The Reaction of 1-Substituted Isoquinolines and 3H-2-Benzazepines with Dimsylsodium

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The benzyne reaction has been used for the syntheses of numerous synthetic intermediates and natural products, usually with sodium amide or potassium amide as a base. Dimsylsodium[1] was found to be useful benzyne reagent for the syntheses of 6a,7-dehydroaporphines (1)[2,3] and the 5,6-dihydroindolo[2,1-a]-isoquinoline (2)[2] from 1-halogenobenzyl-3,4-dihydroisoquinolines (3) and (4), respectively. Furthermore, treatment of 1-halogenophenethylisoquinoline (5) with dimsylsodium yielded the 13a-(methylsulfinyl)methyldibenzo[a,f]quinolizine (6) by the nucleophilic attack of dimsyl anion to the -C=N-, followed by cyclization of the amino group to the benzyne intermediate[4]

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(1) E. J. Corey and M. Chaycovsky, J. Am. Chem. Soc., 87 1345 (1965).

(2) T. Kametani, S. Shibuya, and S. Kano, J. Chem. Soc., Perkin Trans.1, 1212 (1973).

(3) S. Kano, Y. Takahagi, E. Komiyama, T. Yokomatsu, and S. Shibuya, Heterocycles, 4, 1013 (1976).

(Scheme I). We had successively an occasion to examine the similar reaction using a series of 1,2,3,4-tetrahydroisoquinolines and 1,2,4,5-tetrahydro-3H-2-benzazepines possessing a halogenobenzyl or halogenophenethyl group at the 1-positon. We will limit our discussion to ring expansion of 1-substituted isoquinolines and 3H-2-benzazepines leading to nine and ten-membered ring compounds which result from the cleavage of the C-N bond of the tetracyclic ammonium salts, formed as intermediates, by the nucleophilic action of dimsylsodium.

Treatment of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (7) with dimsylsodium gave the 5-methyl-12-(methylsulfinyl)methyldibenzo[b,f]azonine (8)[5], which would be formed, apparently, through the N-methylindolo[2,1-a]isoquinolinium salt (9). The dibenzo[b,f]azonine (10) was also obtained[6] from the 1-benzyl-7-hydroxyisoquinoline (11) by the similar fassion. This method was applied to the formation of the dibenzo[b,g]azecine (13)[5] by using 1-phenethylisoquinoline (14) (Scheme II).

The formation of dibenzo[b,f]azecine system would be expect-

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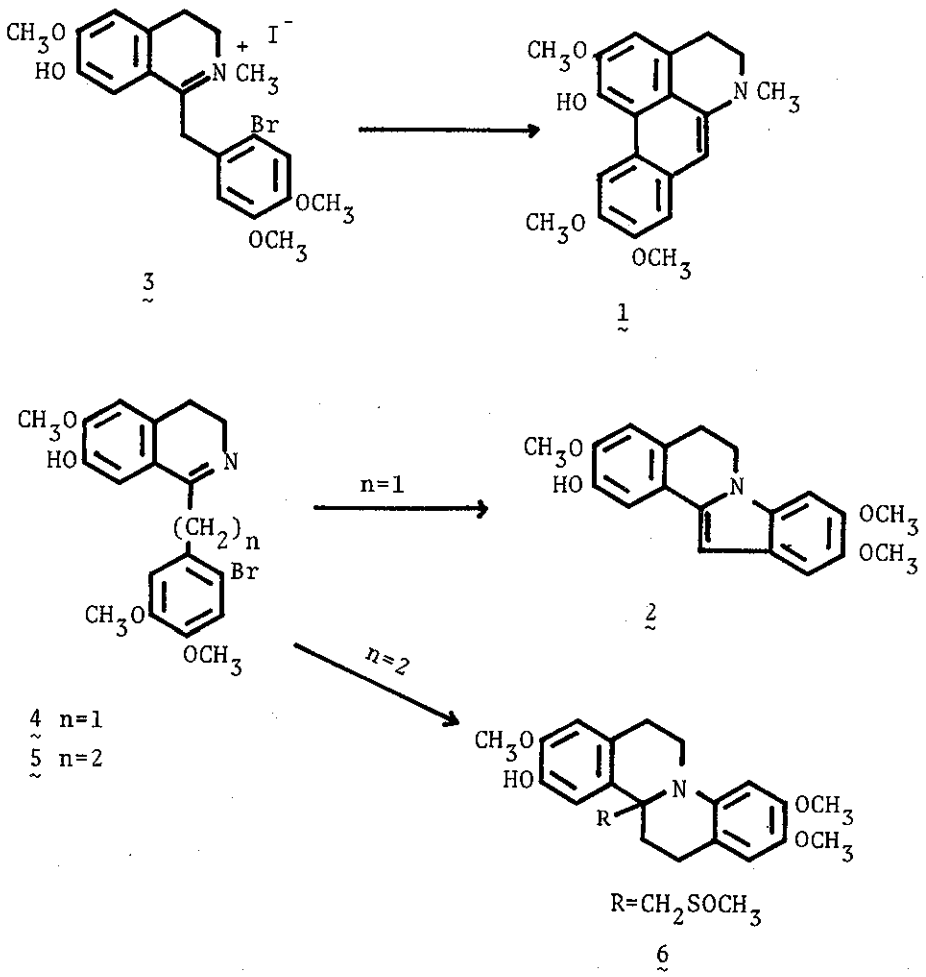
(4) S. Kano, T. Yokomatsu, and S. Shibuya, Chem. Pharm. Bull.(Tokyo), 23, 1098 (1975).

