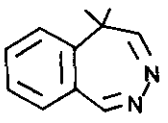
SYNTHESIS OF THE FIRST EXAMPLES OF N-UNSUBSTITUTED 1,3-BENZODIAZEPINES

Jyoji Kurita, Michiko Enkaku, and Takashi Tsuchiya*

School of Pharmacy, Hokuriku University,
Kanagawa-machi, Kanazawa 920-11, Japan

Abstract —— Treatment of both 3-benzyloxycarbonyl-3H-1,3- (6) and 1-benzyloxycarbonyl-1H-1,3-benzodiazepine (9) with trimethylsilyl iodide resulted in decarboxylation to give the N-unsubstituted 3H-1,3-benzodiazepine hydroiodide (8), which, on treatment with base, yielded the free bases (11). The 1,3-thienodiazepines (14) and (15) gave similar results. These results may indicate that the 3H-tautomers are most stable in the possible three 1,3-benzodiazepine tautomers.

The aza-cycloheptatrienes, such as azepines and diazepines, can in theory display annular tautomerism between one or more NH and CH forms. The tautomerism of these systems has been widely investigated.[1] In the monocyclic 1,2-diazepines, the 3H-,[2] 4H-, and 5H-tautomers[3] are known to be stable, but antiaromatic NH tautomers are unstable and can be isolated only as iron tricarbonyl complexes[4a] or N-substituted derivatives with electron-withdrawing substituents.[4b] Similarly, the 5H-2,3-benzodiazepines (1), one of CH forms, are more stable than the 1H-tautomers (2) which readily tautomerized to the 5H-tautomers (1) by treatment with bases, but antiaromatic NH forms have not been isolated.[5] In contrast, three tautomers of 1,2-benzodiazepines, i.e., 1H- (3),[6] 3H- (4),[7] and 5H-1,2-benzodiazepines (5),[8]



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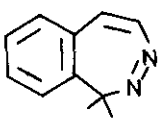

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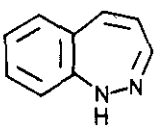

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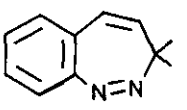

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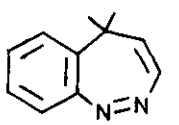


(5)

are known. The antiaromatic NH form (3) is more stable than the two CH forms (4) and (5), which are also tautomerized to the NH-isomer (3) by bases. Recently, we reported the first syntheses of 1-acyl-1H-1,3-[9] and 3-acyl-3H-1,3-benzodiazepines.[10] Therefore, we were interested in the preparation of N-unsubstituted 1,3-benzodiazepines in connection with the above-mentioned results.

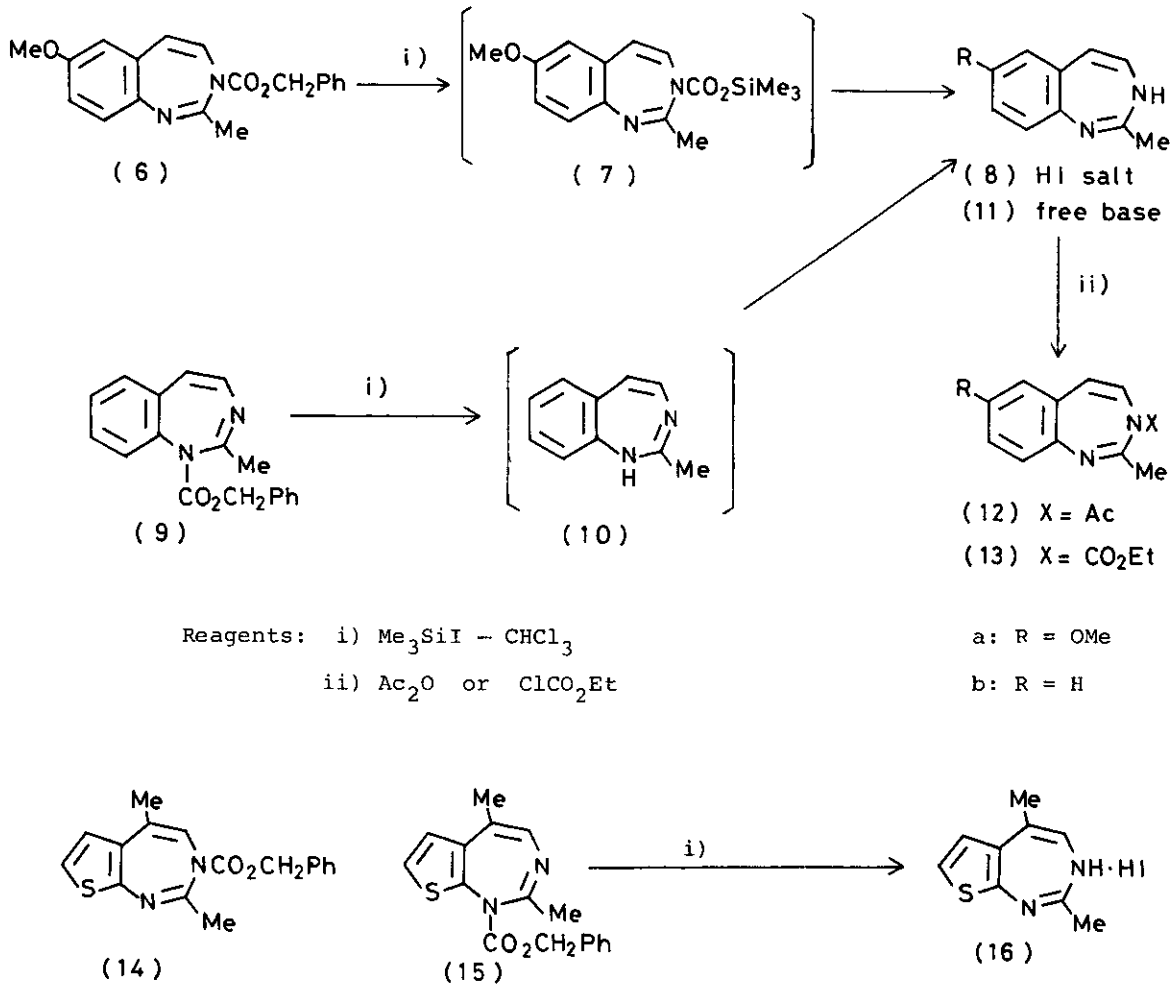
The N-acyl-1,3-benzodiazepines are extremely susceptible to ring-opening by either acids or bases.[9,10] Thus, attempts to remove the acyl groups such as acetyl, benzoyl, and ethoxycarbonyl group by hydrolysis have not been successful. However, treatment of the 3-benzyloxycarbonyl-3H-1,3-benzodiazepine (6)[11] with trimethylsilyl iodide[12] in chloroform at room temperature resulted in decarboxylation to give the desired N-unsubstituted 3H-1,3-benzodiazepine hydriodide (8a)[13] in 70% yield via the trimethylsilyl ester (7). The presence of the intermediate (7) was confirmed by NMR spectral analysis[14] in the reaction in $CDCl_3$ in an NMR sample tube, but it could not be isolated. Next, a similar reaction of the 1-benzyloxycarbonyl-1H-1,3-benzodiazepine (9) also gave the 3H-1,3-benzodiazepine salt (8b) presumably via the 1H-isomer (10), which is the noticeable result.

