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

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The reaction between a series of 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-5H-2-benzazepines (1), (2), (3) and dimsylsodium 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)methyldibenz[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 cyclization[2] of the corresponding amide.

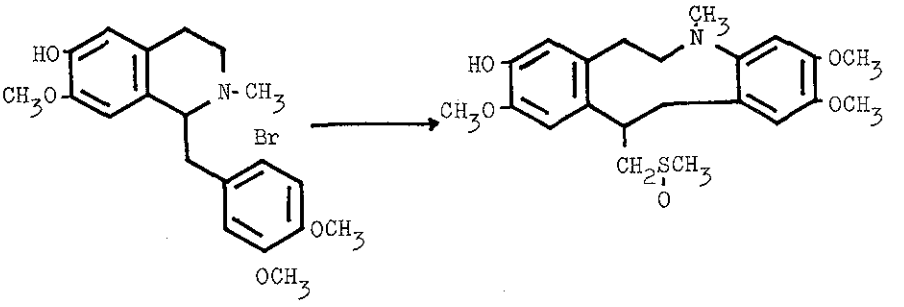
First, the 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-5H-2-benzazepine (1) was treated with sodium methylsulfinylmethanide in DMSO at room temperature to give two products (4), 15 %, and (5), 65 % yield, which were separated by column chromatography on silica gel. The first product (4), mp 143-145° (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 ($CDCl_3$) 2.77 (NCH_3), 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-domethoxybenzyl)-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.

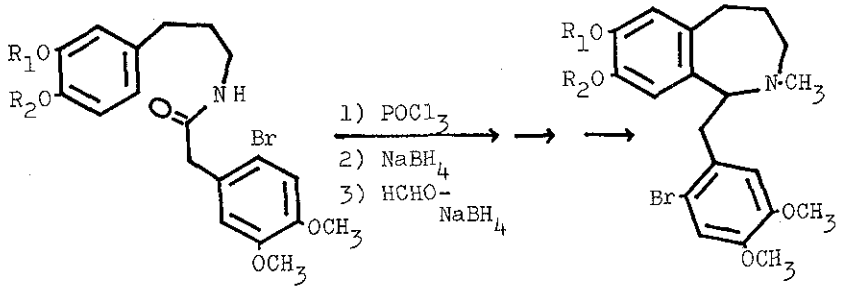
Deoxygenation of the second product (5) with zinc amalgam afforded the 14-(methylthio)methyl derivative (10), mp 109-112° (from methanol), which showed δ 2.02 (SCH_3), 2.50 (NCH_3) in its n.m.r. spectrum ($CDCl_3$).

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 ($CDCl_3$) 2.19 (NCH_3), 3.63 (OCH_3), 3.76 (OCH_3), 3.83 (2xOCH_3), 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 NCH_3 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 ($CDCl_3$) 2.48 (NCH_3), 3.76 (12H, 4xOCH_3), 6.49 (3H, 3xAr-H), 6.55 (1H, Ar-H)]. Deoxygenation of (12) afforded the 14-(methylthio)methyl derivative (14), mp 135-137°, [δ ($CDCl_3$) 1.98 (SCH_3), 2.49 (NCH_3), 3.76 (12H, 4xOCH_3), 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 ($CDCl_3$) 2.74 (NCH_3), 3.82, 3.83, 3.86 (9H, each s, 3xOCH_3), 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 ($CDCl_3$) 2.18 (NCH_3), 3.71, 3.74, 3.76 (9H, each s, 3xOCH_3), 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 ($CDCl_3$) 2.03 (SCH_3), 2.50 (NCH_3), 3.77 (9H, s, 3xOCH_3), 6.43 (1H, Ar-H), 6.50





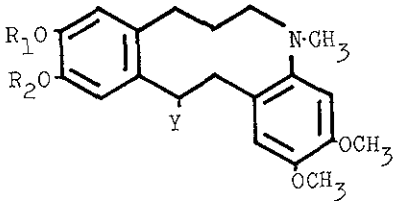
R_1=CH_3 or $C_6H_5CH_2$

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=$CH_2\overset{\overset{O}{\|}}{S}CH_3$

