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Acid-Induced Rearrangements of 2,8-Diazabicyclo[3.2.1]octa-3,6-dienes Leading to 1,4-Dihydropyridine and Pyrrole Derivatives†

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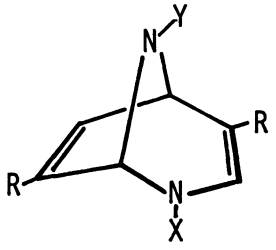
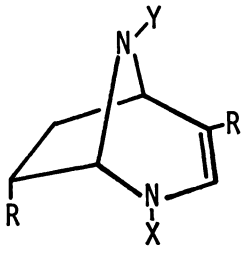
2,8-Dimethoxycarbonyl, 8-methoxycarbonyl, and 2,8-dimethyl derivatives of bicyclo[3.2.1]octa-3,6-diene gave 4-imino-1,4-dihydropyridines and pyrroles under acidic conditions. In addition, the C_6-C_7 dihydro-analogue produced 2-vinylpyrrole by the methyl carbamate elimination.

Nitrogen-bridged heterocycle, 2,8-diazabicyclo[3.2.1]octa-3,6-diene 1 is considered to be a good model for investigations of electronic interaction among nitrogen bridge at 8-position, C_6-C_7 double bond, and enamine moiety. The first synthesis of this diazabicyclic diene 1a possessing 2,8-dimethoxycarbonyl and 4,7-di-t-butyl substituents was described in a previous paper,[1] This molecular skeleton is hitherto unknown and therefore the chemical properties are of interest from view point of nitrogen lone pair influence toward the conjugative and homoconjugative interactions. We wish to present the novel acid-induced rearrangements of 1a-d and the C_6-C_7 dihydro-analogues (2a-b) in this paper.



