A NEW PHOTOCHEMICAL SYNTHETIC ROUTE TO 2,3-BENZODIAZEPINES FROM ISOQUINOLINE N-IMIDES

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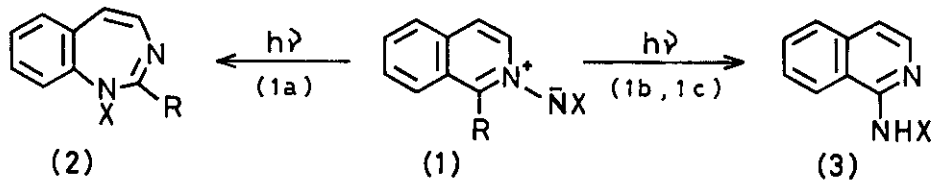
Abstract ——— Photolysis of the isoquinoline N-imides (6) under a basic condition gave the corresponding 5H-2,3-benzodiazepines (7), which were converted to the 3-acetyl-3H-2,3-benzodiazepines (11) by treatment with acetic anhydride.

In recent years, the synthesis of new conjugated seven-membered heterocyclic rings, heteropines, has been an object of extensive study.[1] As for benzodiazepines, we have already reported the first syntheses of fully unsaturated 1,2-[2,3] and 1,3-benzodiazepines[4] and the analogous diazepines condensed with aromatic heterocyclic rings such as pyridine, thiophene, furan, and pyrrole.[5] We now report the first photochemical route to 2,3-benzodiazepines from isoquinolines.

It is known that the 1-substituted isoquinoline N-acylimides (1a) undergo a photo-induced two-step rearrangement to give the corresponding 1H-1,3-benzodiazepines (2),[4] whereas the 1-unsubstituted N-imides (1b) and (1c), upon irradiation, give only 1-aminoisoquinolines (3) and/or the parent isoquinolines, and no diazepines.[6] On the other hand, the quinoline N-imides (4) are known to undergo photochemical rearrangement to give the 1H-1,2-benzodiazepines (5).[2] However, an analogous route to 2,3-benzodiazepines from isoquinoline N-imides had not been successful. Therefore, we reexamined the photochemical behavior of the N-imides (6) in more detail.

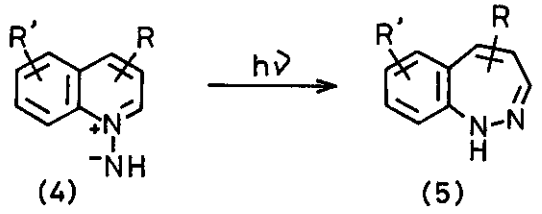
Irradiation (400 W, high-pressure Hg lamp; Pyrex filter) of the isoquinoline N-imides (6a-d) in methanol containing potassium hydroxide for 1-2 hr gave the 5H-2,3-benzodiazepines (7a-d) in 30-50% yields,[7] together with the corresponding parent isoquinolines in 10-35% yields, whereas the irradiation of the N-imides (6)



a: R = Me, CO_2Et; X = CO_2Et, Ac

b: R = H; X = CO_2Et, Ac, COPh

c: R = H; X = H



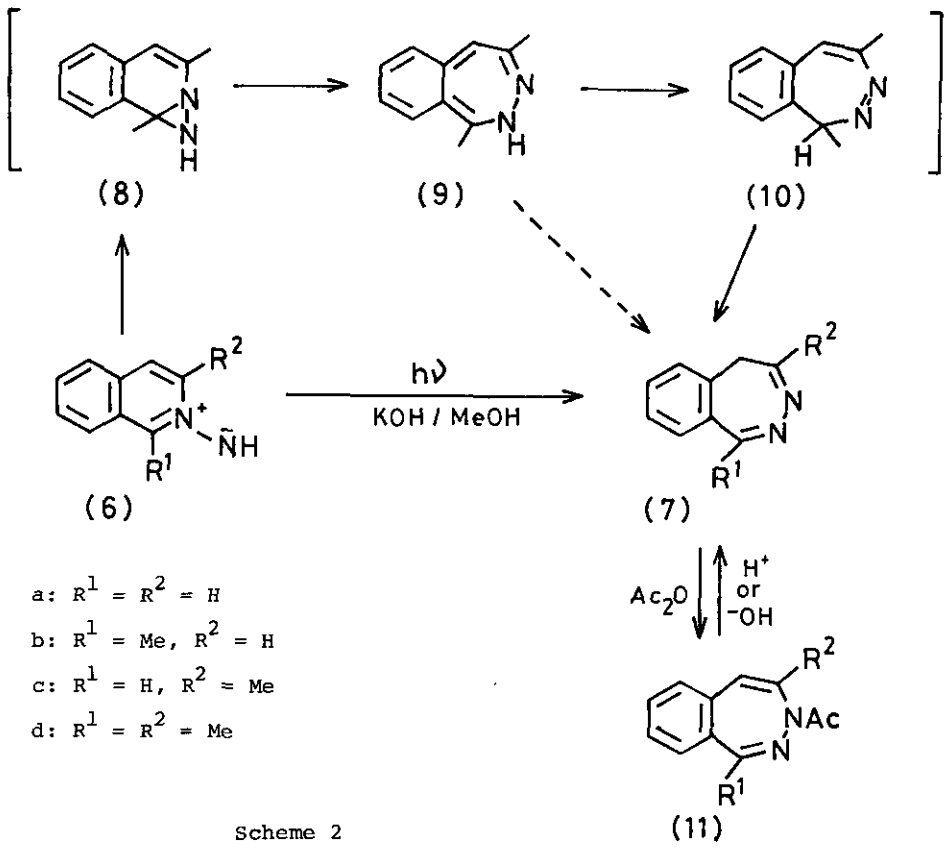
R, R'= H, Me, OMe, Cl, CO_2Et, etc.