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

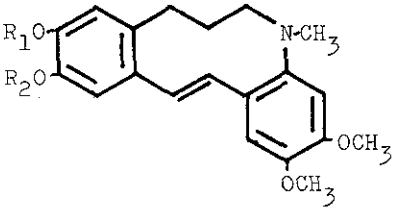
(12) R_1=R_2=CH_3, Y=$CH_2\overset{\overset{O}{\|}}{S}CH_3$

(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=$CH_2\overset{\overset{O}{\|}}{S}CH_3$

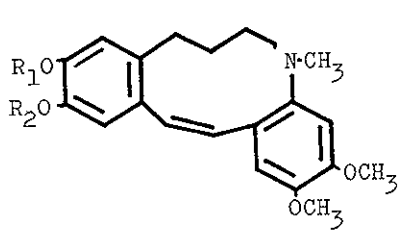
(18) R_1=CH_3, R_2=H, Y=CH_2SCH_3



(4) R_1=H, R_2=CH_3

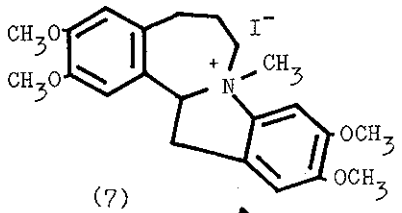
(6) R_1=R_2=CH_3

(15) R_1=CH_3, R_2=H

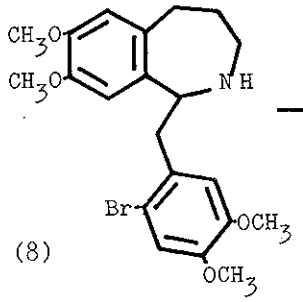


(11) $R_1=R_2=CH_3$

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



(7)



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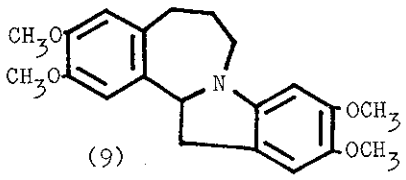

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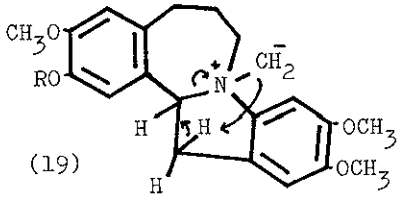
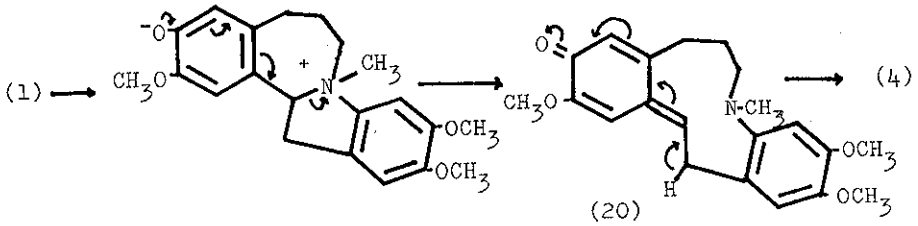
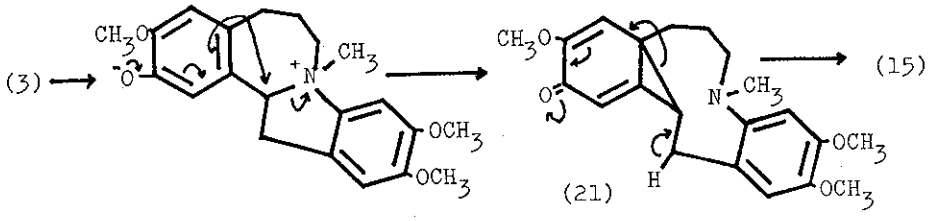


(19)



(1) (4) (20)



(3) (15) (21)

(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-halogenobenzyl-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.

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