1a: X=Y=COOMe
1b: X=Y= H
1c: X= H, Y=COOMe
1d: X=Y= Me



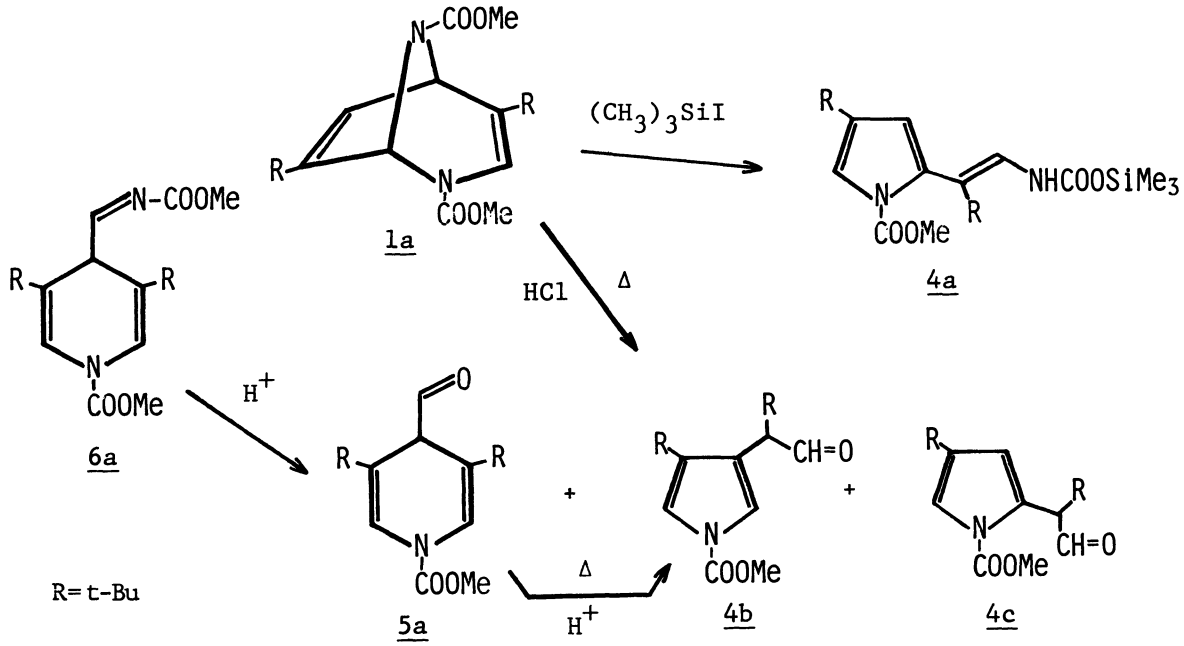
R= t-Bu

2a: X=Y=COOMe
2b: X=Y= Me

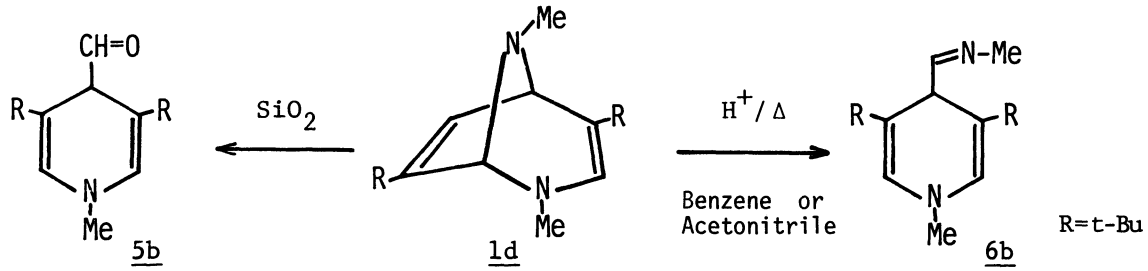
Attempts to prepare the N,N-unsubstituted molecule 1b have been unsuccessful in this stage. The decarboxylation of 1a using acidic and basic conditions resulted in the formation of ploymeric materials. The mono-ester derivative 1c,[2] which was prepared by the reaction of 1a with methyl lithium at -35 °C, was also unstable and transformed into 3,5-di-t-butylpyridine 3[3] by standing in a carbontetrachloride solution at room temperature. For the synthesis of 1b, trimethylsilyl iodide method[4] was applied to 1a, but the pyrrole derivative 4a[5] was obtained as a sole product. These unexpected findings prompted us to investigate the chemical behavior of this new heterocycle in more detail under various conditions.

When a methanol solution of 2,8-dimethoxycarbonyl derivative 1a was refluxed for 12 h in the presence of 2 M hydrochloric acid, 1-methoxycarbonyl-4-formyl-1,4-

† This paper is dedicated to late Professor Ryozo Goto, Kyoto University.

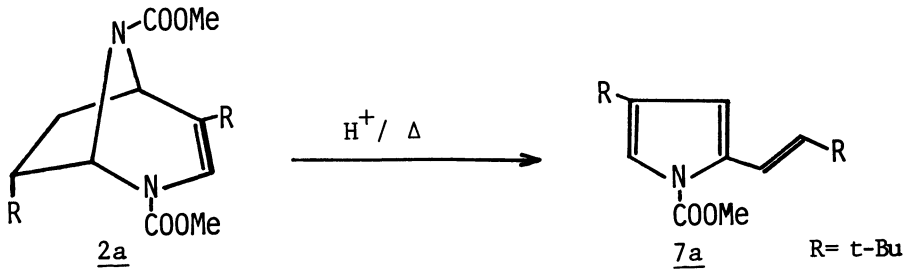


dihydropyridine (5a)[6] and (1-formyl-2,2-dimethyl)propylpyrroles (4b and 4c)[7] were obtained in 31, 14, and 10% yield, respectively. The structures of products were determined on the basis of the spectral properties shown in references. The imaginated precursor, 4-(N-methoxycarbonylimino)-1,4-dihydropyridine (6a,[8] mp 108-109 °C) which was independently synthesized from 2,8-diazatricyclo[4.2.0.$0^{5,7}$]oct-3-ene,[9] has actually afforded the degradation products 5a and 4b under similar acidic conditions indicating the correctness of the reaction pathway shown in Scheme 1.



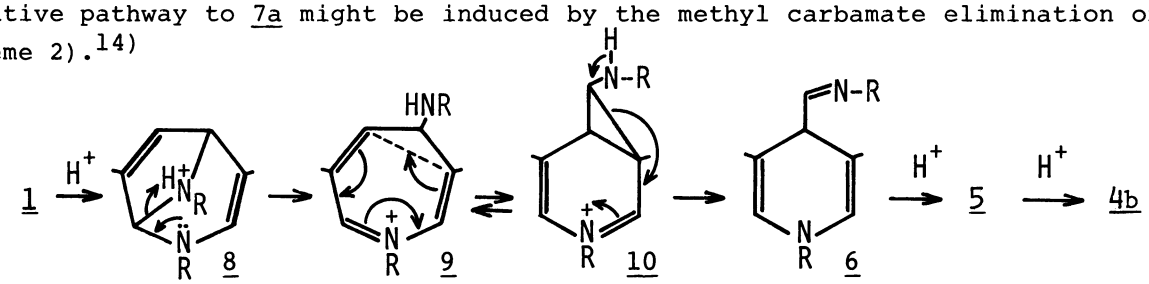
2,8-Dimethyl derivative 1d was prepared by the $LiAlH_4$ reduction of 1a in 93% yield: m/e 248(M^+,20%), 206(base); IR(neat) 2960, 1640, 1350 cm^{-1}; NMR(90 MHz, C_6D_6) δ 1.03 (s, 9H), 1.10 (s, 9H), 2.12 (s, 3H), 2.54 (s, 3H), 3.42 (dd, J= 2.5, 1.2 Hz, 1H), 3.90 (brs, 1H), 5.40 (dd, J= 1.2, 1.4 Hz, 1H), 5.67 (d, J= 2.5 Hz, 1H); UV(cyclohexane) λmax= 246 (4010) nm. This compound was also extremely acid sensitive and immediately converted into 1-methyl-4-formyl-1,4-dihydropyridine 5b[10] by contacting with silica gel. When a benzene solution of 1d was carefully treated with a trace of p-toluenesulfonic acid, 4-(methylimino)dihydropyridine (6b,[11] mp 81-82 °C) was isolated in 92% yield. This novel ring construction leading into 1,4-dihydropyridine could be observed in the absence of acid catalyst, i.e., 1d was converted to 6b by standing in a benzene solution at 25 °C for 6 h, and in an acetonitrile solution within 1 min. Here, we wish to emphasize that this novel transformation reaction is inherent in this 2,8-diazabicyclo[3.2.1]-octadiene moiety being accelerated by the higher lone-pair density on nitrogen atoms.

