A NOVEL ABNORMAL REARRANGEMENT IN THE FISCHER INDOLE SYNTHESIS

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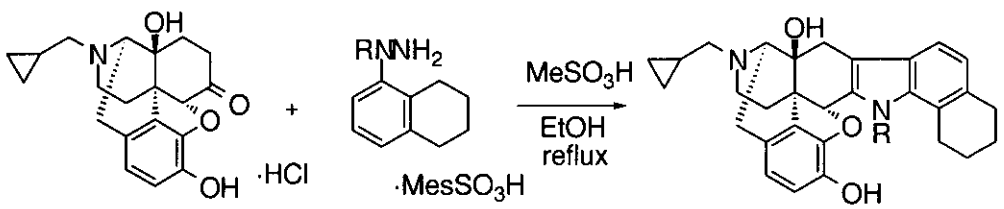
Abstract - In the Fischer indole synthesis of naltrexone *N*-methyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazone, an abnormal rearrangement of the fused 6-membered ring was observed. This abnormal rearrangement was not observed without the *N*-alkyl group of the hydrazone. The mechanism for the unexpected product was assumed to involve the [3,3] sigmatropic rearrangement at the substituted and more hindered ortho position and the subsequent rearrangement of the fused 6-membered ring *via* a spiro intermediate.

Many kinds of natural products, bioactive compounds, or important medicines including indole ring have widely known, therefore it is important to develop the efficient synthesis of indole ring. Among the syntheses, the Fischer indole synthesis[1] is one of the most effective and widely used methods and has been investigated in detail. Especially in the Fischer indole synthesis of 2,6-dialkylarylhydrazones, the migrations of alkyl group *e. g.* the 1,2-shift of methyl group,[2] the double 1,2-shift of methylene group,[3] and 1,4-shift of methyl group[4] were reported. In addition, the migration of 2-substituent such as methyl and phenyl group was also reported in the case of 2-substituted phenylhydrazones.[5] The example of the elimination of the methyl group is known as well.[6] In this paper, we wish to report a novel abnormal rearrangement in the Fischer indole synthesis of hydrazone derived from naltrexone, which is opioid antagonist, with *N*-alkyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazine.



Naltrexone **1a - 1d** **2a - 2d**

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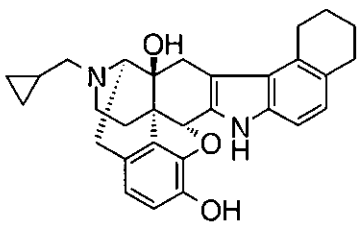

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a : R = Me
b : R = Et
c : R= *i* - Pr
d : R = H

$MesSO_3H$: mesitylenesulfonic acid

Table 1. The ratio of the reaction products of naltrexone hydrochloride with *N*-alkyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazine mesitylenesulfonate

Entry	R	Ratio of **2a**-**2d** : **3**	Yield of **2**(%)	Yield of **3**(%)
1	Me (**a**)	55 : 45	52	43
2	Et (**b**)	65 : 35	62	34
3	*i* - Pr (**c**)	70 : 30	60	26
4	H (**d**)	100 : 0	77	0

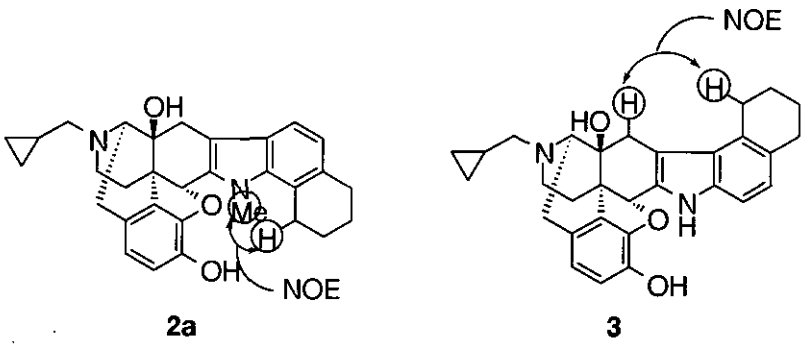
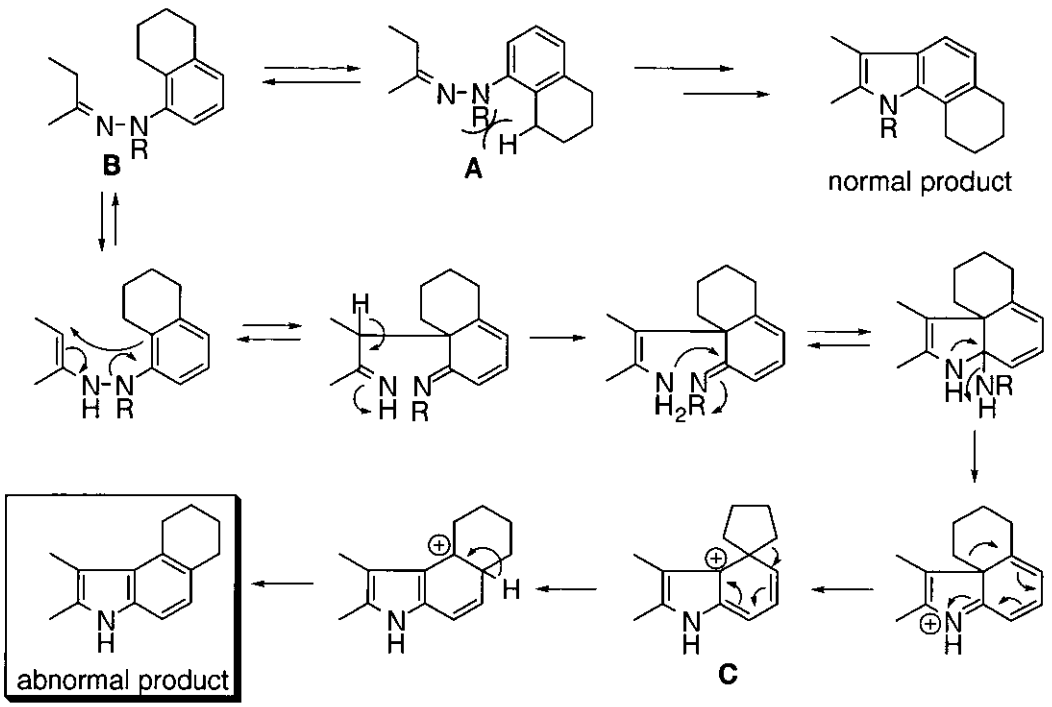


