Studies of Enamines. VI.[1] The Formation of New Michael Type Adducts and Pyrrolizine Compounds in the Reaction of Enamines with Pyrrole

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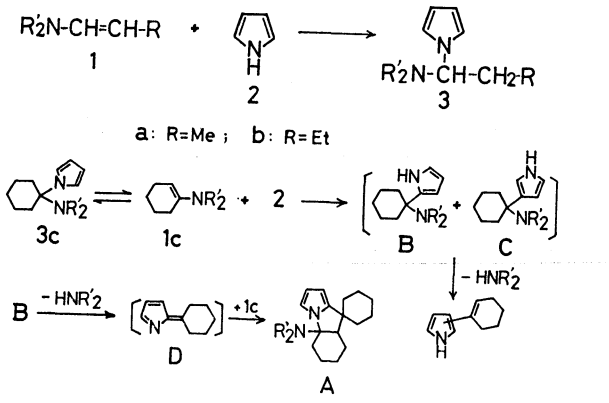
While the reaction of 1-(1-pyrrolidinyl)propene (**1a**) and -1-butene (**1b**) with pyrrole (**2**) under mild conditions afforded the Michael type N,N–1 : 1 adducts **3**, under forcing conditions enamines **1** reacted with **2** to give the Michael type C,N– 1: 1 adducts **4**, accompanied with pyrrolizine compounds **5**. It has been shown that the pyrrolizine **5** was formed *via* the cycloaddition reaction of **1** with an azafulvene intermediate arising from **4** by the elimination of pyrrolidine.

In a previous communication,[2] we have reported that under mild conditions 1-(1-pyrrolidinyl)propene (**1a**), -1-butene (**1b**), and -cyclohexene (**1c**) reacted with pyrrole (**2**) to give the Michael type N,N-1 : 1 adducts **3a**, **3b**, and **3c**, respectively. It has been also found that the adduct **3c** decomposed at elevated temperature to regenerate **1c** and **2**, and that the reaction of **1c** with **2** under forcing conditions afforded the novel pyrrolizine compound **A**, accompanied with cyclohexenylpyrroles. The pathway depicted in Scheme 1 has been tentatively proposed for this novel reaction: under forcing conditions the reaction would proceed *via* an initial formation of Michael type C,N–1 : 1 adducts, **B** and **C**, followed by the elimination of pyrrolidine to yield cyclohexenylpyrroles and azafulvene intermediate **D**. The azafulvene **D** would undergo cycloaddition reaction with **1c** to afford the pyrrolizine **A**.[1]



NR_2': 1-pyrrolidinyl

Scheme 1.

During the course of a further investigation of the reaction of enamines with pyrrole (**2**), it has been found that enamines **1a** and **1b** reacted with **2** to give the new Michael type C,N–1 : 1 adducts whose structures correspond to that of **B**. This paper deals with the reaction of **1a** and **1b** with **2**, and with the discussion of the pathway for the formation of pyrrolizine compounds.

Results and Discussion

The reaction of **1a** with **2** at 110 °C for 12 hr in a stream of nitrogen gave two new compounds **4a**, mp 93—94 °C, and **5a**, bp 124—126 °C/4 mmHg, in 20.6 and 6.1% yields respectively, and Michael type N,N–1 : 1 adduct **3a**, which is a main product in the reaction at 80 °C for 5 min,[2] was not formed.

The molecular formula of **4a** agreed with that of a 1 : 1 adduct of **1a** and **2**, that is, **4a** is an isomer of **3a**, and the IR spectrum showed the band ascribable to NH absorption at 3190 cm^{-1}. The NMR spectrum in carbon tetrachloride (CCl_4) exhibited signals at δ 3.03 (1H, q, $\rightarrow$CH), 5.89 (2H, m, β-protons of pyrrole ring (β-**H**)), and 6.52 ppm (1H, dd, α-proton of pyrrole ring (α-**H**)), besides methylene and methyl protons. On the basis of above spectral data, **4a** was clearly assigned as 1-(1-pyrrolidinyl)-1-(2-pyrrolyl)propane, whose structure corresponds to that of a compound of type **B** assumed as an initial intermediate in Scheme 1.

The minor product **5a**, whose molecular formula corresponded to that of a compound arising from a 2 : 1 adduct of **1a** and **2** by the elimination of one mole of pyrrolidine, was deduced to be 1,2-dihydro-1-ethyl-2-methyl-3-(1-pyrrolidinyl)-3H-pyrrolizine. The IR spectrum showed no NH absorptions, and the NMR spectrum in CCl_4 exhibited signals at δ 4.65 (1H, d, $\rightarrow$**CH**, J=4.5 Hz), 5.60, 5.97 (each 1H, m, β-**H**), and 6.41 ppm (1H, dd, α-**H**), besides methyl, methylene, and methine protons.