In order to gain insights of this rearrangement, the C_6-C_7 dihydro-analogues 2a-b[12] were prepared using diimide reduction. When compound 2a was refluxed with 2 equivalent of p-toluenesulfonic acid in benzene for 30 min, vinylpyrrole 7a[13] was produced in 59% yield. The dimethyl derivative 2b gave a labile one-to-one salt under the same conditions.

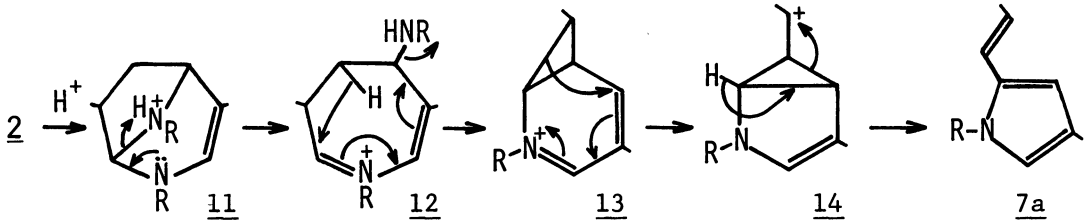


2a 7a R= t-Bu

From these experimental results, the reaction pathway leading to 1,4-dihydropyridine 6 is depicted in Scheme 1. Protonation at the nitrogen lone-pair at 8-position associated with the electron donating effect of 2-nitrogen initiates the C_1-N_8 bond fission leading to azepinium cation 9. This species is equilibrated with homopyridinium cation 10 which smoothly rearranges to 4-imino-1,4-dihydropyridine 6. The ring contraction of the homopyridinium ion to the dihydropyridine is not possible to undergo in the case of the dihydro-derivative 2, where an alternative pathway to 7a might be induced by the methyl carbamate elimination of 12 (Scheme 2).[14]



Scheme 1.



Scheme 2.

These unique acid-induced rearrangements of 2,8-diazabicyclo[3.2.1]octadienes giving 1,4-dihydropyridines and pyrroles are useful as a synthetic procedure of related heterocycles.

References

1) T. Kumagai, K. Satake, K.Kidoura, and T. Mukai, Tetrahedron Lett., 24, 2275 (1983).

2) Compound 1c : colorless needles mp 82.0-83.0 °C, m/e 278(M^+,72%), 263(base); IR(KBr) 3440, 2950, 1710, 1620 cm^{-1}; NMR(C_6D_6) δ 1.03 (s, 18H), 3.47 (s, 3H), 3.57 (brs, 1H), 4.40 (brs, 1H), 5.23 (brs, 1H), 5.37 (brs, 1H), 5.59 (d, J=

3.0 Hz, 1H); UV λmax= 233 (ε 3290) nm in ethanol.

3) Product 3 : colorless needles mp 60-61 °C, m/e 191(M^+,28%), 176(base); IR(KBr) 2950, 1475, 1425, 1110, 725 cm^{-1}; NMR($CDCl_3$) 1.34 (s, 18H), 7.58 (t, J= 2.3 Hz, 1H), 8.40 (d, J= 2.3 Hz, 2H); UV λmax= 262 (2420) nm in cyclohexane.

4) T.L. Ho and G.A. Olah, Angew. Chem., 88, 847 (1976).

5) Product 4a : NMR($CDCl_3$) δ 1.04 (s, 9H), 1.23 (s, 9H), 3.83 (S,3H), 5.90 (m, 2H), 6.58 (dd, J= 3.8, 9.6 Hz, 1H), 7.03 (m, 1H).

6) Product 5a : colorless oil, m/e 251(21%), 250(base), 191(24)); IR(neat) 2970, 1725, 1675, 1635 cm^{-1}; NMR($CDCl_3$) δ 1.12 (s, 18H), 3.83 (s, 3H), 3.85 (brs, 1H), 6.81 (brs, 2H), 9.05 (d, J= 5.0 Hz, 1H); UV λmax= 213 (11670), 239 (13060) nm in acetonitrile.