Scheme 1

in the absence of the base gave complex mixtures of products and no diazepines. The 2,3-diazepines (7) thus obtained are susceptible to decomposition by silica gel and alumina, and thus can be isolated only by Sephadex chromatography.

Sharp et al. have already reported the synthesis of some 2,3-benzodiazepines from α-(o-alkenylaryl)diazoalkenes by thermal intramolecular cyclization.[8] The present result provides a new convenient method for preparation of 2,3-benzodiazepines from isoquinolines by direct ring-conversion.

The formation of the 5H-2,3-benzodiazepines (7) from the N-imides (6) may proceed by photo-induced rearrangement to the diaziridines (8) followed by ring-expansion to the o-quinonoid intermediates (9), which would tautomerize to the more stable 1H-diazepines (10). The 1H-diazepines (10) may then isomerize to the products (7) under the basic reaction condition. The 1H-2,3-benzodiazepines are known to readily tautomerize to the 5H-isomers by treatment with bases and also known to very sensitive to light giving complex mixtures of products *via* the tricyclic compounds.[9] The latter fact may cause the irradiation of the N-imides (6) in neutral condition to give no diazepines. Therefore, another possible route, direct formation of 7 from 9 by a 1,5-hydrogen shift, seems less likely.



Scheme 2

Treatment of the 5H-diazepines (7) with acetic anhydride gave the 3-acetyl-3H-diazepines (11) in good yields,[10] which readily reverted back to the 5H-diazepines (7) when treated with either hydrochloric acid or sodium hydroxide solution.

The n.m.r. spectrum of the 5H-diazepine (7b) showed a similar temperature dependence to those of 1-phenyl-5H-2,3-benzodiazepine,[8] 4H-1,2-diazepines,[11] and 3H-1,2-benzodiazepines[3] consistent with the predictable temperature-dependent inversion of the diazepine ring. The C-5 methylene protons show a doublet at δ 2.96 at 140°, which broadens with decreasing temperature and splits into ABX quartets centered on δ 2.76 and 3.16 below 90°; the change being complete at 29°. The energy of activation for ring inversion was estimated by the spectral analysis using the literature method.[3,11] The $\Delta G^{\ddagger}$ value (17.5 ± 0.3 Kcal mol^{-1}) for 7b at the coalescence temperature (90 °C) is slightly lower than those for the phenyl substituted 2,3-benzodiazepines, and is similar to that for 3,5,7-triphenyl-4H-1,2-diazepines.

References and Footnotes

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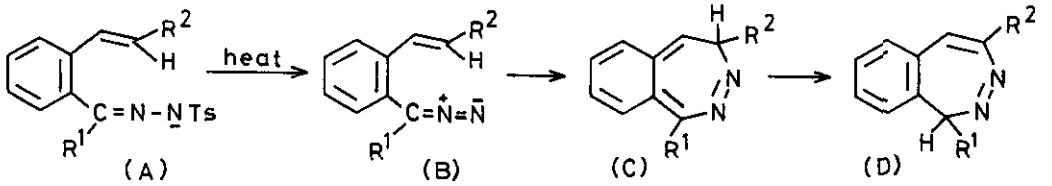
7 The new diazepines (7c: mp 106.5-108°; 45-50%) and (7d: oil; 30-35%) were characterized by elemental analysis and by spectral comparison with the diazepines (7a: oil; ca. 30%) and (7b: oil; 35-40%) which were identified by comparison with authentic samples prepared by the literature method.[8]

8 A.A. Reid, J.T. Sharp, H.R. Sood, and P.B. Thorogood, J. Chem. Soc. Perkin I, 1973, 2543; which has reported that the tosylhydrazone salts (A), upon heating, give the 1H-2,3-diazepines (D) via the diazo (B) and 4H-2,3-diazepine (C) intermediates.



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10 Satisfactory elemental analyses and spectral data were obtained for the 3H-diazepines; e.g., (11b): mp 110-111°, ν (KBr) 1660 cm^{-1}, δ ($CDCl_3$) 2.20 (3H, s, Ac-Me), 2.40 (3H, s, 1-Me), 6.07 (1H, d, J = 9 Hz, 5-H), 6.67 (1H, d, J = 9 Hz, 4-H), 7.0-7.4 (4H, m, Ar-H).

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