A potential structure, 1-ethyl-3-methyl-2-(1-pyrrolidinyl)pyrrolizine **5'**, might be excluded from the structure for the minor product, because the signal at δ 4.65 ppm in the NMR spectrum might be assignable to the 3-methine proton of **5a**, but not to 2- or 3-methine proton of **5'**. Furthermore, the relative arrangements of substituents of **5a** are similar to those of the pyrrolizine **A** whose structure has been clearly established.[1]

The configuration of **5a** is not clear, because of appearance of 1- and 2-methine protons in a region of methylene protons. In view of the value of coupling constant of 3-methine proton (J=4.5 Hz), however, it may be thought that the 2-methyl and 3-pyrrolidinyl groups are situated *trans*.

Similarly, the reaction of **1b** with **2** at 100 °C for 11 hr afforded the corresponding Michael type C,N–1 : 1 adduct **4b** and pyrrolizine compound **5b** in 44.1 and 7.7% yields, respectively.

When the *N,N*-adduct **3a** was heated at 120 °C for 10 hr, **4a** was obtained in 22.6% yield, along with traces of **5a**. Under similar conditions, however, **3b** gave only **4b**, and no **5b** could be isolated. These facts indicate that **3a** and **3b** as well as **3c** decomposed at elevated temperature to regenerate the correspond-

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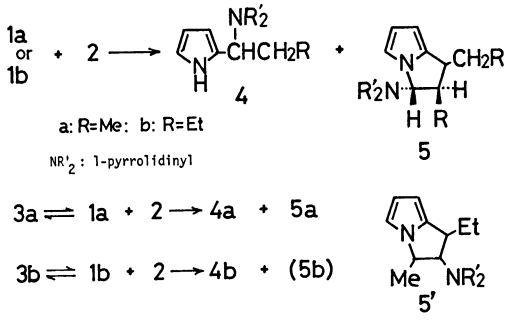


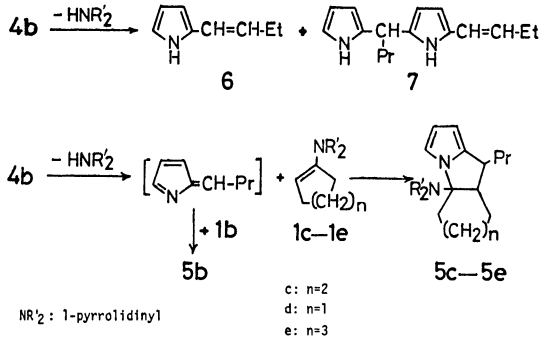
Scheme 2.

ing enamines **1** and **2** (Scheme 2).

In order to know whether the Michael type C,N–1 : 1 adduct is a real intermediate producing alkenylpyrrole and pyrrolizine compound or not, several reactions toward **4b** were investigated.

On heating of **4b** at 150 °C for 5 hr in a stream of nitrogen, the expected 2-(1-butenyl)pyrrole (**6**) and a dimer **7** of **6** were obtained in 34.6 and 39.4% yields, respectively. On the basis of the spectral data, the structure of dimer **7** has been tentatively assigned 1-(2-pyrrolyl)-1-{2-[5-(1-butenyl)]pyrrolyl}butane.

On the other hand, heating of **4b** in the presence of **1b** at 100 °C for 10 hr afforded the expected pyrrolizine compound **5b** in 31.2% yield. Furthermore, **4b** was allowed to react with 1-(1-pyrrolidinyl)cyclohexene (**1c**), -cyclopentene (**1d**), and -cycloheptene (**1e**) under similar conditions, giving the corresponding pyrrolizine compounds **5c**, **5d**, and **5e**, in 65.0, 60.0, and 98.7% yields, respectively (Scheme 3). These facts strongly indicate that an azafulvene intermediate would be initially formed by an alternative elimination mode of pyrrolidine from **4b**, followed by cycloaddition reaction of the azafulvene with enamine **1** to give pyrrolizines **5**.

