REACTION OF 1-METHYL- $\Delta^{1(8)}$-DEHYDROPYRROLIZIDINE WITH DIMETHYL ACETYLENEDICARBOXYLATE[1]

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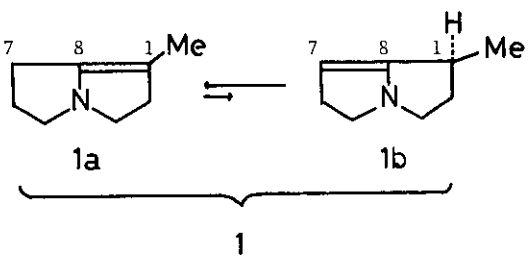
Abstract— The reaction of 1-methyl- $\Delta^{1(8)}$-dehydropyrrolizidine with dimethyl acetylenedicarboxylate in hexane gave dimethyl 7-methyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine-8,9-dicarboxylate (3a) and dimethyl 1-methyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine-8,9-dicarboxylate (4a). The choice of protic solvent like methanol gave rise to the formation of a tricyclic compound.

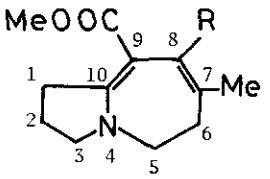
Recently, we have synthesized 1-methyl- $\Delta^{1(8)}$-dehydropyrrolizidine (1)[2], the fundamental constituent of nesine moiety of purrolizidine alkaloids, and observed the isomerization between the $\Delta^{1(8)}$-isomer (1a) and $\Delta^{7(8)}$-isomer (1b), in which 1a is predominant. As a part of our studies on the chemistry of pyrrolizidines and related compounds[2-5], particularly on the potential reactivities of the new heterocyclic enamine 1, we examined the reaction of 1 with dimethyl acetylenedicarboxylate (DMAD; 2). In this paper, we wish to deal with the structures of the products as well as the reaction mechanism.



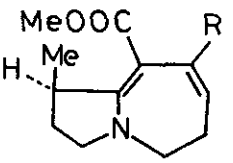
An equivalent molar amount of DMAD was added dropwise to a stirred solution of the enamine 1 in dry n-hexane under ice cooling. After stirring for 2 hours at room temperature, the solvent was evaporated under reduced pressure and the residue was chromatographed by a column of silica gel to give 1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine derivatives 3a and 4a in 36 and 20 % yield, respectively[6].

The structures of the products were confirmed by their spectral evidence. Thus, the both products 3a and 4a showed the correct molecular ion peak ($C_{14}H_{19}NO_4$) in the high resolution mass spectra, and had two strong absorptions at 1635-1695 and 1720-1730 cm^{-1}, indicating the presence of two dissimilar C=O groups, in the IR spectra. In the NMR spectrum of 3a, the signals of a singlet at δ 2.00 ppm being assignable to the allylic methyl protons of C_7 and of two singlets at δ 3.59 and 3.71 ppm ascribable to the two $COOCH_3$ (C_8 and C_9), are characteristic. On the other hand, the NMR spectrum of 4a revealed a signal at δ 6.58 ppm as a triplet (J=7.5 Hz), assignable to the vinyl proton of C_7, aliphatic methyl protons at δ 1.19 ppm as a doublet (J=7.0 Hz), and two singlets at δ 3.58 and 3.70 ppm attributable to two $COOCH_3$ (C_8 and C_9). Further support for the assingment of the other signals of compounds 3a and 4a could be obtained by spin-spin decoupling method, the results of which are recorded in the experimental section.

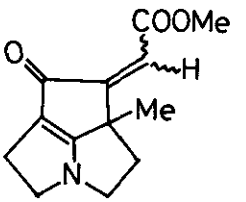
When methanol was used as the solvent in above reaction, the novel tricyclic compound (5) having cyclopenta[3,2,1-g,h]pyrrolizine skeleton could be isolated in 28 % yield, in addition to the compound 3a (33 % Yield)[7]. The structure of 5 was established by spectroscopic method (see experimental section), together with other chemical data[8].



3a : R=COOMe
3b : R H



4a : R= COOMe
(4b : R= H)



