A New Photochemical Spiroannelation Method. Access to Substituted Spirocyclohexanepiperidines

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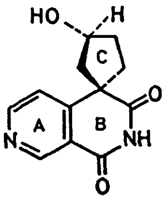
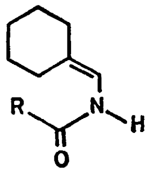
Summary A variety of substituted spirocyclohexanepiperidines are obtained by the photocyclisation of enamides in which the double bond α to the nitrogen atom is exocyclic to the cyclohexane ring.

Sesbanine (**1**), recently isolated in small quantities from the seeds of *Sesbania Drummondi*,[1] has been shown to possess a highly unusual structure characterised by a spiro-junction of the B and C rings. Spiro-fused rings are present in the framework of a variety of other natural compounds.[2]



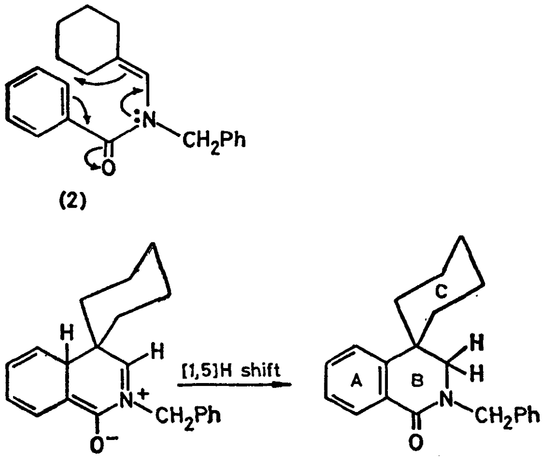
(1)



(4) a; R = Ph
b; R = 3-Pyridyl

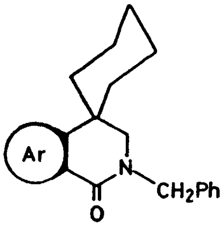
We now report a new method for synthesizing spiro heterocyclic frameworks the spiro-carbon of which is α to an aromatic nucleus. Creation of the spiro-carbon β to the nitrogen atom was made possible by the use of an enamide in which the double bond α to the nitrogen atom was exocyclic (to a carbon ring).

Photocyclisation of enamides has been widely applied to the synthesis of alkaloids and related products[3] by the construction of a nitrogen-containing six-membered ring. Thus, irradiation (Pyrex reactor, medium-pressure 250 W mercury lamp, 6 h) of the enamide (**2**)† (prepared by acylation with benzoyl chloride of the imine obtained by the condensation of cyclohexanecarbaldehyde and benzylamine) in cyclohexane or methanol afforded compound (**3**) (80% yield) (Scheme).

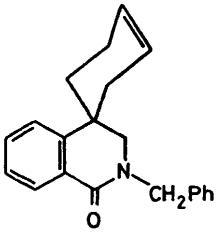


(3)

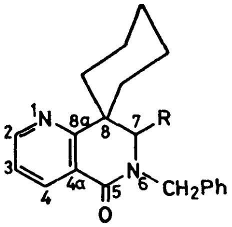
Scheme



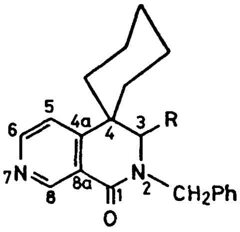
(5)



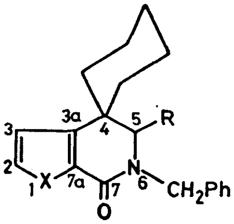
(6)



(7a) R = H
(7b) R = OMe
(13) R = OMe; 4a,8a-dihydro



(8a) R = H
(8b) R = OMe
(14) R = OMe; 4a,8a-dihydro



(9); X = O, R = H
(10); X = S, R = H
(11); X = O, R = OMe; 3a,7a-dihydro
(12); X = S, R = OMe; 3a,7a-dihydro

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† All new compounds exhibited spectroscopic (i.r., u.v., ^{1}H and ^{13}C n.m.r., and m.s.) and analytical data consistent with their proposed structures.

