

A STUDY OF THE REACTION BETWEEN 1-HALOGENOBENZYL-
2-BENZAZEPINES AND DIMSYLSODIUM

Shinzo Kano^{*}, Tsutomu Yokomatsu, and Shiroshi Shibuya
Tokyo College of Pharmacy, 3-20-1, Kitashinjuku,
Shinjuku-ku, Tokyo, Japan

The reaction between a series of 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-5H-2-benzazepines (1), (2), (3) and dimsylysodium was examined to give 5,6,7,8-tetrahydrodibenz[b,f]azecines possessing a cis and trans double bond at the 13,14-position together with formation of 14-(methylsulfinyl)methylidibenz[b,f]azecine derivatives.

In continuation of our study on the reaction between 1-halogenobenzylisoquinolines, 1-halogenophenethyl-5H-2-benzazepines and sodium methylsulfinylmethanide^{1,2,3}, we found that a hydroxyl group on the benzene ring played an important role during the ring expansion of isoquinoline and 2-benzazepine ring. In this communication, we wish to report syntheses of 5,6,7,8-tetrahydrodibenz[b,f]azecines possessing a cis and trans double bond at the 13,14-position through the benzyne reaction of phenolic and non-phenolic 1-halogenobenzyl-5H-2-benzazepines (1), (2) and (3) using sodium methylsulfinylmethanide as a base. These 1-substituted-5H-2-benzazepines were easily synthesized through the Bischler-Napieralski type cyclization² of the corresponding amide.

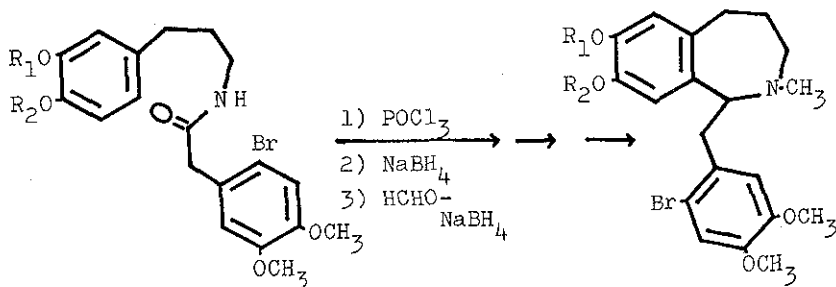
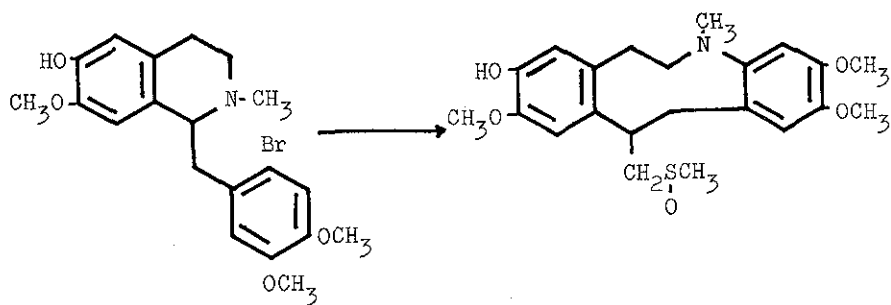
First, the 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-5H-2-benzazepine (1) was treated with sodium methylsulfinylmethanide in DMSO at room temperature to give two products (4), 15 %, and (5), 65 % yield, which were separated by column chromatography on silica gel. The first product (4), mp 143-145° (from methanol), showed a pair of doublets (J=17 Hz) at 6.24 and 7.63 ppm attributable to trans -CH=CH-, and four aromatic proton signals at 6.60, 6.70, 6.75 and 6.84 ppm as singlets, respectively, in its n.m.r. spectrum, m/e 355 (M⁺) in its mass spectrum. O-Methylation of (4) with diazomethane gave (6), mp 150-152° (from methanol), whose n.m.r. [δ (CDCl₃) 2.77 (NCH₃), 6.28 (1H, d, J=17 Hz, olefinic H), 6.61 (1H, Ar-H), 6.70 (2H, Ar-H), 6.88 (1H, Ar-H), 7.64 (1H, d, J=17 Hz, olefinic H)] and mass spectra [m/e 369 (M⁺)] were superimposable on those of the authentic specimen prepared from the quaternary salt (7) by Hofmann degradation. The compound (7) was synthesized through cyclization of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-5H-2-benzazepine (8) with sodium methylsulfinylmethanide, followed by methylation of (9) with methyl iodide. Thus, the geometry of the double bond at the 13,14-position of (4) was assigned to trans.

Deoxygenation of the second product (5) with zinc amalgam afforded the 14-(methylthio)methyl derivative (10), mp 109-112° (from methanol), which showed δ 2.02 (SCH₃), 2.50 (NCH₃) in its n.m.r. spectrum (CDCl₃).