(5) S. Kano, E. Komiyama, T. Ogawa, Y. Takahagi, T. Yokomatsu, and S. Shibuya, Chem. Pharm. Bull.(Tokyo), 23, 2058 (1975).

(6) S. Kano, E. Komiyama, K. Nawa, and S. Shibuya, Chem. Pharm. Bull.(Tokyo), 24, 310 (1976).

Scheme I


CH3O
HO
+ I-
N CH3
Br
OCH3
OCH3
3
CH3O
HO
N CH3
CH3O
OCH3
1
CH3O
HO
N
(CH2)n
Br
CH3O
OCH3
4 n=1
5 n=2
n=1
CH3O
HO
N
OCH3
OCH3
2
n=2
CH3O
HO
N
R
OCH3
OCH3
R=CH2SOCH3
6

ed by the use of 1-halogenobenzyl-3H-2-benzazepines. 1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,4,5-tetrahydro-7-hydroxy-8-methoxy-2-methyl-3H-2-benzazepine (15) was treated with dimsyl-sodium to give the 5-methyl-13-(methylsulfinyl)methyldibenzo-[b,f]azecine (16) as expected, in addition to the 13,14-trans-5,6,7,8-tetrahydrodibenzo[b,f]azecine (17). The same reaction using the 8-hydroxy isomer (18) afforded the 13,14-trans-5,6,7,8-tetrahydrodibenzo[b,f]azecine (19), 13,14-cis-isomer (20), and the 13-(methylsulfinyl)methyl derivative (21). In the case of the non-phenolic 3H-2-benzazepine (22), the 13,14-cis-5,6,7,8-tetrahydrodibenzo[b,f]azecine (23) was obtained as a main product, in addition to 24[7] (Scheme III). However, the different mode of ring expansion was observed in the case of 1-halogenophenethyl-3H-2-benzazepines. The reaction of 1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,4,5-tetrahydro-7,8-dimethoxy-2-methyl-3H-2-benzazepine (25) with dimsylsodium gave the trans-13,14-methano-5-methyldibenzo[b,f]azecine (26) and the cis-isomer (27)[8]. The structures of 26 and 27 were determined by the chemical and spectroscopic methods. The similar reaction by the use of the phenolic 1-(2-bromophenethyl)-3H-2-benzazepine (29) also afforded the cis-13,14-methanodibenzo[b,f]azecine (30) (Scheme IV).

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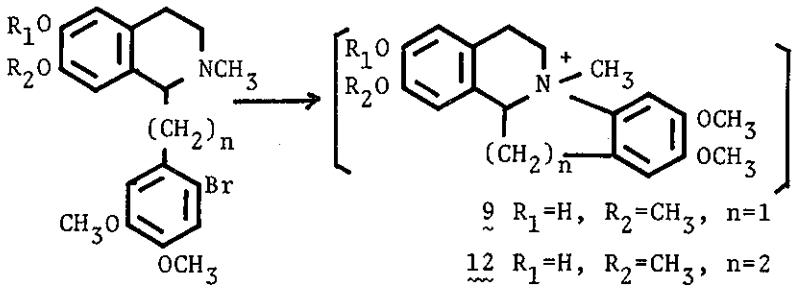
(7) S. Kano, T. Yokomatsu, and S. Shibuya, Heterocycles, 4, 933 (1976).