Figure 1. The identification of the compounds (**2a**) and (**3**) by the observation of their NOE spectra

In the first place, the ethanol solution of naltrexone hydrochloride and *N*-methyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazine (**1a**) mesitylenesulfonate was refluxed in the presence of methanesulfonic acid to give two products (Table 1, Entry 1). The one was the predictable normal fused product (**2a**), and the other was an unexpected compound (**3**).[7] These compounds were identified by the observation of their NOE spectra between the indicated protons (Figure 1). In the reaction of naltrexone hydrochloride with some *N*-alkyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazines (**1a**-**1d**) mesitylenesulfonates, the ratios of the normal products (**2a**-**2d**) and the abnormally rearranged product (**3**) were shown in Table 1. These results indicate that the novel abnormal rearrangement occurs only when the *N*-alkyl hydrazines are used.

The normal product should be obtained by [3,3] sigmatropic rearrangement toward the unsubstituted and less hindered ortho position. On the other hand, the mechanism of the abnormal rearrangement was assumed as shown in Scheme 1. The hydrazone intermediate may mainly exist in a conformation **B** in order to avoid the steric repulsion between *N*-alkyl group and the hydrogen on the fused cyclohexeno ring. In the conformation **B**, the [3,3] sigmatropic rearrangement would occur toward the substituted and more hindered ortho position, subsequently a ring closure would proceed with an elimination of the alkyl amino group,[8] followed by a rearrangement of the fused 6-membered ring *via* a spiro intermediate **C** to afford the abnormal product.

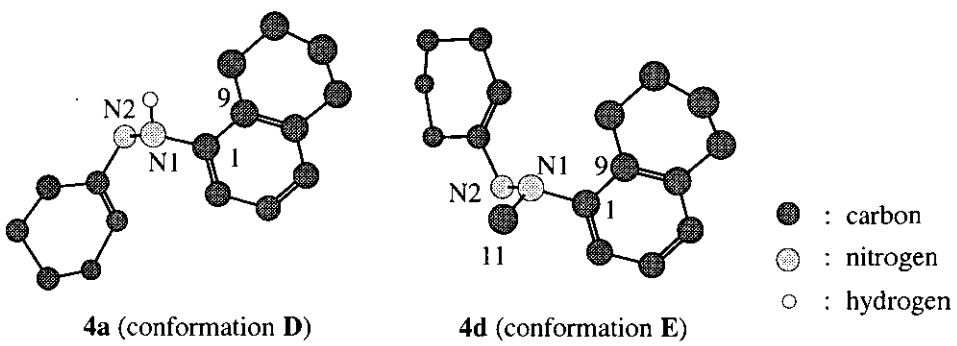
A stable conformational analysis[9] of enehydrazine intermediates (**4a**) and (**4d**) having cyclohexene ring supported above hypothetical mechanism of the abnormal rearrangement. The most energetically stable



Scheme 1. The hypothetical mechanism of the novel abnormal rearrangement

conformations of the N1-H enehydrazine (**4a**) and the N1-Me one (**4d**) are shown as conformation **D** and **E** in Figure 2. These results clearly demonstrate the favorable reaction center on the [3,3] sigmatropic rearrangement *via* the each intermediate. That is, the usual [3,3] sigmatropic rearrangement would occur *via* the conformation **D** of intermediate (**4a**), on the other hand, the abnormal one would occur *via* the conformation **E** of intermediate (**4d**).