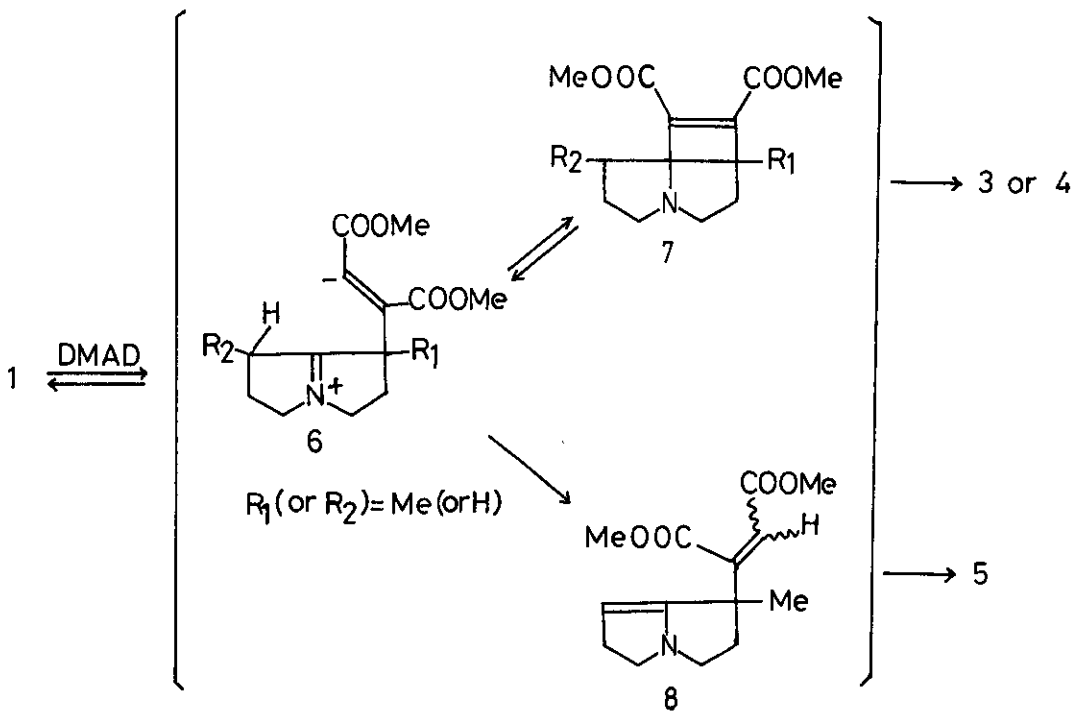
5

In the reaction of the enamine 1 with methyl acetylenecarboxylate in ether the compound 3b could be obtained in 41 % yield, attempts to isolate the compound 4b and the tricyclic compound corresponding to 5, however, failed.

It is apparent that the reaction of the enamine 1 (1a ⇌ 1b) with DMAD proceeded via thermal [2+2] cycloaddition[11] followed by isomerization of the resulting labile cyclobutene intermediate such as 7 to the products 3a and 4a. To our knowledge, concerning the cycloaddition of DMAD to heterocyclic enamines, no report has appeared on the isolation of the two adducts derived from the possible two isomers in the isomerization of enamines.

Furthermore, we are considering that the mechanism of the formation of 5, the ratio of which is dependent on the polarity of the solvent, merits some comment. Thus, the initial product of addition

of the enamine 1 to DMAD may be represented as the dipolar species (6)[12]. The dipolar species 6 would result in a prototropic shift of the C_7 proton to the anionic side chain and then cyclization giving the tricyclic compound 5. The idea of the intramolecular prototropic shift (or proton abstraction of carbanion) process (6→8) was supported by experiment used deuterated methanol[14].



EXPERIMENTAL

IR spectra were recorded with a Hitachi-295 instrument and NMR spectra were measured with a Hitachi-R-22 spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a JEOL-01-SG instrument with a direct inlet system operating at 75 eV.

Preparation of the enamine (1) : The enamine 1, bp 94°C (73 mmHg), was prepared by the method described previously[2] in 73 % yield as a colorless oil from γ-(N-2-oxopyrrolidinyl)-α-methylbutylic acid.

Reaction of the enamine (1) with dimethyl acetylenedicarboxylate (DMAD) : To a solution of the enamine 1 (1.00g, 8.12 mmole) in dry n-hexane (20ml) was slowly added dropwise a solution of DMAD (1.20g, 8.45mmole) in n-hexane (5ml) with stirring under ice cooling. After stirring for 2 hours

at room temperature, evaporation of the solvent gave an oily residue which was purified by a column of silica gel (Wakogel C-300). Successive elution with n-hexane and ether afforded dimethyl 7-methyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine-8,9-dicarboxylate (3a) and dimethyl 1-methyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine-8,9-dicarblxylate (4a) in 36 and 20 % yield, respectively[13]. With ether as a solvent in above reaction, the isolated yields of 3a and 4a were 29 and 15 %, respectively.

Compound 3a : IR (liq. film) max 1695 and 1730 cm^{-1} (two dissimilar ester C=O groups); NMR ($CDCl_3$) δ 1.55-2.10(2H, m, C_2-methylene protons), 2.00(3H, s,C_7-methyl protons), 2.28-2.45(2H, m, C_6-methylene protons), 3.20-3.60(6H, m, C_1,$C_3$and C_5-methylene protons), 3.59(3H, s, C_8-$COOCH_3$), 3.71 (3H, s, C_9-$COOCH_3$) ppm. Analysis was carried out by high-resolution mass spectrometry :calcd for $C_{14}H_{19}NO_4$, 265.1313; found, 265.1321.

Compound 4a : IR (liq. film) max 1635 and 1720 cm^{-1} (two dissimilar ester C=O groups); NMR ($CDCl_3$) δ 1.19(3H, d, C_1-CH_3, J=7.0 Hz), 1.4-2.3(2H, m, C_2-methylene protons), 2.40-2.65(2H, m, C_6-methylene protons), 3.15-3.70(4H, m $C_3$and C_5-methylene protons), 3.58(3H, s, C_8-$COOCH_3$), 3.70(3H, s, C_9-$COOCH_3$) and 6.58(1H,t, C_7-H, J=7.5 Hz) ppm. Analysis was carried out by hith-resolution mass spectrometry: calcd for $C_{14}H_{19}NO_4$, 265.1313; found, 265.1318.