(8) S. Kano, T. Ogawa, T. Yokomatsu, Y. Takahagi, E. Komiyama, and S. Shibuya, Heterocycles, 3, 129 (1975).

Scheme II



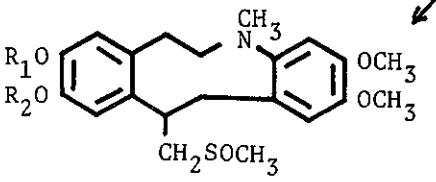
7 R_1=H, R_2=CH_3, n=1

11 R_1=CH_3, R_2=H, n=1

13 R_1=H, R_2=CH_3, n=2

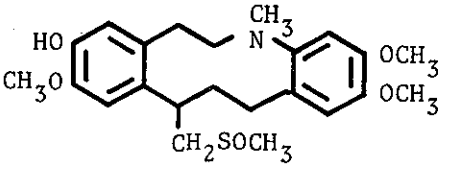
9 R_1=H, R_2=CH_3, n=1

12 R_1=H, R_2=CH_3, n=2



8 R_1=H, R_2=CH_3

10 R_1=CH_3, R_2=H



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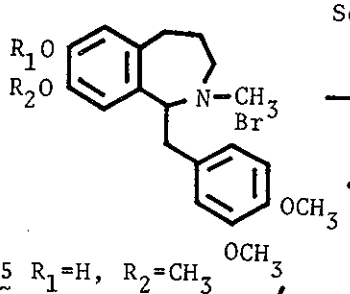
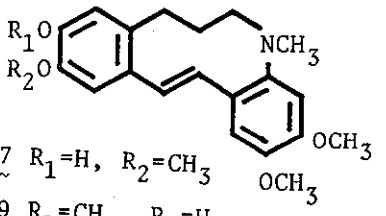
Scheme III



15 R_1=H, R_2=CH_3

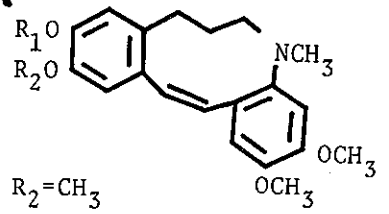
18 R_1=CH_3, R_2=H

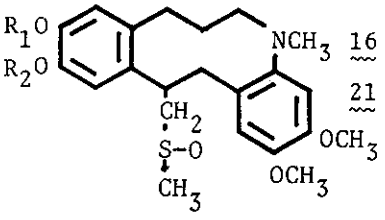
22 R_1=R_2=CH_3



17 R_1=H, R_2=CH_3

19 R_1=CH_3, R_2=H





16 R_1=H, R_2=CH_3

21 R_1=CH_3, R_2=H

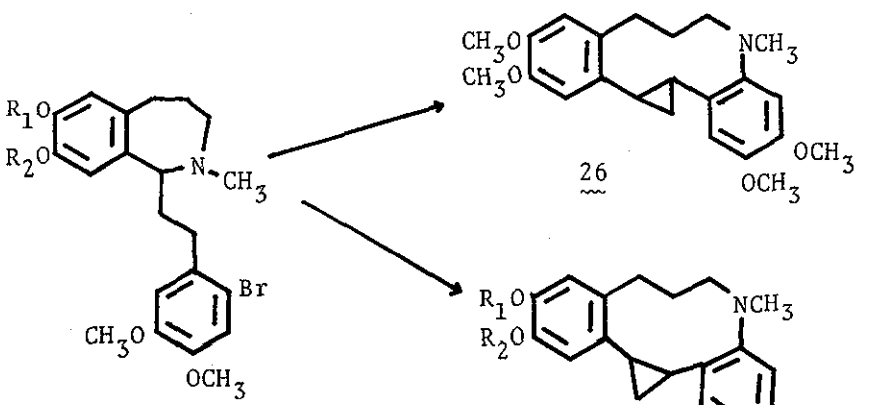
24 R_1=R_2=CH_3

20 R_1=CH_3, R_2=H

23 R_1=R_2=CH_3

Thus, the benzyne reaction using dimsylsodium starting with 1,2,3,4-tetrahydroisoquinolines and 1,2,4,5-tetrahydro-3H-2-benzazepines possessing a halogenobenzyl or halogenophenethyl group at the 1-position led to a novel ring expansion.

Scheme 1V



25 $R_1=R_2=CH_3$

29 $R_1=CH_3$, $R_2=H$

26

27 $R_1=R_2=CH_3$

30 $R_1=CH_3$, $R_2=H$