This reaction mechanism is supported by the report of the Fischer indole synthesis of 2-substituted phenylhydrazone.[5] However the tendency of migration of methyl group was not always remarkable in that report and a yield of the abnormal product was not so high. In our cases, on the other hand, abnormal



4a (conformation **D**) **4d** (conformation **E**)

Figure 2. The most energetically stable conformations of enehydrazine intermediates (**4a**) and (**4d**)

products were obtained in moderate yields. Therefore, it is assumed that a steric repulsion due to a *N*-alkyl group of the hydrazone leads to the abnormal rearrangement, although the relationship between the *N*-alkyl groups of the hydrazines and the ratios of the reaction products (Table 1) is not yet clear. Further investigation of this point of view is in progress.

In conclusion, a novel abnormal rearrangement of the fused 6-membered ring was observed in the Fischer indole synthesis of naltrexone *N*-alkyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazone. This rearrangement would occur *via* [3,3] sigmatropic rearrangement toward the substituted and more hindered ortho position in spite of the presence of the unsubstituted and less hindered one. This novel rearrangement would make it possible to design the new compounds including indole ring which were hardly synthesized by the normal Fischer idole synthesis. Efforts to broaden the scope and develop synthetic applications of this rearrangement are currently in progress.

REFERENCES AND NOTES

1. Review: B. Robinson, *Chem. Rev.*, 1963, **63**, 373; 1969, **69**, 227; B. Robinson, 'The Fischer Indole Synthesis', Wiley Interscience, Inc., New York, 1982.
2. R. B. Carlin, W. O. Henley, Jr., and D. P. Carlson, *J. Am. Chem. Soc.*, 1957, **79**, 5712; R. B. Carlin, A. J. Magistro, and G. J. Mains, *ibid.*, 1964, **86**, 5300.
3. R. Fusco and F. Sannicolò, *Gazz. Chim. Ital.*, 1973, **103**, 197.
4. R. B. Carlin and M. S. Moores, *J. Am. Chem. Soc.*, 1959, **81**, 1259; 1962, **84**, 4107.
5. Y. Murakami, T. Watanabe, Y. Yokoyama, J. Naomachi, H. Iwase, N. Watanabe, M. Morihata, N. Okuyama, H. Kamakura, T. Takahashi, H. Atoda(née Tatsuno), T. Toji, K. Morita, and H. Ishii, *Chem. Pharm. Bull.*, 1993, **41**, 1910.
6. R. Huisgen, *Ann.*, 1948, **559**, 101; G. S. Bajwa and R. K. Brown, *Can. J. Chem.*, 1968, **46**, 1927; 1970, **48**, 2293.
7. The typical NMR data of normal and abnormal products are as follows. (**2a**) methanesulfonate: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.38-0.55 (2H, m), 0.58-0.67 (1H, m), 0.67-0.77 (1H, m), 1.02-1.13 (1H, m), 1.66-1.88 (5H, m), 2.32 (3H, s), 2.45-2.53 (1H, m), 2.60 (1H, dt, *J* = 4.9, 13.2 Hz), 2.56-2.82 (3H, m), 2.88 (1H, d, *J* = 16.1 Hz), 2.88-2.98 (1H, m), 3.11 (1H, br d, *J* = 9.8 Hz), 3.19 -3.48 (5H, m), 4.02-4.09 (1H, m), 4.07 (3H, s), 5.86 (1H, s), 6.23 (1H, br s), 6.33 (1H, d, *J* = 7.8 Hz), 6.59 (1H, d, *J* = 8.3 Hz), 6.69 (1H, d, *J* = 8.3 Hz), 7.06 (1H, d, *J* = 8.3 Hz), 8.90 (1H, br s) (An exchangeable proton was not detected.); (**3**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08-0.21 (2H, m), 0.51-0.63 (2H, m), 0.83-0.94 (1H, m), 1.63-1.89 (5H, m), 2.25 (1H, dt, *J* = 3.1, 12.1 Hz), 2.32- 2.47 (3H, m), 2.68 (1H, dd, *J* = 4.4, 11.2 Hz), 2.67-2.83 (3H, m), 2.84 (1H, d, *J* = 15.6 Hz), 3.00 (1H, dt, *J* = 5.4, 16.6 Hz), 3.08 (1H, d, *J* = 18.6 Hz), 3.17 (1H, dd, *J* = 7.8, 16.1 Hz), 3.23 (1H, d, *J* = 15.6 Hz), 3.33 (1H, d, *J* = 6.4 Hz), 5.39 (1H, br s), 5.67 (1H, s), 6.42 (1H, d, *J* = 7.8 Hz), 6.50 (1H, d, *J* = 8.3 Hz), 6.76 (1H, d, *J* = 8.3 Hz), 6.95 (1H, d, *J* = 8.3 Hz), 8.24 (1H, s) (An exchangeable proton was not detected.)
8. In the normal Fischer indole synthesis, instead of this alkyl amino group, the other one eliminates .
9. The energetically stable conformations were searched by using the systematic search option of SPARTAN (Wavefunction, Inc.). HF/MNDO PM 3 approximation was used. In conformation **E** of intermediate (**4d**), the torsion angle C9-C1-N1-N2 was 117.4 degree. Every other local minimum conformation indicated at least 2.2 kcal / mol higher energies than conformation **E**.

Received, 11th August, 1997