When the reaction described above was carried out in methanol as the solvent[14], the tricyclic compound (5) was obtained as a pale yellow oil in 28 % yield, in addition to the compound 3a (33 % yield).

Compound 5 : IR ($CHCl_3$) max 1725 and 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.52(3H, s, C-CH_3), 1.85-3.95(8H, m, methylene protons of pyrrolizidine ring), 3.80(3H, s, -$COOCH_3$), and 6.98(1H, s, =C=CH-COOMe) ppm. Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{13}H_{15}NO_3$, 233.1052; found, 233.1060.

Reaction of the enamine (1) with methyl acetylencarboxylate: By using the similar procedure as described above, methyl 7-methyl-1,2,5,6-tetrahydro-3H-pyrrolo[1,2-a]azepine-9-carboxylate(3b) was obtained by the reaction of the enamine 1 (2.255 g, 18.3 mmole) with methyl acetylenecarboxylate (1.74 g, 20.7 mmole) in ether. The yield was 41 %.

Compound 3b : IR (liq. film) max 1670 cm^{-1}(C=O); NMR ($CDCl_3$) δ 1.82(3H, s, C_7-CH_3), 1.70-2.10 (2H, m, C_2-methylene protons), 2.30-2.45(2H, m, C_6-methylene protons), 3.20(2H, t, C_1-methylene protons, J=8.0 Hz), 3.30-3.55(4H, m, C_3 and C_5-methylene protons), 3.68(3H, s, C_9-$COOCH_3$), and 6.32 (1H, bs, C_8-H) ppm. Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{12}H_{17}NO_2$, 207.1259; found, 207.1261.

REFERENCES AND NOTES

(1) Part VI in this series of studies on pyrrolizidines and related compounds. For Part V, see S. Miyano, S. Fujii, O. Yamashita, N. Toraishi and Kunihiro Sumoto, J. Heterocycl. Chem., 19, 1465 (1982).

(2) This chemical name is convenient for discussion, especially, including the isomerization of enamines. The alternate name 1-methyl-2,3,5,6-tetrahydro-1H-pyrrolizine also can be used. For the preparation, see S. Miyano, S. Fujii, O. Yamashita, K. Sumoto, F. Satoh and T. Masuda, J. Org. Chem., 46, 1737 (1981).

(3) S. Miyano, O. Yamashita, S. Fujii, T. Somehara, K. Sumoto, F. Satoh and T. Masuda, Heteracycles, 16, 755 (1981).

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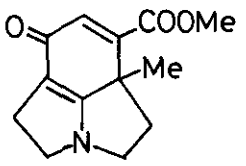
(6) A small amount of the compound 5 (ca 10 %) was detectable by GC analysis of the reaction mixture.

(7) Trace amount of 4a was detected by GC analysis of the reaction mixture, however, our attempts to isolate failed.

(8) Despite careful analysis of the spectra it remaines difficult to exclude the alternative tricyclic structure A being expected from the cyclization of 8, however, the items that (i) in the reaction of 1 with methyl acetylenecarboxylate in methanol the corresponding tricyclic derivative coule not be obtained; (ii) the intermediate (8) having cis-configuration regarding two ester groups would not give the compound A, but for the isomerization into trans-configuration[9]; (iii) the similar cyclization process (8 → 5) has observed in the reaction of DMAD with some nucleophiles having two nucleophilic centers in the molecule[10], would allow us to define the structure 5.



A

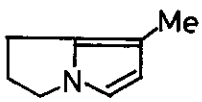
(9) M. D. Menachery. J. M. Saá and M. P. Cava, J. Org. Chem., 46, 2584 (1981).

(10) H. Nagase, Chem. Pharm. Bull., 21, 270 (1973); H. Nagase, Chem. Pharm. Bull., 21, 279 (1963).

(11) A. G. Cook, "Enamine: Synthesis, Structure and Reactions", Marcel Dekker, New York and London, 1969, and related references cited therein.

(12) For example, see W. Verboom, G. W. Visser, W. P. Trompenaars, D. N. Reinhoudt, S. Harkema and G. J. van Hummel, Tetrahedron, 37, 3525 (1981), and related references are cited therein.

(13) In some runs, a small amount of 1-methyl-1,2-dihydro-3H-pyrrolizine (B) was obtained. This compound is formed by dehydrogenation or disproportionation of the enamine 1 (unpublished work in this laboratory), which will be described in the future communication.



B

(14) When the reaction was carried out in CH_3OD (99%), the signal at δ 6.98 ppm showed the integration being equivalent to 7% of the theoretical integration, which would be sufficient to explain the least of intramolecular prototropic shift, considering the proton exchangeability[11] at C_1 and C_7 of the enamine 1. However, we have no evidence to rule out the proton abstraction from CH_3OD.

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