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NEW FINDINGS IN BISCHLER-NAPIERALSKI REACTION: FORMATION OF 12-AZONIANAPHTH[1. 2-*b*]AZULENES FROM 2-ARYL-1-NAPHTHYLFORMAMIDES AND THEIR UNEXPECTED TRANSFORMATION INTO BENZ[*g*]INDOLES THROUGH HYDRIDE REDUCTION

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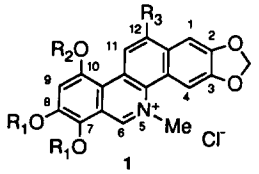
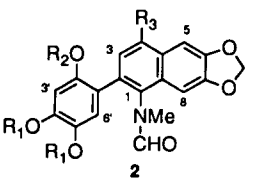
Abstract: The Bischler-Napieralski Reaction (BNR) of *N*-[2-(2-alkoxy-4, 5-methylenedioxyphenyl)-1-naphthyl]-*N*-methylformamides using $POCl_3$ abnormally gave 12-azonianaphth[1. 2-*b*]azulene derivatives, which could be effectively transformed into benz[*g*]indoles with a 1-alkoxy-8-oxabicyclo[3. 2. 1]oct-2-ene skeleton through hydride reduction, as additional cyclized products. In contrast, the BNR of naphthylformamides with methoxy groups in place of a methylenedioxy function at the same position in the phenyl ring led to normal cyclization to give benzo[*c*]phenanthridinium chlorides quantitatively. The speculative mechanism for the abnormal BNR and the indole formation will be discussed.

Bischler-Napieralski Reaction (BNR)[1] is one of the most important methods for the construction of an isoquinoline skeleton. For the synthesis of antitumor-active benzo[*c*]phenanthridine alkaloids **1**[2] we have adopted the BNR of *N*-(2-aryl-1-naphthyl)-*N*-methylformamides **2** as a key step. In the course of reinvestigation[3] of the BNR of *N*-[2-(2-alkoxy-4, 5-methylenedioxyphenyl)-1-naphthyl]-*N*-methylformamides **2a** and **2b** using phosphorus oxychloride ($POCl_3$) the unexpected formation of benz[*g*]indoles **4** fused to a 1-alkoxy-8-oxabicyclo[3. 2. 1]oct-2-ene skeleton was observed after the reduction of the crude BNR products with $NaBH_4$. We report here abnormal generation of 12-azonianaphth[1. 2-*b*]azulene derivatives **3** under the BNR condition and their anomalous transformation into **4** through mild hydride reduction.



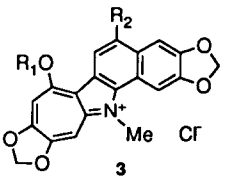
1

a: $2R_1 = CH_2$, $R_2 = i$-Pr, $R_3 = H$
b: $2R_1 = CH_2$, $R_2 = Me$, $R_3 = OMe$
c: $R_1 = Me$, $R_2 = i$-Pr, $R_3 = H$
d: $R_1 = R_2 = Me$, $R_3 = H$



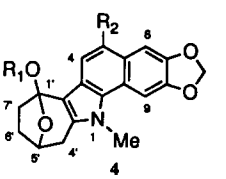
2

a: $2R_1 = CH_2$, $R_2 = i$-Pr, $R_3 = H$
b: $2R_1 = CH_2$, $R_2 = Me$, $R_3 = OMe$
c: $R_1 = Me$, $R_2 = i$-Pr, $R_3 = H$
d: $R_1 = R_2 = Me$, $R_3 = H$



