Preparation and Reactions of Spirodihydropyridines Formed by Acylation of Imines with Isonicotinoyl Chloride: a Synthesis of the Alkaloid Naucléfine

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Summary The spirodihydropyridines (**2**), (**7**), and (**10**), which were prepared from the corresponding imines with isonicotinoyl chloride, readily underwent photorearrangement and hydrolysis to give heterocyclic compounds related to alkaloids including naucléfine (**9**).

WE report a simple preparation of stable, synthetically useful spirodihydropyridine derivatives, which have been reported to be inaccessible or unstable[1,2] and their conversion into compounds directly or indirectly related to natural alkaloids and some new heterocyclic compounds.

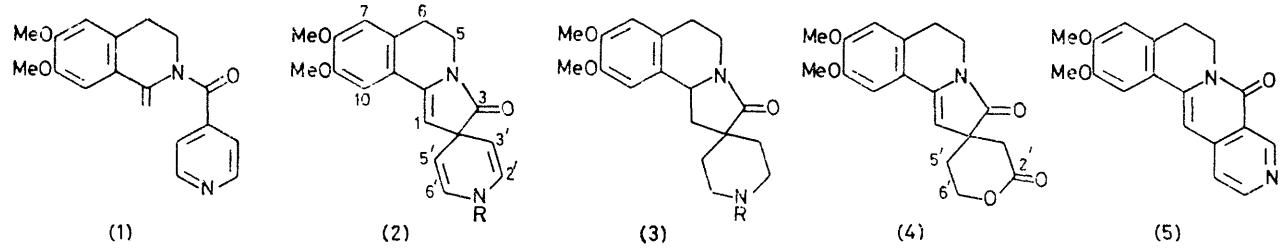
Although acylation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline with an equimolar amount of isonicotinoyl chloride in the presence of triethylamine yielded the *N*-isonicotinoylenamine (**1**),[3] treatment with an excess of the acid chloride led to the spirodihydropyridine (**2a**) in 75% yield [ν_{max} 1690, 1660, and 1620 cm^{-1}; δ 8·77 (dd, *J* 5 and 2 Hz, 2″- and 6″-H) (double primed nos. refer to the isonicotinoyl group), 7·43 (dd, *J* 5 and 2 Hz, 3″- and 5″-H), 6·98 (s, 10-H), 7·00 (v br., 2′- and 6′-H), 6·70 (s, 7-H), 5·50 (s, 1-H), 4·87 (br. d, *J* 8 Hz, 3′- and 5′-H), 3·93 (s, OMe × 2), 3·75 (t, *J* 6 Hz, 5-H_2), and 2·90 (t, *J* 6 Hz, 6-H_2); *m/e* 415

(M^+)]. The n.m.r. data, particularly for the *N*-isonicotinoyldihydropyridine chromophore, are similar to data for an analogous spiro-compound reported by Sainsbury *et al.*[4] When the enamide (**1**) was treated with excess of isonicotinoyl chloride, the spirodihydropyridine (**2a**) was also obtained. We therefore suggest that *N*-acylation of the pyridine ring of the enamide (**1**) might be the driving force in the formation of the spiro compound (**2**). Catalytic hydrogenation of (**2a**) on platinum oxide afforded the piperidine (**3a**) in a good yield.

5:1 (total yield 50%); compound (**6**) has already been obtained[3] by photocyclisation of the enamide (**1**).

A similar reaction sequence with harmalan (4,9-dihydro-1-methyl-3*H*-pyrido[3,4-*b*]indole) afforded the spirodihydropyridine (**7a**) in 35% yield. Hydrolysis of (**7a**) with 20% KOH–MeOH afforded the spirolactone (**8**) in 50% yield, which is known to be a potential key intermediate[5] for the synthesis of indole alkaloids such as quebrachamine.

Irradiation of compound (**7b**), prepared by hydrolysis of (**7a**) with 5% KOH–MeOH, yielded naucléfine (**9**) in



a; R = isonicotinoyl
b; R = H

Heating the spiro compound (**2a**) in 5% KOH–MeOH for 10 s caused *N*-deacylation to give the *N*-unsubstituted spirodihydropyridine (**2b**) in 88% yield. However, prolonged heating (2 h) of both the *N*-isonicotinoyl (**2a**) and the *N*-unsubstituted compounds (**2b**) with 20% KOH–MeOH afforded the spirolactone (**4**); ν_{max} 1730 and 1700 cm^{-1}; δ 5·57 (s, 1-H), 4·57 (m, 6′-H_2), and 2·90 and 2·47 (ABq, J 16 Hz, 3′-H_2); *m/e* 329 (M^+).

Irradiation of the spirodihydropyridine (**2b**) in benzene with a high pressure mercury lamp at room temperature for 1 h brought about rearrangement to afford a mixture of the two types of naphthyridine (**5**) and (**6**) in a ratio of

55% yield, m.p. 285—289 °C (lit.,[6] 285—290 °C), identical with the natural alkaloid.

Similarly, the acyclic imine, *N*-cyclohexylidenebenzylamine, was also acylated to give the spirodihydropyridine (**10a**), which was hydrolysed to the corresponding spirolactone and rearranged photochemically to the known naphthyridines.[3b]

We thank the Ministry of Education (Japan) for a research grant and Professor T. Kametani for spectra (i.r. and n.m.r.) of naucléfine.

(*Received, 27th February* 1979; *Com.* 189.)

[1] U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.
[2] J. S. Foos, W. Killian, S. Q. A. Rizvi, M. Unger, and G. Fraenkel, *Tetrahedron Letters*, 1978, 1407.
[3] (a) I. Ninomiya, O. Miyata, and T. Naito, unpublished results; (b) I. Ninomiya, T. Kiguchi, S. Yamauchi, and T. Naito, *J.C.S. Perkin I*, 1976, 1861.
[4] M. Sainsbury and N. L. Uttley, *J.C.S. Perkin I*, 1977, 2109.
[5] J. P. Kutney, in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, New York, 1977, vol. 3, p. 273.
[6] (a) F. Hottellier, P. Delaveau, and J-L. Pousset, *Phytochemistry*, 1975, **14**, 1407; (b) T. Kametani, M. Takeshita, and M. Ihara, *Heterocycles*, 1976, **4**, 247.