THE REACTION OF 1-(1-PYRROLIDINYL)CYCLOHEXENE WITH PYRROLE AND PYRAZOLE[1]

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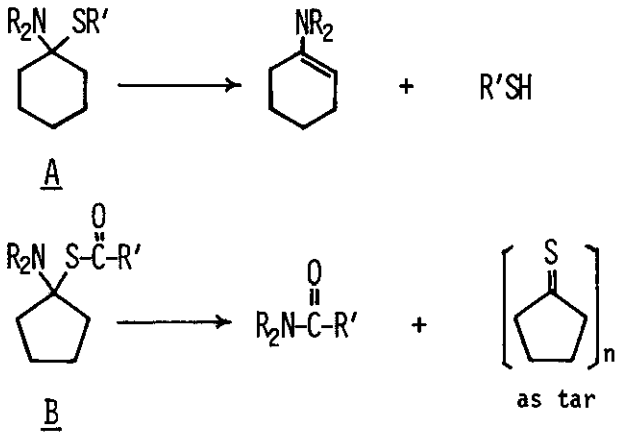
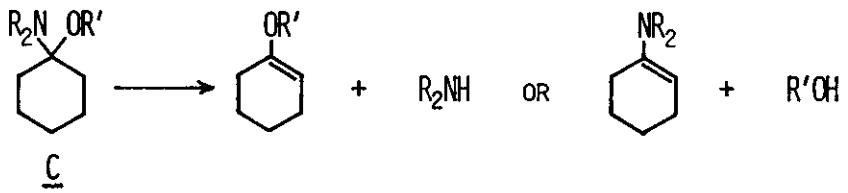
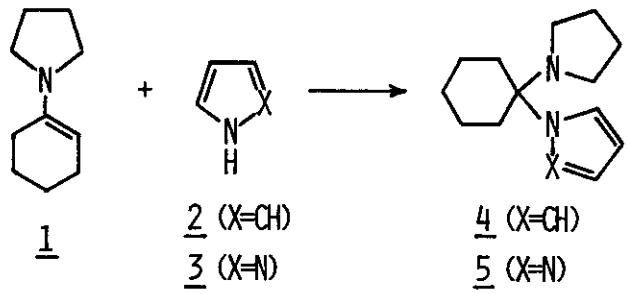
Michael type adducts of pyrrole (2) and pyrazole (3) to enamine (1), 4 and 5, decompose at elevated temperature to regenerate 1 and 2 or 3. On prolonged heating of 4, the novel hexahydro-4H-pyrrolo[1,2-a]indole-4-spiro-1'-cyclohexane derivative (8) was obtained along with four cyclohexenyl-substituted pyrroles, 6a, 6b, 7a, and 7b. The reaction of 1 with 2 under forcing conditions directly afforded 6, 7, and 8, whose relative amounts depended on the reaction conditions. On the other hand, both the thermal decomposition of 5 and the reaction of 1 with 3 under forcing conditions gave 4-(1-cyclohexenyl)pyrazole (13) as a sole isolated product.

Only a few examples of Michael type additions to enamines have hitherto been reported, although enamines are well known to be excellent addends in many Michael type reactions. It has been also reported that Michael type adducts of thiols,[2] thiocarboxylic acids,[3] and alcohols[4] to enamines, A, B, and C, decom-

pose at elevated temperature in several manners, depending on the nature of adducts (Scheme 1). Recently, we reported that under mild conditions[5] 1-(1-pyrrolidinyl)cyclohexene (1) reacted with pyrrole (2) and pyrazole (3) to give the new Michael type adducts, 4 and 5, in good yields, respectively.[1] For comparison with the thermal decomposition of adducts A—C, it seemed to be of







Scheme 1

interest to investigate the thermal decomposition of 4 and 5.

We now found that 4 and 5 decomposed at elevated temperature to regenerate 1 and 2 or 3, and that on prolonged heating novel products were formed. In this context, the reaction of 1 with 2 and 3 was investigated under more forcing conditions than those employed for the formation of 4 and 5.

