SYNTHESIS AND CHARACTERIZATION OF 1H-2,4-BENZODIAZEPINES

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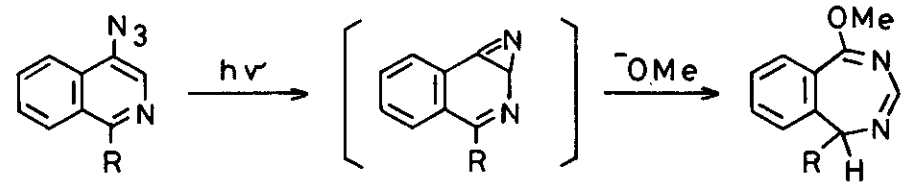
Abstract —— Photolysis of the 4-azidoisoquinolines (1) in the presence of sodium methoxide afforded the 1H-2,4-benzodiazepines (3); this new ring system was characterized by some photochemical and thermal reactions.

In recent years, the synthesis of new conjugated seven-membered heterocycles has been an object of extensive study.[1,2] As for fully unsaturated benzodiazepines, 1,2-,[3,4] 1,3-,[5] and 2,3-benzodiazepines[6] and related fused diazepines condensed with aromatic heterocyclic rings[2] have been prepared by the photo-induced rearrangement of fused pyridine N-imides or by the thermal cyclization of o-substituted styrene derivatives, but 2,4-benzodiazepines had not been reported. Very recently, Suschitzky et al.[7] reported that the photolysis of 4-azidoisoquinoline (1a) in the presence of methoxide ions resulted in ring-expansion via the singlet nitrene and the azirine intermediate (2) to give the 1H-2,4-benzodiazepine derivative (3a). As part of our continuous studies on diazepines[2] and on aryl azides,[8] we were interested in the preparation and properties of the novel 2,4-benzodiazepine ring, and now report that the 1H-2,4-benzodiazepines obtained by us are different from that already reported.[7]

The 4-azidoisoquinolines (1a,b) were irradiated (400 W, high-pressure Hg lamp; Pyrex filter) in methanol-dioxane (1:1)[9] containing sodium methoxide under ice cooling for 40-50 min. After removal of the solvents, the residue was extracted with n-hexane to give the 5-methoxy-1H-2,4-benzodiazepines (3) in 50-60% yields as the sole products [(3a): mp 34-37 °C; MS m/z: 174 (M^+); ^{1}H-NMR δ ($CDCl_3$): 3.96 (3H, s, OMe), 4.26 (2H, s, 1-H_2), 7.61 (1H, s, 3-H), 7.24-7.72 (4H, m, Ar-H); ^{13}C-NMR δ: 46.8 (t, C_1), 148.8 (d, C_3), 160.4 (s, C_5); IR νmax: 1625 (C=N) cm^{-1}.



(1) a : R = H
b : R = OMe

(2)

(3)