3

a: $R_1 = i$-Pr, $R_2 = H$
b: $R_1 = Me$, $R_2 = OMe$



4

a: $R_1 = i$-Pr, $R_2 = H$
b: $R_1 = Me$, $R_2 = OMe$

Heating **2a**[4] in $POCl_3$ without solvent[5] followed by the treatment with $NaBH_4$ at room temperature gave two products,[6] one of which was a 5, 6-dihydrobase (44 %) of the expected **1a**. An alternative product **4a** (22 %) was obtained as colorless prisms (from AcOEt), mp 237-239 °C. The molecular formula was determined as $C_{22}H_{23}NO_4$ by the elemental analysis and the appearance of a parent peak at *m/z*: 365.1635 (Calcd: 365.1627) in the HRFABMS. This was a replaced equivalent of CO by 2H in the 5, 6-dihydrobase ($C_{23}H_{21}NO_5$) of **1a**. In the ^1H NMR spectrum appearance of signals attributable to four aromatic protons, composed of two singlets [δ 7.27 (6-H) and 7.84 (9-H)] and a pair of doublets (*J*=8.5 Hz) [δ 7.37 (5-H) and 7.67 (4-H)], and one methylenedioxy group (δ 6.05) indicated the loss of two aromatic protons and one methylenedioxy group from the starting **2a**[7] during the reactions. Instead seven new aliphatic signals [δ 1.53 (1H, m, 6'-H), 2.22 (2H, m, 7'-H_2), 2.32 (1H, m, 6'-H), 2.42 (1H, d, *J*=15 Hz, 4'-H), 3.38 (1H, dd, *J*=15, 5 Hz, 4'-H), and 4.96 (1H, diffused t, *J*=5 Hz, 5'-H)] assignable to a four carbon sequence of $CH_2CH_2CH(O)CH_2$ were observed by decoupling, ^{13}C DEPT, and 2D NMR experiments. These signals became gradually complicated during measurement of NMR in $CDCl_3$. This phenomenon could be caused by trace amounts of acid in the solvent,[8] suggesting that an acid-sensitive acetal function is contained in the structure of the product. The full structure of 2, 3-(1-isopropoxy-8-oxabicyclo[3. 2. 1]octeno)-1-methyl-7, 8-methylenedioxybenz[*g*]indole for **4a** was unambiguously established by X-ray crystallographic analysis.[9] (Figure 1)

Next, we attempted to isolate the BNR products of **2a** before reduction. Carefully fractional recrystallization of the reaction residue from MeOH afforded two products. One of them, obtained as the second crystal (dark red needles, mp 253-259 °C) from the mother liquor, was established to be an intended quaternary benzo[*c*]phenanthridine base **1a** (35 %) by the appearance of a signal due to 6-H at δ 10.00 in the ^1H NMR spectrum (in DMSO-d_6) and by the chemical evidence giving the same dihydrobase obtained above by hydride reduction.

A less soluble product **3a** was given as light orange needles (21 %, mp >300 °C). An isomeric structure to **1a** was suggested by the HRFABMS (*m/z*: 390.1345. Calcd for $C_{23}H_{20}NO_5$: 390.1341). The UV spectrum[10] showed the presence of a longer conjugated system in **3a** than in **1a**. The ^1H NMR spectrum exhibited the same signal pattern of aromatic protons[11] as that in **2a**.[7] Two methylenedioxy, an isopropoxy, and an *N*-methyl groups remained in its molecule but a formyl proton disappeared. No carbonyl absorption was observed in the IR spectrum. In the NOE experiments two aromatic protons of singlets at δ 7.93 and 8.24 due to 1- and 11-H showed strong enhancements of their integrals on irradiation of the *N*-methyl signal at δ 4.34 and *vice versa*, indicating a planar structure of **3a** in which these protons were situated spatially close to each other. Furthermore characteristic cross peaks depending on two bond connection of C_{11a}-C_{11}-H together with three bond connection of C_{11a}-N-C-H_3 were observed in the 2D COLOC (4 Hz) experiment. (Figure 2) These data allowed us to deduce that **3a** should be assigned to a 12-azonianaphth[1. 2-*b*]azulene derivative.[12]

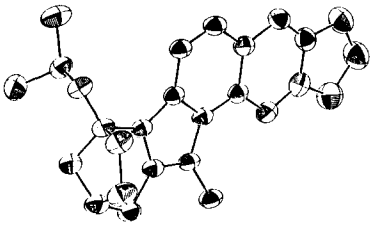


Figure 1. ORTEP drawing of a molecular structure of **4a** with thermal ellipsoids drawn at the 30 % probability level.