On the other hand, the similar reaction using the non-phenolic 1-(2-bromo-4,5-dimethoxybenzyl)-5H-2-benzazepine (2) gave the 5,6,7,8-tetrahydrodibenz[b,f]azecine (11), 35 % yield, mp 159-160° (from methanol), accompanying with formation of 14-(methylsulfinyl)methyl-dibenz[b,f]azecine (12), mp 175-177°. The geometry of the double

bond located at the 13,14-position of (11) was assigned to cis based on the following spectral analyses [δ (CDCl₃) 2.19 (NCH₃), 3.63 (OCH₃), 3.76 (OCH₃), 3.83 (2xOCH₃), 6.22, 6.31 (2xAr-H), 6.58 (2H, s, olefinic H), 6.63, 6.68 (2xAr-H), m/e 369 (M⁺)]. The considerable upfield shift of the NCH₃ signal would be caused by the anisotropy of the benzene A ring. Moreover catalytic hydrogenation of (11) over Adams catalyst yielded the 5,6,7,8,13,14-hexahydrodibenz[b,f]azecine (13) which was identical with the authentic specimen, obtained from the trans-isomer (6), in all respects [δ (CDCl₃) 2.48 (NCH₃), 3.76 (12H, 4xOCH₃), 6.49 (3H, 3xAr-H), 6.55 (1H, Ar-H)]. Deoxygenation of (12) afforded the 14-(methylthio)methyl derivative (14), mp 135-137°, [δ (CDCl₃) 1.98 (SCH₃), 2.49 (NCH₃), 3.76 (12H, 4xOCH₃), m/e 431 (M⁺)].

Finally, the 8-hydroxy-5H-2-benzazepine (3) was treated with sodium methylsulfinylmethanide to give three products (15), (16) and (17), which were separated by column chromatography on silica gel. Elution with benzene-chloroform (2:3) gave (15), in 20 % yield, [δ (CDCl₃) 2.74 (NCH₃), 3.82, 3.83, 3.86 (9H, each s, 3xOCH₃), 6.21 (1H, d, J=17 Hz, olefinic H), 6.58, 6.64, 6.67, 6.68 (4H, each s, 4xAr-H), 7.61 (1H, d, J=17 Hz, olefinic H)] and the cis-isomer (16), 22 % yield, [δ (CDCl₃) 2.18 (NCH₃), 3.71, 3.74, 3.76 (9H, each s, 3xOCH₃), 6.31 (2H, s, 2xAr-H), 6.52 (2H, s, olefinic H), 6.59 (1H, Ar-H), 6.62 (1H, Ar-H)]. O-Methylation of both products (15), (16) with diazomethane afforded, quantitatively, the corresponding 2,3,10,11-tetramethoxy derivatives (6) and (11), respectively. Deoxygenation of the third product (17), obtained from 2 % methanol-chloroform fraction, yielded the 14-(methylthio)methyl derivative (18), mp 122-124° (from methanol), [δ (CDCl₃) 2.03 (SCH₃), 2.50 (NCH₃), 3.77 (9H, s, 3xOCH₃), 6.43 (1H, Ar-H), 6.50



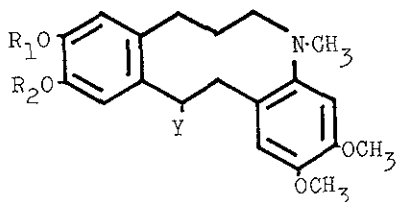
$R_1 = CH_3$ or $C_6H_5CH_2$

$R_2 = CH_3$ or $C_6H_5CH_2$

(1) $R_1 = H$, $R_2 = CH_3$

(2) $R_1 = R_2 = CH_3$

(3) $R_1 = CH_3$, $R_2 = H$



(5) $R_1 = H$, $R_2 = CH_3$, $Y = CH_2SCH_3$

(10) $R_1 = H$, $R_2 = CH_3$, $Y = CH_2SCH_3$

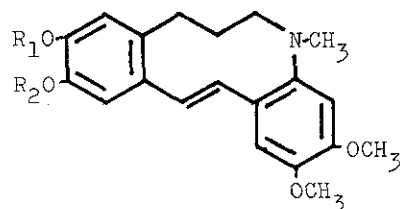
(12) $R_1 = R_2 = CH_3$, $Y = CH_2SCH_3$