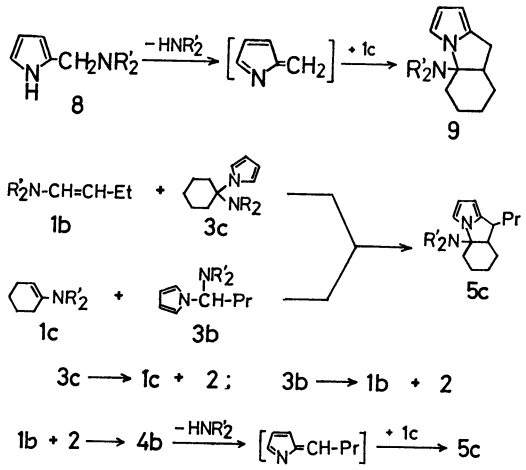


Scheme 3.

Furthermore, the following results seem to provide evidence for the formation of pyrrolizine compound *via* the cycloaddition reaction of an azafulvene with enamine.

2-(1-Pyrrolidinylmethyl)pyrrole (**8**), which would form only an azafulvene by the elimination of pyrrolidine, reacted with enamine **1c** at 120 °C to give the expected pyrrolizine compound **9** in 49.3% yield.

In both reactions of enamine **1b** with the *N,N*-adduct **3c**, and of enamine **1c** with the *N,N*-adduct **3b** at 120 °C, pyrrolizine compound **5c** as a sole isolated product was obtained in 35.3 and 33.7% yields, respectively. These facts indicate the participation of the same intermediate for the formation of **5c** in both reactions. Under the reaction contitions, both *N,N*-adducts **3b** and **3c** decompose to regenerate the respective enamines, **1b** and **1c**, and pyrrole (**2**). This is followed by the reaction of regenerated pyrrole (**2**) with more reactive enamine **1b** than **1c** to form the C,N-adduct **4b**. Then, **4b** is converted to an azafulvene, and the azafulvene undergoes cycloaddition reaction with the remaining enamine **1c** to give **5c** (Scheme 4).



Scheme 4.

In conclusion it is now clear that the reaction of enamine **1** with pyrrole (**2**) proceeds through the pathway illustrated by the reaction of **1c** with **2** in Scheme 1.

Experimental

All melting and boiling points are uncorrected. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV. The NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with TMS as an internal reference.

*Reaction of 1-(1-Pyrrolidinyl)propene (**1a**) with Pyrrole (**2**).* A mixture of 10.0 g (0.09 mol) of **1a** and 4.0 g (0.06 mol) of **2** was stirred at 110 °C for 12 hr in a stream of nitrogen. The reaction mixture was subjected to fractional distillation to give 2.2 g (20.6% based on **2**) of 1-(1-pyrrolidinyl)-1-(2-pyrrolyl)-propane (**4a**), bp 90—93 °C/5 mmHg, as colorless oil which solidified, and 0.8 g (6.1% based on **2**) of 1,2-dihydro-1-ethyl-2-methyl-3-(1-pyrrolidinyl)-3H-pyrrolizine (**5a**), bp 124—126 °C/4 mmHg, as pale yellow oil. Recrystallization from petroleum ether (bp 40—65 °C) afforded pure **4a**, mp 93—94 °C, as colorless prisms.

4a; IR (KBr): 3190 cm^{-1} (ν_{NH}). NMR (CCl_4): δ 0.7 (3H, t, CH_3), 1.5—2.1 (6H, m, CH_2), 2.1—2.9 (4H m, CH_2), 3.03 (1H, q, >CH), 5.89 (2H, m, β-**H**), 6.52 (1H, dd, α-**H**), 9.32 (1H, broad **NH**). Mass: *m/e* 178 (M^+). Found: C, 74.30; H, 10.43; N, 15.85%. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71%.

5a; NMR (CCl_4): δ 1.1 (6H, m, CH_3), 1.4—1.95 (6H, m, CH_2), 2.0—3.1 (6H, m, $2\times CH_2+2\times$ >CH), 4.65 (1H,

d, >CH, J=4.5 Hz), 5.60, 5.97 (each 1H, m, β-H), 6.41 (1H, dd, α-H). Mass: *m/e* 218 (M^+). Found: C, 76.85; H, 10.19; N, 12.77%. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.71%.

*Reaction of 1-(1-Pyrrolidinyl)-1-butene (**1b**) with **2**.* A mixture of 40.0 g (0.32 mol) of **1b** and 43.0 g (0.64 mol) of **2** was stirred at 100 °C for 11 hr in a stream of nitrogen. Excess of **2** was removed by vacuum distillation, and the residue was allowed to stand over night to give colorless crystals. Filtration and recrystallization from petroleum ether (bp 40—65 °C) afforded 26.5 g of 1-(2-pyrrolyl)-1-(1-pyrrolidinyl)butane (**4b**), mp 89 °C, as colorless prisms.