Spectroscopic data confirmed the formation of the spiro-structure (in particular, the n.m.r. spectra were simple on account of the symmetry of these molecules): in the ^{1}H n.m.r. spectrum, the methylene group α to the nitrogen atom in the lactam ring gave a singlet at δ *ca.* 3·4 whilst in the ^{13}C n.m.r. spectrum the carbon of this methylene group resonated at δ *ca.* 50 p.p.m. (t) and the spiro-carbon at *ca.* 38 p.p.m. (s).

Unexpectedly, the non-*N*-benzylated enamides (**4**) did not photocyclise under the conditions used. Literature reports show that, for these sorts of compounds, photocyclisation only occurs when an anilide,[4] a pyridylenamide,[5] or an enamide in which the double bond α to the nitrogen atom is further conjugated with a carbonyl group,[6] is used.

It was possible to obtain a large variety of type-(**5**) compounds [related to (**3**) by modifying the A and/or C ring] by replacing benzoyl chloride with another aromatic acid chloride and/or cyclohexanecarbaldehyde with another cycloalkanecarbaldehyde.

For instance, the spiro-lactam (**6**), in which the C ring can easily be functionalized, was quantitatively formed on irradiation of the enamide obtained from cyclohex-3-enecarbaldehyde.

Irradiation (cyclohexane, Pyrex reactor, 250 W mercury lamp, 4 h) of the enamide derived from nicotinoyl chloride afforded two isomeric photoproducts (**7a**) and (**8a**) (ratio 1 : 1, total yield 45%) separated by silica chromatography. Differences in the pyridyl proton resonance positions in the ^{1}H n.m.r. spectra permitted the ready identification of each isomer.

Under analogous conditions, the enamides obtained from 2-furoyl- and 2-thenoyl-chloride led to the cyclised products (**9**) (m.p. 98 °C, 43% yield) and (**10**) (m.p. 107—108 °C, 59% yield), respectively.

When chlorides of non-benzoic aromatic acids were used for the formation of the corresponding enamides, the [1,5] hydrogen shift (Scheme) was slow enough for the intermediary iminium ion to be trapped by a nucleophilic solvent (*e.g.* methanol). Compounds functionalized α to the nitrogen in ring B were thus obtained. Upon irradiation in methanol (Pyrex reactor, medium-pressure 250 W mercury lamp, 6 h), the enamides prepared from 2-furoyl and 2-thenoyl chlorides produced the dihydro-compounds (**11**) and (**12**). The ring hydrogen atom α to nitrogen was deshielded by the methoxy-group and resonated at δ 4·59 p.p.m., and the asymmetry of the carbon α to the nitrogen was reflected by the strong non-equivalence of the benzylic methylene group, which appeared as an AB system centred at *ca.* 7·45: (**11**), m.p. 118 °C, 80% yield, J_{AB} 15 Hz, $\Delta\nu$ = 1·02 p.p.m.; (**12**), oil, 86% yield, J_{AB} 14·3 Hz, $\Delta\nu$ = 1·28 p.p.m.

When the enamide was prepared from nicotinoyl chloride, the intermediates (**13**) and (**14**) were spontaneously oxidized and the aromatised compounds (**7b**) and (**8b**) (ratio 1 : 1, total yield 55%) were isolated: (**7b**), oil, J_{AB} 16·1 Hz, $\Delta\nu$ = 1·16 p.p.m.; (**8b**) m.p. 99 °C, J_{AB} = 12·8 Hz, $\Delta\nu$ = 1·48 p.p.m.

This photocyclisation reaction is therefore a fast and efficient method for preparing a wide variety of spiroamides, from easily available starting materials. In particular, it provides a solution to a problem often encountered in organic synthesis since it creates a spiro-carbon centre in one step. Such compounds can indeed be prepared by only a few restricted methods.[7,8]

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[2] For examples in the alkaloid field see R. H. F. Manske and R. G. A. Rodrigo, 'The alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1979, Vol. XVII, 501.

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[6] I. Ninomiya, T. Naito, and T. Kiguchi, *J. Chem. Soc., Perkin Trans.* 1, 1973, 2257.

[7] For a comprehensive review of the methodology of construction of quaternary carbon centres see S. F. Martin, *Tetrahedron*, 1980, **36**, 419.

[8] For a review of heterocyclic spiro-compounds see A. P. Krapcho, *Synthesis*, 1978, 77.