The salt (8) were treated with sodium bicarbonate in ether to give the 3H-free bases (11a,b)[15] and no 1H- and 5H-isomers. The free bases (11) decompose gradually at room temperature, so cannot be isolated as pure state. However, they were treated with acetic anhydride and ethyl chloroformate to give the corresponding 3-acyl-3H-1,3-benzodiazepines (12) and (13), respectively, which were identical with authentic samples.[10]

The spectral (NMR and UV) data of the 3H-1,3-benzodiazepines (8 and 11) are similar to those for the 3-acyl-3H-1,3-benzodiazepines[10] including the reported diazepines (6, 12, and 13) and consistent with the proposed structures, thus eliminating other possible structures such as their 1H- and 5H-isomers.

Although the 3H-free bases (11) are not so stable, the present results may indicate that the antiaromatic 3H-form is the most stable in the possible three 1,3-benzodiazepine tautomers, in contrast to the cases of 1,2- and 2,3-benzodiazepines and monocyclic 1,2-diazepines.

Similarly, both 3-benzyloxycarbonyl-3H-1,3-thienodiazepine (14) and 1-benzyloxycarbonyl-1H-1,3-thienodiazepine (15),[16] upon treatment with trimethylsilyl-iodide, gave the same product, the N-unsubstituted 3H-1,3-thienodiazepine hydriodide (16).



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11. The starting compounds (6) and (9) were prepared photochemically from the corresponding quinoline and isoquinoline N-benzyloxycarbonylimides according to the reported procedures.[9,10]
12. M.E. Jung and M.R. Lyster, J. Chem. Soc., Chem. Commun., 1978, 315; E. Vogel, H.-J. Altenbach, J.-M. Dressard, H. Schmickler, and H. Stegelmeier, Angew. Chem., Int. Ed. Engl., 1980, 19, 1016.
13. Satisfactory elemental analyses and spectral data were obtained for the 3H-diazepine salts (3); (3a): m.p. 217-219 °C; λ (ε) (EtOH) 220 (20900), 242 (17400), 250 (19000), 263 (28000); δ ($CDCl_3$) 2.09 (3H, s, 2-Me), 3.76 (3H, s, OMe), 5.12 (1H, d, 5-H), 5.29 (1H, d, 4-H), 6.3-6.7 (3H, m, Ar-H), $J_{4,5}$= 10 Hz. (3b): m.p. 197-198 °C.
14. (7a): δ ($CDCl_3$) 0.29 (9H, s, $SiMe_3$), 2.46 (3H, s, 2-Me), 3.82 (3H, s, OMe), 6.19 (1H, d, 5-H), 6.35 (1H, d, 4-H), 6.7-7.2 (3H, m, Ar-H), $J_{4,5}$= 8 Hz.
15. (11a): λ (ε) (EtOH) 220 (25000), 262 (20200), 270 (sh.); δ ($CDCl_3$) 1.75 (3H, s, 2-Me), 3.59 (3H, s, OMe), 4.75 (1H, d, 5-H), 5.29 (1H, d, 4-H), 5.91 (1H, d, 8-H), 6.25 (1H, d, 9-H), 6.27 (1H, s, 6-H), $J_{4,5}$= 9, $J_{8,9}$= 3 Hz.
16. The compounds (14) and (15) were prepared from the corresponding thieno-[2,3-b]pyridine and thieno[2,3-c]pyridine N-imides according to the reported procedures, respectively [T. Tsuchiya, M. Enkaku, and S. Okajima, Chem. Pharm. Bull., 1981, 29, 3173; T. Tsuchiya, H. Sawanishi, M. Enkaku, and T. Hirai, ibid., 1981, 29, 1539].

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