[5] 162—163°).

(b) *Diethyl pyridine-3,5-dicarboxylate* (1). The ester (1) (500 mg) in acetic acid (5 ml) was reduced as under (a). The yield of (3) was 77%. Reduction could also be carried out in ethanol (5 ml) by addition of sodium cyanoborohydride (376 mg) followed by 10% acetic acid (70 ml); the yield was then 79%.

(c) *Pyridine-3,5-dicarboxylic acid.* This was reduced as under (a) affording the acid (7) as a yellow solid, m.p. 300° (decomp.) (77%), $\lambda_{max.}$ 218, 240s, and 374 nm (ε 11,000, 5000, and 6300) [Found (sample crystallised from aqueous dimethylformamide): C, 49·8; H, 4·2; N, 8·5. $C_7H_7NO_4$ requires C, 49·7; H, 4·2; N, 8·3%].

(d) *Pyridine-3,5-dicarbonitrile.* The pyridine (200 mg) in acetic acid (5 ml) was treated with sodium cyanoborohydride (200 mg) and set aside for 40 min. The solution was neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate, affording 1,4-dihydropyridine-3,5-dicarbonitrile (8) (197 mg), m.p. 197—199° (from acetone–cyclohexane), identical (mixed m.p. and u.v., i.r., and n.m.r. spectra) with an authentic sample.[7]

(e) *Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate.* The pyridine (200 mg) in N-hydrochloric acid (5 ml) was treated with sodium hydrogen carbonate to reduce the acidity. Sodium cyanoborohydride (200 mg) was added, the solution was set aside for 1 h and the resulting precipitate (9) (121 mg) was filtered off; m.p. 181—183° (from aqueous ethanol), identical (mixed m.p. and u.v. spectra) with an authentic sample.[12]

Diethyl 1,2-Dihydropyridine-3,5-dicarboxylate (5).—(a) *By catalytic hydrogenation.* The pyridine (1) (446 mg) in ethanol (20 ml) was hydrogenated over 5% palladium–charcoal (55 mg) (uptake 57·5 ml in 3·25 h; theoretical uptake 49·2 ml). The solution was filtered and evaporated to dryness to give the product (241 mg, 54%). Repeated chromatography on silica gel (chloroform–2% acetone or benzene–10% ethyl acetate as eluant) followed by crystallisation from benzene–hexane gave the pure 1,2-dihydropyridine (5) as an unstable yellow solid, m.p. 84—87° (lit.,[5] 86—88°).

(b) *By reduction with diborane.* The pyridine (1) (500 mg) in dry tetrahydrofuran (3 ml) was cooled in ice and a M-solution of diborane in tetrahydrofuran (5 ml) was introduced through a rubber serum cap with a hypodermic syringe under nitrogen with stirring. After 5 min, 10% acetic acid (20 ml) was carefully added and the solution was kept at 0° overnight. The oily precipitate was collected and dried, affording the 1,2-dihydropyridine (5) in 35% yield.

Dimethyl 1,2-Dihydropyridine-3,5-dicarboxylate (6).—(a) *By catalytic hydrogenation.* The pyridine (2) (390 mg) in ethanol (10 ml) was hydrogenated as above affording the crude 1,2-dihydropyridine (6) (211 mg) after crystallisation from benzene–hexane. After several more crystallisations from the same solvents or from water it had m.p. 120—124° but still contained some of the 1,4-isomer (4) as shown by t.l.c. It was finally purified by thick-layer chromatography and then had m.p. 118—120°.*

(b) *By reduction with diborane.* The pyridine (2) (4·85 g) in dry tetrahydrofuran (8 ml) was treated with M-diborane in tetrahydrofuran (25 ml) at 0°. After 5 min, 30% acetic acid (15 ml) was added and the solution was extracted with chloroform, affording the crude 1,2-dihydropyridine (2·4 g) which was chromatographed on silica gel G (for t.l.c.) with chloroform as eluant. The product (6) was crystallised from benzene–light petroleum to give 590 mg of pure material, which may be sublimed at 120° and 0·01 mmHg.

Diethyl 1,4,5,6-Tetrahydropyridine-3,5-dicarboxylate (10).—The pyridine (1) (400 mg) in ethanol (10 ml) was hydrogenated over 5% palladium–charcoal (100 mg) until uptake ceased (96·5 ml in 18 h; uptake of the first 2 mol. equiv. of hydrogen proceeds at a constant rate but the reaction becomes imperceptibly slow thereafter). The solution was filtered and evaporated to dryness. The residue was crystallised from cyclohexane affording the tetrahydropyridine (10) as an unstable solid, m.p. 53—54·5°, containing traces of the 1,4-dihydropyridine (3). A second crop (25·3 mg) had m.p. 52—53° and was essentially pure. It was sublimed at 50° and 0·01 mmHg and had m.p. 51—53° (Found: C, 58·3; H, 7·6; N, 6·3. $C_{11}H_{17}NO_4$ requires C, 58·1; H, 7·5; N, 6·2%); for spectral data see ref. 3.

Reduction of Diethyl Pyridine-3,5-dicarboxylate with Aluminium Amalgam.—The pyridine (1) was reduced by the method of Mumm [10] affording mainly the tetrahydropyridine (10), identified by t.l.c. and u.v. spectrum, together with some 1,2-dihydropyridine (5).

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* Our m.p. is lower than that given in ref. 5 but the material is pure (t.l.c. and n.m.r.).

[12] W. Traber and P. Karrer, *Helv. Chim. Acta*, 1958, **41**, 2086.