7) Product 4b : NMR($CDCl_3$) δ 1.02 (s, 9H), 1.22 (s, 9H), 3.89 (s, 3H), 4.74 (d, J= 2.6 Hz, 1H), 6.11 (d, J= 1.8 Hz, 1H), 6.99 (d, J= 1.8 Hz, 1H), 9.70 (d, J= 2.6 Hz, 1H); UV λmax= 228 (8720), 296 (850) nm in acetonitrile.
Product 4c : NMR($CDCl_3$) δ 1.09 (s, 9H), 1.26 (s, 9H), 3.59 (d, J= 4.9 Hz, 1H), 3.97 (s, 3H), 6.98 (d, J= 2.3 Hz, 1H), 7.25 (d, J= 2.3 Hz, 1H), 9.53 (d, J= 4.9 Hz, 1H); UV λmax= 233 (13270), 304 (540) nm in acetonitrile.

8) Compound 6a : colorless prisms, m/e 336(M^+,1.2%), 250(base); IR(KBr) 2950, 1725, 1670, 1645 cm^{-1}; NMR($CDCl_3$) δ 1.13 (s, 18H), 3.75 (s, 3H), 3.82(s, 3H), 3.99 (dt, J= 7.5, 1.2 Hz, 1H), 6.77 (brs, 2H), 7.63 (d, J= 7.5 Hz, 1H); UV λmax= 239 (6400) nm in cyclohexane.

9) The acetone-sensitized irradiation of 1a gives two diazatricyclic octenes. The detail will be described in a different paper.

10) Product 5b : yellow prisms mp 84.5-85 °C, m/e 235(M^+,2.5%), 206(base), 176(31), 78(19); IR(KBr) 2970, 1720, 1670, 1610, 1350 cm^{-1}; NMR($CDCl_3$) δ 1.08 (s, 18H), 2.97 (s, 3H), 3.78(dt, J= 4.4, 1.5 Hz, 1H), 5.90 (d, J= 1.5 Hz, 2H), 9.22 (d, J= 4.4 Hz, 1H).

11) Product 6b : colorless needles, m/e 248(M^+,4.8%), 206(base); IR(KBr) 2950, 1665, 1615, 1345 cm^{-1}; NMR($CDCl_3$) δ 1.08 (s, 18H), 2.96 (s, 3H), 3.13 (d, J= 1.5 Hz, 3H), 3.85 (dt, J= 7.2, 1.5 Hz, 1H), 5.82 (d, J=1.5 Hz, 2H), 7.15 (dq, J= 7.5, 1.5 Hz, 1H); UV λmax= 241 (7090), 314 (1120) nm in cyclohexane.

12) Compound 2a : colorless oil, 338 (M^+,23%), 195(base), 181(65%), 166(44%); IR (neat) 2950, 1715, 1645 cm^{-1}; NMR($CDCl_3$) δ 0.93 (s, 9H), 1.08 (s, 9H), 1.66 (d, J= 4.8 Hz, 1H), 2.05-2.50 (m, 2H), 3.66 (s, 3H), 3.77 (s, 3H), 4.36 (brs, 1H), 6.06 (brs, 1H), 6.37 (d, 1H); UV λmax= 227 (14940) nm in cyclohexane.
Compound 2b : colorless needles mp 26.5-27.5 °C, m/e 250(M^+,12%), 166(73%), 151 (base); IR(neat) 2950, 1640, 1355 cm^{-1}; NMR(C_6D_6) δ 0.96 (s, 1H), 1.02 (s, 9H), 1.63 (d, J= 4.8 Hz, 1H), 2.20 (s, 3H), 2.20 (m, 2H), 2.47 (s, 3H), 3.23 (d, J= 5.2 Hz, 1H), 3.50 (m, 1H), 5.50 (dd, J= 0.7, 0.7 Hz, 1H); UV λmax= 252 (4830) nm in cyclohexane.

13) Product 7a : colorless powder mp 65.0-66.0 °C, m/e 263(M^+,54.8%), 248(base), 192 (28), 56 (28); IR(KBr) 1755, 1430, 1340, 1245 cm^{-1}; NMR($CDCl_3$) δ 1.10 (s, 9H), 1.20 (s, 9H), 3.89 (s, 3H), 6.02 (d, J= 16.0 Hz, 1H), 6.27 (m, 1H), 6.84 (d, J= 16.0 Hz, 1H), 6.92 (d, J= 1.8 Hz, 1H); UV λmax= 230 (8810), 285 (10140) nm in cyclohexane.

14) The formation of 4a and 4c would be elucidated by the N_2-protonation of 1a.

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