Attempts to distil 4 were unsuccessful and resulted in the production of 1 and 2: vacuum distillation (20 mmHg, 120°C of bath temp.) afforded 1 and 2 in almost quantitative yields. When a solution of 4 in two equivalents of bromobenzene was heated at 150°C for 8 h, no enamine 1 was detected in the solution and five new products, 6a, 6b, 7a, 7b, and 8, whose structures will be discussed below, were formed. The quantitative estimation of all products was carried out by gas chromatography,[6] and the result is given in entry 1 of Table I. It has been also found that the reaction of 1 with 2 under forcing conditions directly afforded 6, 7, and 8, whose relative amounts depended on the reaction conditions: the results are also given in Table I.

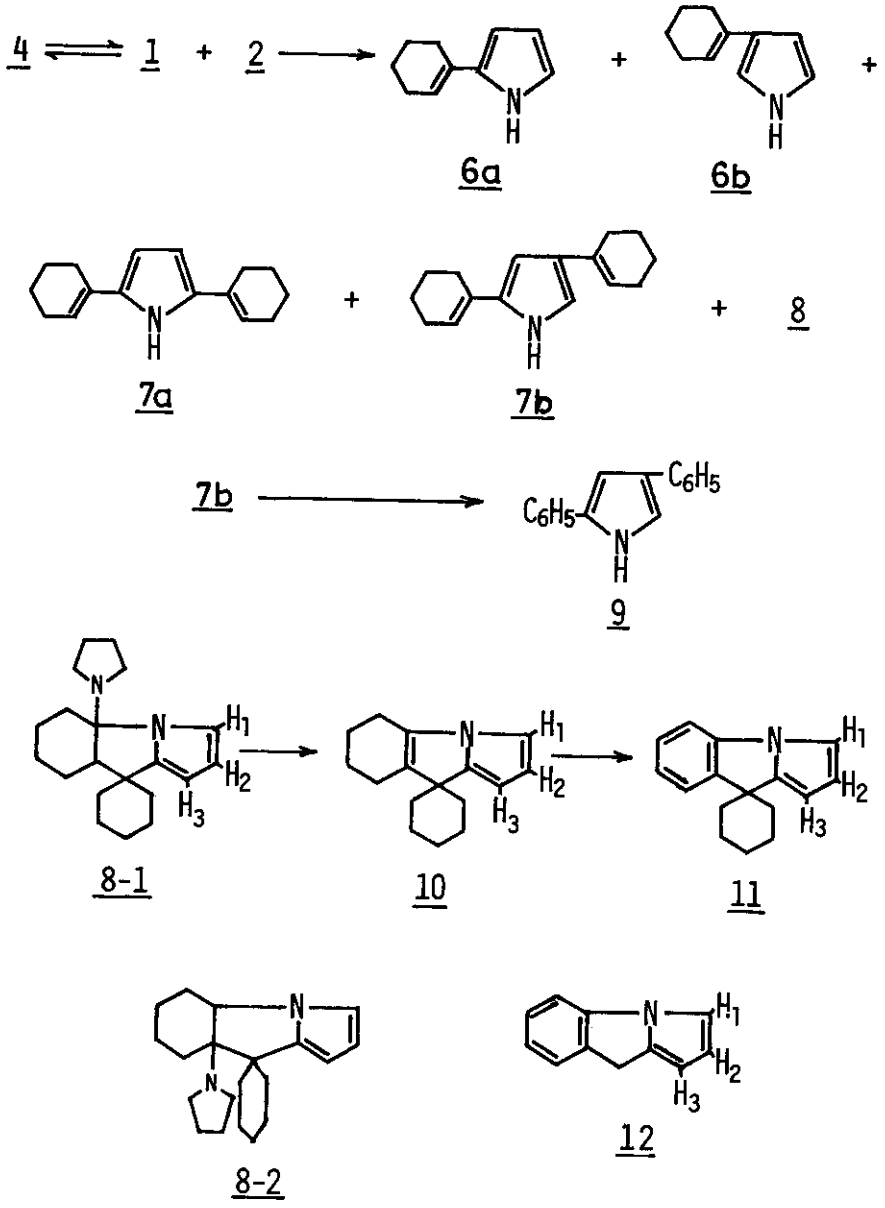
Among products, 6a (mp 45-46°C, bp 142-148°C/19 mmHg), 6b (bp 158-161°C/17 mmHg, colorless oil), and 7a (mp 85-86°C, bp 185-200°C/2 mmHg) were clearly assigned as 2-(1-cyclohexenyl)-, 3-(1-cyclohexenyl)-, and 2,5-di(1-cyclohexenyl)-pyrrole on the basis of their spectral data, respectively.