Vacuum distillation of the filtrate afforded 0.6 g of **4b** and 6.06 g (7.7%) of 1,2-dihydro-2-ethyl-1-propyl-3-(1-pyrrolidinyl)-3H-pyrrolizine (**5b**), bp 117—118 °C/2 mmHg, as pale yellow oil.

The total yield of **4b** was 27.1 g (44.1% based on **1b**). IR (KBr): 3180 cm^{-1} (ν_{NH}). NMR (CCl_4): δ 0.7—1.4 (5H, m, CH_3+CH_2), 1.5—2.0 (6H, m, CH_2), 2.1—2.9 (4H, m, CH_2), 3.15 (1H, q, >CH), 5.99 (2H, m, β-H), 6.54 (1H, dd, α-H), 9.37 (1H, broad, NH). Mass: *m/e* 192 (M^+). Found: C, 75.18; H, 10.71; N, 14.66%. Calcd for $C_{12}H_{20}N_2$: C, 74,95; H, 10.48; N, 14.57%.

5b; NMR (CCl_4): δ 1.0 (6H, m, CH_3), 1.2—3.1 (16H, m, 7×CH_2+2× >CH), 4.8 (1H, d, >CH, J=4.5 Hz), 5.54 (1H, m, β-H), 5.99 (1H, dd, β-H), 6.39 (1H, dd, α-H). Mass: *m/e* 246 (M^+). Found: C, 78.12; H, 10.60; N, 11.44%. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37%.

*Thermal Decomposition of 1-(1-Pyrrolidinyl)-1-(1-pyrrolyl)propane (**3a**).* After 6.45 g of the *N,N*-adduct **3a**[2] was stirred at 120 °C for 10 hr, the reaction mixture was subjected to fractional distillation to give 1.46 g (22.6%) of **4a** and 0.16 g (2.0%) of **5a**.

Under similar conditions heating of 12.0 g of **3b**[2] afforded 2.4 g (20.2%) of **4b**.

*Thermal Decomposition of **4b**.* i) Twenty grams of the *C,N*-adduct **4b** was heated at 150 °C for 5 hr in a stream of nitrogen, and the reaction mixture was then subjected to fractional distillation to afford 4.46 g (34.6%) of 2-(1-butenyl)-pyrrole (**6**), bp 76—78 °C/3 mmHg, as colorless oil, and 4.95 g (39.4%) of 1-(2-pyrrolyl)-1-{2-[5-(1-butenyl)]pyrrolyl}butane (**7**), bp 167—170 °C/3 mmHg, as pale rose viscous oil.

6; IR (neat): 3500 cm^{-1} (ν_{NH}). NMR (CCl_4): δ 1.07 (3H, t, CH_3), 2.18 (2H, m, CH_2), 5.3—5.9 (1H, m, =CH), 6.03 (3H, m, 2×β-H+=CH), 6.43 (1H, m, α-H), 7.65 (1H, broad, NH). Mass: *m/e* 121 (M^+). Found: C, 79.18, H, 8.89; N, 11.23%. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56%.

7; IR (neat): 3500 cm^{-1} (ν_{NH}). NMR (CCl_4): δ 0.8—1.5 (8H, m, 2×CH_3+CH_2), 1.5—2.4 (4H, m, CH_2), 3.7 (1H, t, >CH), 5.3—5.7 (1H, m, =CH), 5.8—6.15 (5H, m, 4×β-H+=CH), 6.27 (1H, dd, α-H), 7.29 (2H, broad, NH). Mass: *m/e* 242 (M^+). Found: C, 79.26; H, 9.44; N, 11.62%. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56%.

ii) A mixture of 6.0 g (0.031 mol) of **4b** and 16.0 g (0.128 mol) of **1b** was heated at 100 °C for 10 hr. Fractional distillation of the reaction mixture afforded 2.4 g (31.2% based on **4b**) of **5b**.

*1,2-Dihydro-1-propyl-3-(1-pyrrolidinyl)-2,3-tetramethylene-3H-pyrrolizine (**5c**).* After a mixture of 5.0 g (0.026 mol) of **4b** and 3.9 g (0.026 mol) of 1-(1-pyrrolidinyl)cyclohexene (**1c**) was stirred at 100 °C for 5 hr in a stream of nitrogen, vacuum distillation afforded 4.6 g (65.0%) of **5c**, bp 148—149 °C/2 mmHg, as colorless oil. NMR (CCl_4): δ 1.0 (3H, broad t, CH_3), 1,2—3.2 (22H, m, 10×CH_2+2× >CH), 5.65 (1H, m, β-H), 5.95 (1H, dd, β-H), 6.38 (1H, dd, α-H). Mass: *m/e* 272 (M^+). Found: C, 79.41; H, 10.57; N, 10.31%. Calcd for $C_{18}H_{28}N_2$: C, 79.36; H, 10.36; N, 10.28%.

