BENZYNE REACTION OF 1-HALOGENOPHENETHYL-3H-2-BENZAZEPINE

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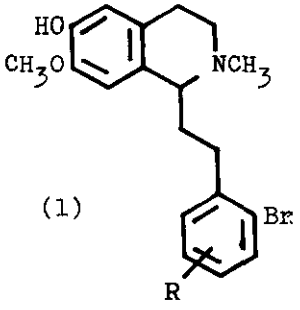
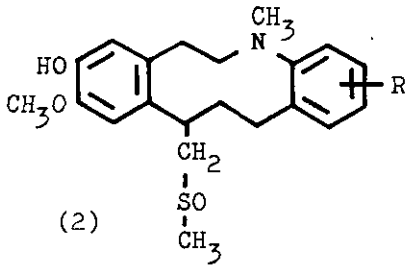
5,6,7,8,13,14-Hexahydro-13,14-methanodibenzo[b,f]azecines were obtained by the reaction of 1,2,4,5-tetrahydro-1-(2-bromo-4,5-dimethoxyphenethyl)-2-methyl-3H-2-benzazepines with sodium methylsulfinylmethanide.

Previously, we examined the reaction of a series of 1-halogenophenethylisoquinolines(1) with sodium methylsulfinylmethanide and found a novel ring expansion to give hexahydrodibenzo[b,g]azecines(2)[1,2]. We successively investigated the similar reaction using 1-halogenophenethyl-3H-2-benzazepines as an extention of the previous works.



(1)



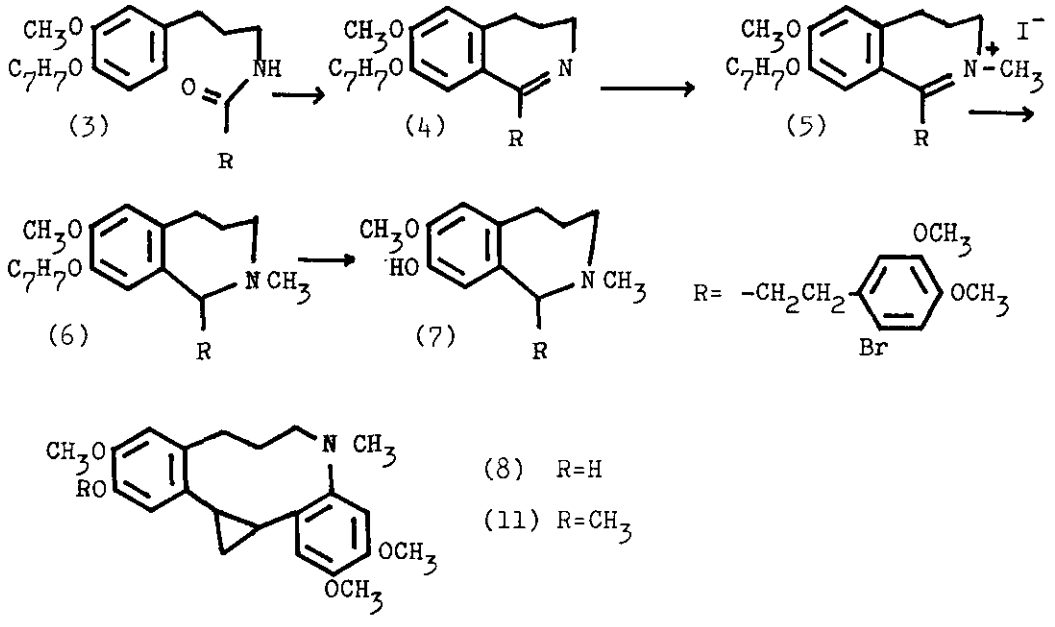
(2)

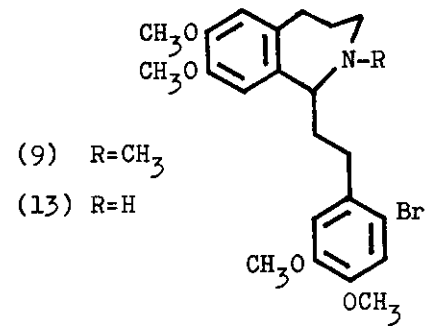
The 1,2,4,5-tetrahydro-3H-2-benzazepine(7) was synthesized as