6a: ν_{max}^{KBr} 3440 cm^{-1} (NH); m/e 147 (M^+); δ (CCl_4) 1.1-2.7 (8H, m, CH_2), 5.7 (1H, m, =CH), 6.0 (2H, m, β-protons of pyrrole ring (β-H)), 6.5 (1H, m, α-proton of pyrrole ring (α-H)), 8.0 (1H, broad, NH).

6b: ν_{max}^{neat} 3400 cm^{-1} (NH); m/e 147 (M^+); δ (CCl_4) 1.4-2.6 (8H, m, CH_2), 5.9 (1H, m, =CH), 6.2 (1H, dd, β-H), 6.5 (2H, m, α-H), 7.75 (1H, broad, NH).

7a: ν_{max}^{KBr} 3460 cm^{-1} (NH); m/e 227 (M^+); δ (CCl_4) 1.4-2.5 (16H, m, CH_2), 5.87 (2H, m, =CH), 5.95 (2H, d, J=2.6 Hz, β-H), 8.0 (1H, broad, NH).

The compound 7b (mp 132-133°C, bp 170-185°C/2 mmHg) which is an isomer of



Scheme 2

Table I

Entry	Reaction Time, h	Solvent	Product, %					Recovered
			6a	6b	7a	7b	8	1
1[a]	8	bromobenzene	13.7	15.1	5.8	4.7	6.5	0
2[b]	2	〃	6.4	5.3	0	0	5.8	75.6
3	4	〃	12.8	10.0	1.0	1.9	7.6	32.0
4	6	〃	15.5	12.8	3.3	5.3	7.2	6.7
5	8	〃	15.5	12.8	3.8	5.3	6.7	0
6[c]	3	———	50 (6a+6b)		+[d]	+	7.2	+

a) Adduct 4 was heated at 150°C. *b)* A mixture of equimolar amounts of 1 and 2 was heated at 150°C in entries 2-5. *c)* 1 was heated with two equivalents of 2 at 150°C. *d)* A sign, +, means a trace amount.

7a, could not be determined whether 2,3- or 2,4-di(1-cyclohexenyl)pyrrole from its spectral data [ν_{max}^{KBr} 3430 cm^{-1} (NH); m/e 227 (M^+); δ (CCl_4) 1.2-2.6 (16H, m, CH_2), 5.6, 5.85 (each 1H, m, =CH), 6.1 (1H, m, β-H), 6.3 (1H, m, α-H), 7.6 (1H, broad, NH)]. However, dehydrogenation of 7b with 5% Pd-C in decalin at 200°C for 15 h gave 2,4-diphenylpyrrole (9) as colorless needles, mp 176-177°C, which was identical with an authentic sample prepared by the reported method.[7] Consequently, 7b was concluded to be 2,4-di(1-cyclohexenyl)pyrrole.

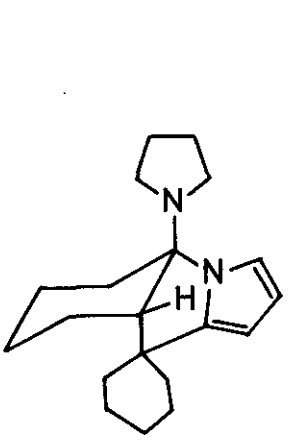
On the basis of the spectral data as well as of the results of chemical conversions, the compound 8 (mp 103-104°C), whose molecular formula corresponded to that of a compound derived from a 2:1 adduct of 1 and 2 with the elimination of one mole of pyrrolidine, was deduced to be 4a,5,6,7,8,8a-hexahydro-8a-(1-pyrrolidinyl)-4H-pyrrolo[1,2-a]indole-4-spiro-1'-cyclohexane (8-1) [m/e 298 (M^+); δ (CCl_4) 1.1-2.1 (22H, m, CH_2), 2.4 (1H, broad d, ≥CH), 2.65-3.3 (4H, m, CH_2), 5.77 (1H, dd, J=1.4 and 3.5 Hz, H_3), 5.97 (1H, dd, J=2.6 and 3.5 Hz, H_2), 6.46

(1H, dd, J=1.4 and 2.6 Hz, $\underline{H_1}$)].