(13) $R_1 = R_2 = CH_3$, $Y = H$

(14) $R_1 = R_2 = CH_3$, $Y = CH_2SCH_3$

(17) $R_1 = CH_3$, $R_2 = H$, $Y = CH_2SCH_3$

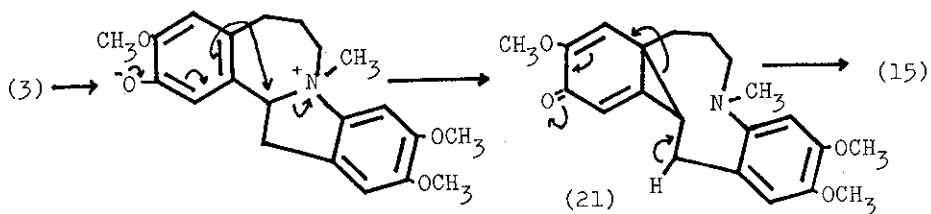
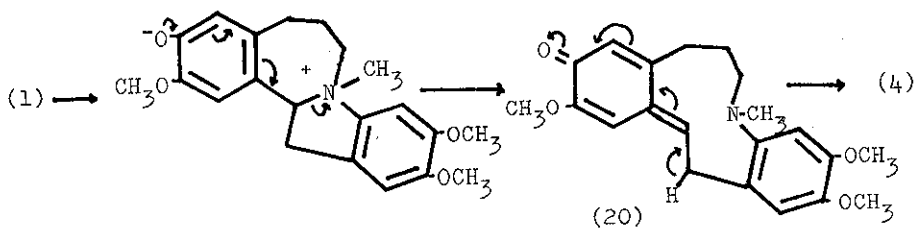
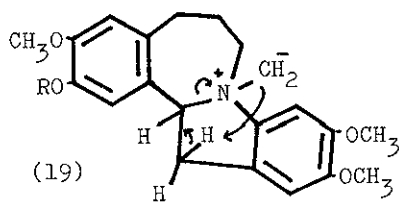
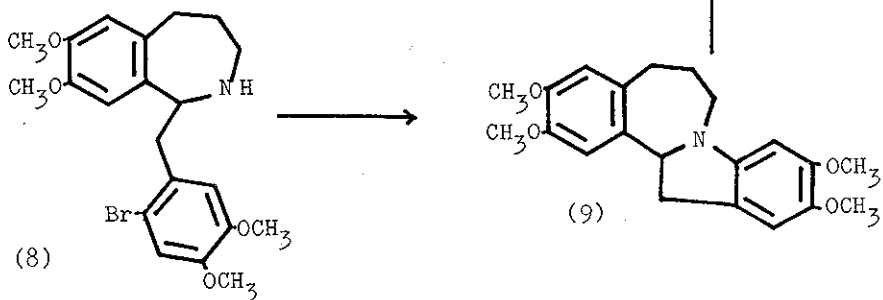
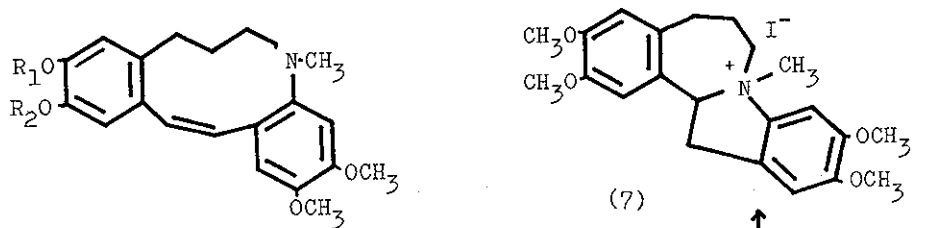
(18) $R_1 = CH_3$, $R_2 = H$, $Y = CH_2SCH_3$



(4) $R_1 = H$, $R_2 = CH_3$

(6) $R_1 = R_2 = CH_3$

(15) $R_1 = CH_3$, $R_2 = H$



(2H, s, 2xAr-H), 6.63 (1H, Ar-H), m/e 417 (M⁺) .

It is of interest that the dibenz[b,f]azecines possessing cis and trans double bond at the 13,14-position were formed from 1-halogeno-benzyl-5H-2-benzazepines. The cis double bond at the 13,14-position would be formed by a spontaneous cis-elimination of the corresponding intermediate (19). The trans-isomer (4) and (15) would be formed through (20) and (21), respectively.

ACKNOWLEDGEMENT We are grateful to Mr. S. Suzuki, Mrs. K. Isobe and Mr. Y. Shida for microanalyses and spectroscopic measurements. We also thank to Mr. T. Sugai and Mr. M. Nakajima for their helpful assistance.

REFERENCES

1. S. Kano, E. Komiyama, T. Ogawa, Y. Takahagi, T. Yokomatsu, and S. Shibuya, Chem. and Pharm. Bull.(Japan), 1975, 23, 2058.
2. S. Kano, T. Ogawa, T. Yokomatsu, Y. Takahagi, E. Komiyama, and S. Shibuya, Heterocycles, 1975, 3, 129.
3. S. Kano, T. Yokomatsu, N. Yamada, K. Matsumoto, S. Tokita, and S. Shibuya, Chem. and Pharm. Bull.(Japan), 1974, 22, 1607.

Received, 22nd January, 1976