follows. The 4,5-dihydro-3H-2-benzazepine(4), obtained by cyclization of the amide(3) with phosphoryl chloride in acetonitrile, was treated with methyl iodide to give the corresponding methiodide(5). Reduction of (5) with sodium borohydride, followed by debenzylation of 1,2,4,5-tetrahydro-3H-2-benzazepine(6) afforded the 8-hydroxy derivative(7). The reaction of (7), thus obtained, with sodium methylsulfinylmethanide afforded colorless needles in 35 % yields, m.p. 133-135° (MeOH). Its molecular formula, $C_{22}H_{27}NO_4$, was confirmed by mass spectrum (M^+, m/e 369) and microanalysis; nmr ($CDCl_3$)δ 2.58 (3H, s, NCH_3), 3.73 (6H, s, 2xOCH_3), 3.78 (3H, s, OCH_3), 6.38, 6.43, 6.47, 6.57 (4H, each s, 4x Ar-H). Extremely high $^{13}CH_2$ signal at 7.75 ppm and ^{13}CH signals at 22.05 and 22.25 ppm, in its ^{13}Cnmr ($CDCl_3$) spectrum, indicated the presence of diphenylcyclopropane system in the product. Furthermore a $^{13}CH_2$ at 54.64 ppm, characteristic of $^{13}CH_2$ adjacent to nitrogen, and aromatic ^{13}C bearing nitrogen at 142.45 ppm supported the presence of $PhNCH_2$- as a partial structure. Based upon these spectroscopic data, the product was assigned to 5,6,7,8,13,14-hexahydro-2-hydroxy-13,14-methano-3,10,11-trimethoxydibenzo[b,f]azecine(8). The configuration of the diphenylcyclopropane system could not be determined. Subsequently, the similar reaction of 1,2,4,5-tetrahydro-3H-2-benzazepine(9), prepared by the method as in formation of (6), was examined. Chromatographic separation of the crude product afforded three components. The benzene fraction gave the first product(10) (15 %), m.p. 138-140° (MeOH), the structure of which is under investigation[3]. The $CHCl_3$ fraction afforded the second one in 30 % yields, m.p. 129-130° (MeOH), which was assigned to 5,6,7,8,13,14-hexahydro-13,14-methano-2,3,10,11-tetramethoxydibenzo[b,f]azecine(11) based upon the following spectroscopic data and microanalysis; nmr ($CDCl_3$)δ 2.58 (3H, s, NCH_3), 3.67,

3.73, 3.77, 3.78 (12H, each s, 4xOCH_3), 6.30, 6.40, 6.52, 6.60 (4H, each s, 4xAr-H); m/e 383 (M^+). Its ^{13}Cnmr ($CDCl_3$) spectrum is similar to that of (8) as shown in Table 1. In addition to the above two products, 1,2,4,5-tetrahydro-1-(2-hydroxy-3-methylthio-4,5-dimethoxyphenethyl)-7,8-dimethoxy-3H-2-benzazepine(12) was obtained from 2 % MeOH-$CHCl_3$ fraction, m.p. 130-131° (Et_2O); m/e 447 (M^+), 220; nmr ($CDCl_3$) δ 2.23 (3H, s, NCH_3), 2.43 (3H, s, SCH_3), 6.50, 6.63, 6.67 (3H, each s, 3xAr-H). Cyclization of the tetrahydro-3H-2-benzazepine(13) with sodium methylsulfinylmethanide gave the quinolonobenzazepine(14), which was treated with methyl iodide to afford the methiodide(15). The reaction of (15) with sodium methylsulfinylmethanide also gave (10) and (11). Therefore, these reactions proceeded through the quarternary salt(16) as an intermediate.

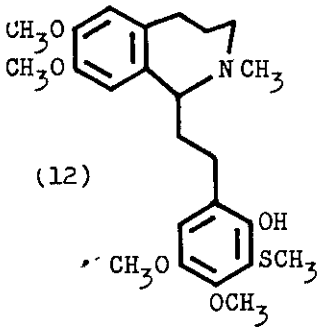
Thus, the benzyne reaction of 1-halogenophenethyl-3H-2-benzazepines was found to show an interesting ring expansion.