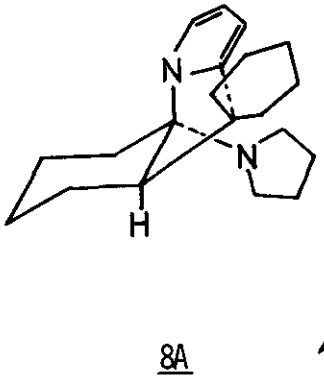
Treatment of 8 with 20% hydrochloric acid at room temperature for 1 h afforded 35% yield of tetrahydro-4H-pyrroloindole-4-spiro-1'-cyclohexane (10), mp 61-62°C, with the elimination of pyrrolidine, together with the recovery of 8 in 23% yield. By the dehydrogenation of 8 with selenium in decalin at 300°C for 4 h, 4H-pyrroloindole-4-spiro-1'-cyclohexane (11), mp 113°C, was obtained in 27% yield, along with unidentified products. The structures of 10 and 11 were confirmed on the basis of their spectral data.

10: m/e 227 (M^+); δ (CCl_4) 0.8-2.6 (18H, m, $\underline{CH_2}$), 5.93 (2H, d, $\underline{H_2}$ and $\underline{H_3}$), 6.46 (1H, dd, $\underline{H_1}$).

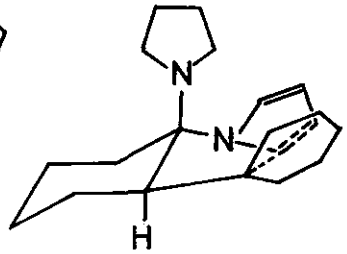
11: m/e 223 (M^+); δ (CCl_4) 1.2-2.1 (10H, m, $\underline{CH_2}$), 6.02 (1H, dd, J=1.2 and 3.2 Hz, $\underline{H_3}$), 6.14 (1H, dd, J=2.5 and 3.2 Hz, $\underline{H_2}$), 6.84 (1H, dd, J=1.2 and 2.5 Hz, $\underline{H_1}$), 7.0-7.3 (4H, m, aromatic protons). Furthermore, the nmr spectral pattern in the region of aromatic protons was closely resemble to that of 4H-pyrrolo[1,2-a]indole (12) prepared by the reported method.[8] 12: δ (CCl_4) 3.8 (2H, m, $\underline{CH_2}$), 6.02 (1H, dd, $\underline{H_3}$), 6.26 (1H, dd, $\underline{H_2}$), 6.99 (1H, dd, $\underline{H_1}$), 7.1-7.4 (4H, m, aromatic protons).



8B



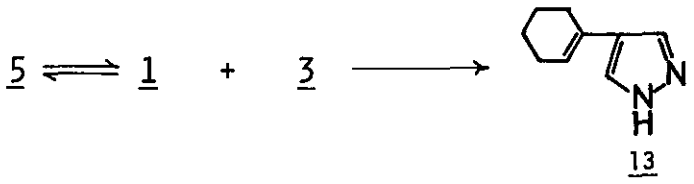
8A



8C

A potential structure, 4a-(1-pyrrolidinyl) derivative 8-2, might be excluded from the structure for 8, because of appearance of the methine proton of 8 at δ 2.4 ppm as shown above.[9] Now, three configurations, 8A, 8B, and 8C, are possible for the structure of 8-1. An inspection of Dreiding models for 8-1 indicates that the axial pyrrolidinyl group in 8B and 8C exerts a significant 1,3-diaxial interaction, and that 8A is the most favorable configuration.