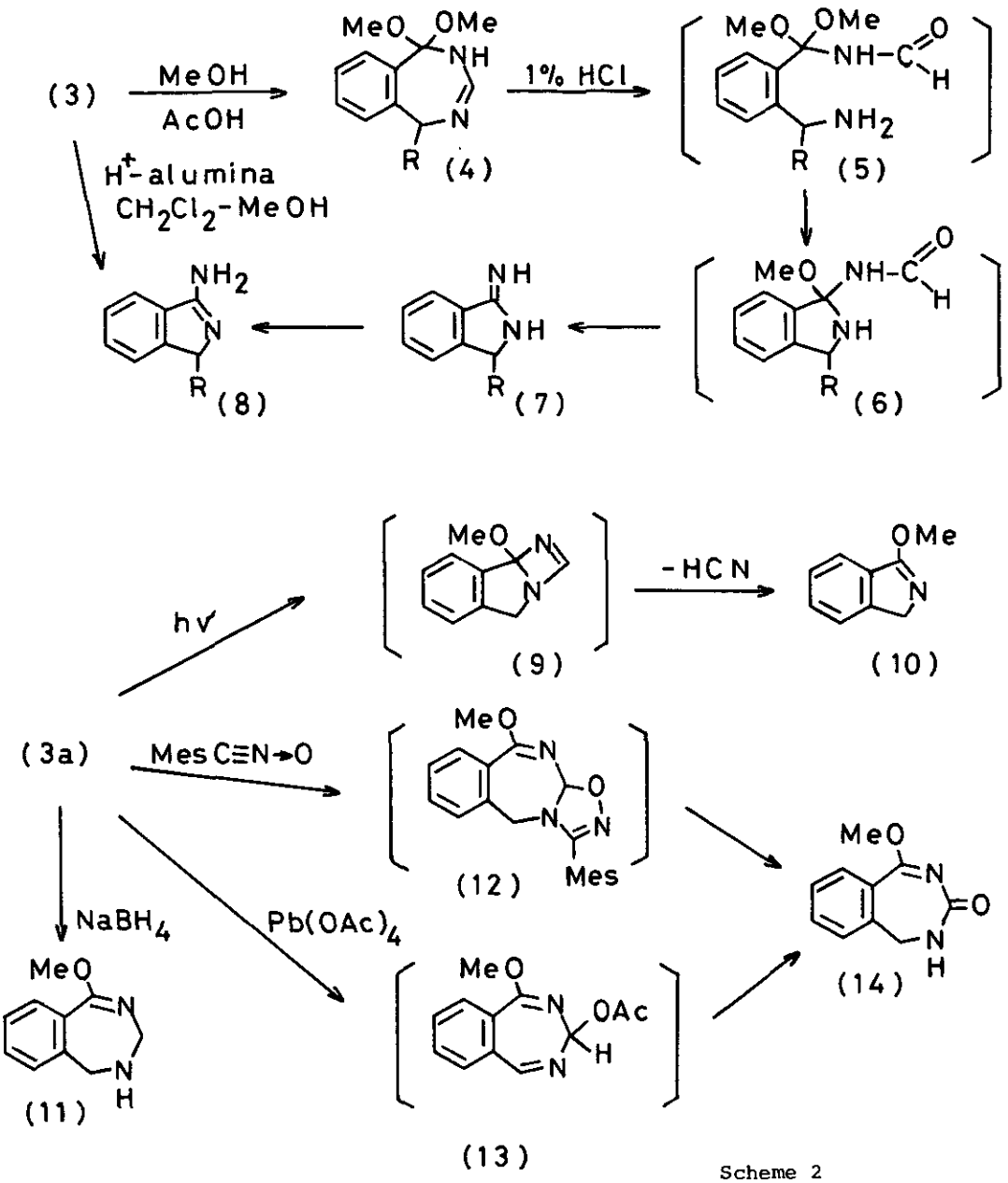
Scheme 1

(3b): oil; ^{1}H-NMR δ($CDCl_3$): 3.60 (3H, s, 1-OMe), 3.96 (3H, s, 5-OMe), 5.00 (1H, s 1-H), 7.65 (1H, s, 3-H), 7.20-7.80 (4H, m, Ar-H); ^{13}C-NMR δ: 88.1 (d, C_1), 151.2 (d, C_3), 165.9 (s, C_5)].

These physical and spectral data for 3a obtained by us are quite different from those already reported[7] [mp 72 °C; ^{1}H-NMR δ($CDCl_3$): 3.4 (3H, s, OMe), 5.4 (2H, s, 1-H_2), 7.0-7.4 (4H, m, Ar-H), 8.4 (1H, s, 3-H); the value of chemical shift for OMe seems to be too high and those for 1-H_2 and 3-H are too low compared to the NMR spectral data of other diazepines.[1-6]].

The diazepines (3) obtained were extremely susceptible to decomposition by silica gel and alumina, and thus purified by only kieselghur chromatography. Although the photolysis was carried out under various conditions, the same product reported by Suschitzky could not be obtained. The spectral data of the products obtained by us and the results of the following chemical studies are consistent with the proposed 1H-2,4-benzodiazepine structure (3) and eliminate other possible structures such as 3H- and 5H-2,4-benzodiazepines and 1,4-benzodiazepines.

In the literature,[7] they reported that the photolysed solution was neutralized with hydrochloric acid in methanol and then chromatographed on acidic alumina to give the 2,4-diazepine (3a) in 20% yield. Therefore, we examined such treatment with acids, but obtained only isoindolenine derivatives and no other compounds. Treatment of the diazepines (3a,b) with acetic acid in methanol gave the adducts (4),[10] which were then treated with 1% hydrochloric acid in methanol to afford the 1-aminoisoindolenines (8)[11] in 85% yields, presumably via the intermediates (5), (6), and (7) successively. Similarly, the diazepines (3) were treated with either acidic alumina or hydrochloric acid in methanol to give the isoindolenines (8) in 60-70% yields. Further irradiation of 3a in CH_2Cl_2 for 6 h afforded 1-methoxyisoindolenine (10)[11] in 40% yield via the tricyclic intermediate (9); this photo-



Scheme 2

chemical behavior is analogous to those observed for 1H-1,3-[5] and 1H-2,3-benzodiazepines.[6] Sodium borohydride reduction of 3a afforded the 2,3-dihydrodiazepine (11) in 90% yield. Treatment of 3a with either mesitylnitrile oxide or lead tetraacetate gave the 3-oxo compound (14) in 30-40% yield, presumably via the intermediate (12) or (13), respectively. These results are also analogous to those for 1,2-[3] and 1,3-benzodiazepines.[5]

In conclusion, these present results reported indicate that the photo-products (3) obtained from 4-azidoisoquinolines by us are 1H-2,4-benzodiazepine derivatives.

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9. It is known that 1,4-dioxane stabilizes the singlet nitrene and thus promotes the azirine formation [cf., H. Takeuchi, K. Kinoshita, S.M. Abdul-Hai, M. Mitani, T. Tsuchida, and K. Koyama, J. Chem. Soc., Perkin Trans. 2, 1976, 1201].
10. Satisfactory elemental analyses and spectral data were obtained for all reaction products; e.g., (4a): oil; (8a): mp 185-190 °C (dec.); (10): oil; (11): mp 97-98 °C; (14): mp 220-221 °C .
11. Heating 10 in NH_4OH-MeOH at 80 °C gave 8a. Both 8a and 10 afforded phthalimidine by hydrolysis with aq. HCl.

Received, 27th August, 1984