Similarly, the reaction of **4b** with 1-(1-pyrrolidinyl)cyclopentene (**1d**) and -cycloheptene (**1e**) afforded 1,2-dihydro-2,3-trimethylene- (**5d**) and -2,3-pentamethylene-3H-pyrrolizine (**5e**) in 60.0 and 98.7% yields, respectively.

5d; bp 163 °C/5 mmHg. NMR (CCl_4): δ 1.0 (3H, m, CH_3), 1.2—3.0 (20H, m, 9×CH_2+2× >CH), 5.45 (1H,m, β-H), 6.02 (1H, dd, β-H), 6.35 (1H, dd, α-H). Mass: *m/e* 258 (M^+). Found: C, 78.80; H, 10.31; N, 10.74%. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84%.

5e; bp 177—179 °C/3.5 mmHg. NMR (CCl_4): δ 1.0 (3H, m, CH_3), 1.2—3.0 (24H, 11×CH_2+2× >CH), 5.52, 5.97 (each 1H, dd, β-H), 6.33 (1H, m, α-H). Mass: *m/e* 286 (M^+). Found: C, 79.65; H, 10.58; N, 9.90%. Calcd for $C_{19}H_{30}N_2$: C, 79.66; H, 10.56; N, 9.78%.

*2-(1-Pyrrolidinylmethyl)pyrrole (**8**).* Twenty grams (0.3 mol) of pyrrole (**2**) was added, drop by drop, to a solution prepared from 21.5 g (0.3 mol) of pyrrolidine and 24.5 ml of 37% aqueous formaldehyde with stirring at 0 °C. The reaction mixture was stirred at room temperature for 3 hr and then at 95 °C for 30 min. The mixture was extracted with diethyl ether and the extract was dried over sodium sulfate, and then evaporated *in vacuo* to leave a residue. Several fractional distillations of the residue afforded 18.5 g (41.2%) of **8**, bp 103—104 °C/5 mmHg, which solidified. Recrystallization from petroleum ether (bp 40—65 °C) gave pure **8**, mp 48 °C, as colorless needles. IR (KBr): 3190 cm^{-1} (ν_{NH}). NMR (CCl_4): δ 1.75, 2.52 (each 4H, m, CH_2), 3.56 (2H, s, CH_2), 5.90 (2H, m, β-H), 6.45 (1H, dd, α-H), 10.05 (1H, broad, NH). Mass: *m/e* 150 (M^+). Found: C, 71.68; H, 9.41; N, 18.68%. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65%.

*1,2-Dihydro-3-(1-pyrrolidinyl)-2,3-tetramethylene-3H-pyrrolizine (**9**).* After a mixture of 4.2 g (0.028 mol) of **1c** and 3.8 g (0.028 mol) of **8** was stirred at 120 °C for 5 hr in a stream of nitrogen, distillation gave 3.0 g (49.3%) of **9**, bp 138—140 °C/3 mmHg, as pale yellow oil. NMR (CCl_4): δ 1.2—3.2 (19H, m, 9×CH_2+ >CH), 5.55 (1H, m, β-H), 5.97 (1H, dd, β-H), 6.50 (1H, dd, α-H). Mass: *m/e* 230 (M^+). Found: C, 78.43; H, 9.45; N, 12.05%. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16%.

*Reaction of **1b** with 1-(1-Pyrrolidinyl)-1-(1-pyrrolyl)cyclohexane (**3c**).* A mixture of 2.9 g (0.023 mol) of **1b** and 5.0 g (0.023 mol) of **3c**[2] was stirred at 120 °C for 7 hr in a stream of nitrogen, and then distillation afforded 2.2 g (35.3%) of **5c**.

Similarly, 2.8 g (33.7%) of **5c** was also obtained from the reaction of 4.7 g (0.031 mol) of **1c** with 6.0 g (0.031 mol) of **3b**.

References

1) Part V of this series: M. Tashiro, Y. Kiryu, and O. Tsuge, *Heterocycles*, **2**, 575 (1974).

2) O. Tsuge, M. Tashiro, and Y. Kiryu, *Chem. Lett.*, **1974**, 795.