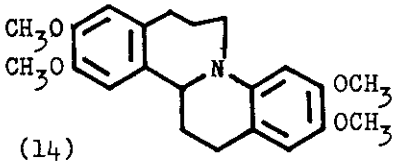


(9) R=CH_3

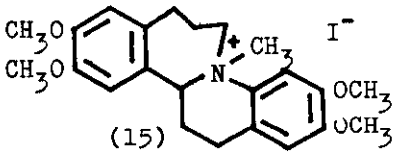
(13) R=H



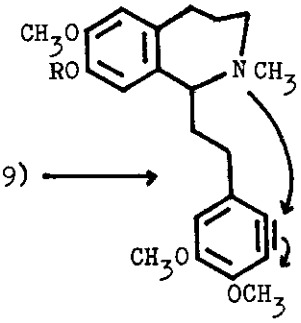
(12)



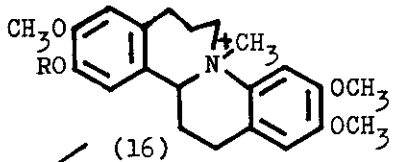
(14)



(15)

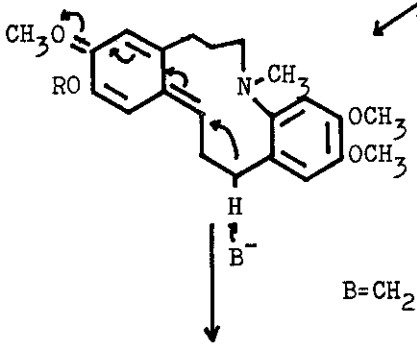


(7) or (9) →



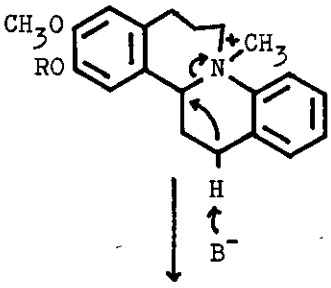
(16)

or



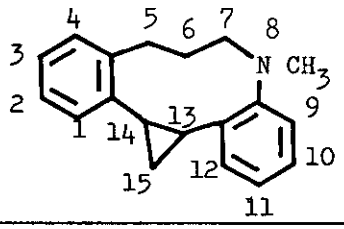
B=CH_2SOCH_3

(8) or (11)



(8) or (11)

Table 1. ^{13}Cnmr ($CDCl_3$) spectra[4] of (8) and (11); ppm



(8)	7.75 (C_{15}), 22.05 (C_{13} or C_{14}), 22.25 (C_{13} or C_{14}), 25.83 (C_6), 28.81 (C_5), 42.32 (NCH_3), 54.64 (C_7), 55.96 ($3xOCH_3$), 106.89, 110.66, 113.18, 113.84, 128.34, 129.54, 134.50, 142.45, 144.83, 145.76, 147.81, 148.15 (Aromatic Carbons)
(11)	7.88 (C_{15}), 21.85 (C_{13} or C_{14}), 22.25 (C_{13} or C_{14}), 25.76 (C_6), 28.61 (C_5), 42.05 (NCH_3), 54.37 (C_7), 55.83 ($3xOCH_3$), 56.23 (OCH_3), 106.89, 111.19, 111.66, 113.44, 128.74, 135.10, 145.56, 145.96, 148.15, 148.61 (Aromatic Carbons)

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REFERENCES

1. S. Kano, E. Komiyama, T. Ogawa, T. Yokomatsu, Y. Takahagi and S. Shibuya, submitted for publication in Tetrahedron.

2. S. Kano, Abstracts of 7th Congress of Heterocyclic Chemistry, Chiba, Japan, 180 (1974).

3. Molecular formula, $C_{23}H_{29}NO_4$, was determined by high resolution mass spectrum and microanalysis; nmr ($CDCl_3$)δ 2.76 (3H, s, NCH_3),

3.88 (12H, s. 4xOCH_3), 6.48, 6.53, 6.70, 6.85 (4H, each s, 4xAr-H); ^{13}Cnmr ($CDCl_3$)δ 14.37 (CH_2), 20.53 (CH), 27.48 (CH_2), 27.81 (CH), 30.60 (CH_2), 36.76 (NCH_3), 52.85 (CH_2), 56.03 (3xOCH_3), 56.42 (OCH_3), 103.31, 107.68, 114.04, 116.42, 124.83, 132.71, 134.90, 143.31, 146.82, 147.09, 147.28, 147.68 (Aromatic Carbons). A comparison of its mass spectrum with that of (11) suggests that it would be the stereoisomer of (11).

4. ^{13}Cnmr spectra were taken with a Varian NV-14 spectrometer using tetramethylsilane as an internal standard.

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