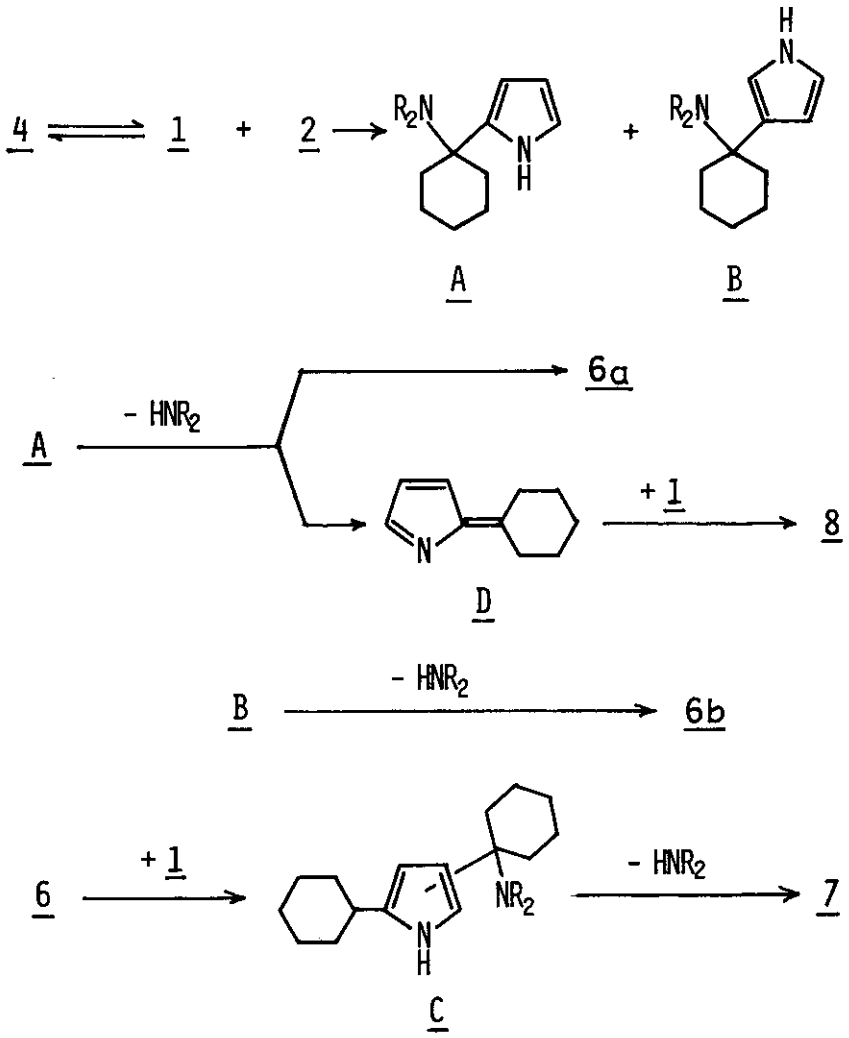
On the other hand, both heating of Michael type adduct 5 and the reaction of enamine 1 with pyrazole (3) at 150°C for 24 h afforded 30-40% yield of 4-(1-cyclohexenyl)pyrazole (13), mp 154°C, as a sole isolated product [ν_{max}^{KBr} 3200 cm^{-1} (NH); m/e 148 (M^+); δ ($CDCl_3$) 1.5-2.5 (8H, m, CH_2), 6.05 (1H, m, =CH), 7.13 (2H, s, pyrazole ring protons), 11.25 (1H, s, NH)].



13

As described above, Michael type adduct 4 easily decomposed at elevated temperature to regenerate enamine 1 and pyrrole (2). Furthermore, we found that on heating with 1 at 150°C, a mixture of 1-cyclohexenylpyrroles 6a and 6b produced a mixture of di(1-cyclohexenyl)pyrroles 7a and 7b in good yield. It is also known that N-alkyl- and N-arylpyrroles isomerize into the corresponding α-substituted pyrroles at a red heat.[10]

Although the exact pathway for the formation of products, 6–8, is not clear, we viewed the pathway as depicted in Scheme 3. Under the conditions in the present work, 4 is not an intermediate for the formation of products, because of the facile dissociation of 4 to 1 and 2. The addition of 2 to 1 would proceed in different manner from that under mild conditions, yielding two new



Scheme 3

Michael type adducts A and B. The formation of 6 could be understood in terms of the elimination of pyrrolidine from A and B. Di(1-cyclohexenyl)pyrroles 7 would be formed via the formation of adduct C of 6 to 1, followed by the elimination of pyrrolidine. On the other hand, an alternative elimination mode of

pyrrolidine from A would result in the formation of an azafulvene intermediate D, which would undergo cycloaddition reaction with 1 to afford 4H-pyrroloindole-4-spiro-1'-cyclohexane derivative 8.

Further investigation of the related reactions is in progress in our laboratory.

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5 Optimum conditions for the formation of adducts 4 and 5 are as follows. For 4 (yield 75%); at 60°C for 5 min: for 5 (yield 87.5%); at 20°C for 12 h.

6 Conditions for the gas chromatographic analyses: Column, 30% high vacuum silicon grease, 75 cm; rate of temperature rise, 12°C/min; carrier gas, H_2, 30 ml/min. Satisfactory analyses were obtained for all new compounds reported in this communication.

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