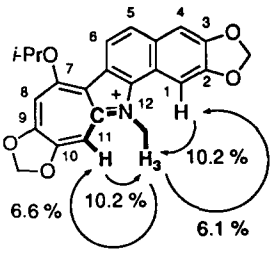


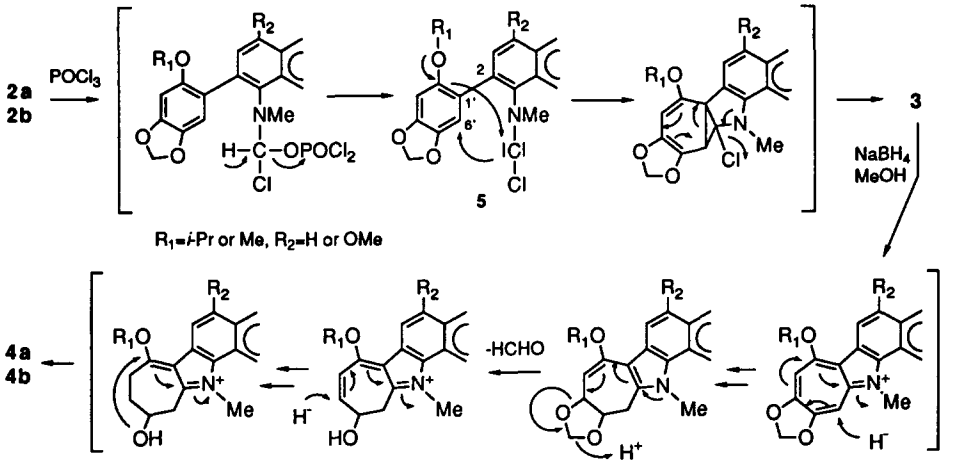
Figure 2. Selected NOE and COLOC data of **3a**.

Reduction of **3a** with $NaBH_4$ smoothly afforded **4a** in 75 % yield, indicating that an azonianaphthoazulene was a real precursor for a benz[*g*]indole with an oxygen-bridged bicyclooctene unit. Thus, it was clear that the observed abnormal ring system in **3a** should be built up under the condition of BNR but not reduction.

Similarly an alternative 2-(2-methoxy-4, 5-methylenedioxyphenyl)-1-naphthylformamide **2b** gave a dihydrobase of macarpine (**1b**)[13] (32 %) and a benz[*g*]indole **4b** (25 %) by combination of BNR and $NaBH_4$ reduction. Trial for isolation of the BNR product of **2b** by recrystallization resulted in affording an azoniaazulene **3b** (28 %) as a sole isolable product, which was easily reduced to give **4b** (73 %).

In contrast, quantitative and normal cyclization to **1c**[5] and chelilutine (**1d**)[3] occurred in the BNR of **2c**[4] and **2d**[3] with methoxy groups in place of a methylenedioxy function at the same position in the phenyl ring and any azoniaazulene products could not be detected in the reaction mixture.

These results suggested that a methylenedioxy group in the 2-phenyl ring of naphthylformamides can play a critical role for azoniaazulene formation. More effective conjugation of a methoxy group to aromatic ring than a methylenedioxy group has been reported in *SEAr* reactions.[14] Thus, it would be reasonable to speculate the mechanism for the abnormal BNR and the succeeding reduction as follows: (i) the generation of a highly reactive carbene derivative **5** or its equivalent, (ii) the insertion of it into the $C_{1'}$-$C_{6'}$ double bond in the 2-phenyl ring triggered by ipso attack depending on the 2-alkoxy group, (iii) rearrangement of a formed 1, 2-cycloadduct to a valence-isomeric seven-membered ring compound **3**, and (iv) benz[*g*]indole formation by repeated hydride attacks and protonations to **3** through the loss of formaldehyde and transanular acetal cyclization. (Scheme) Further investigation on the supposed mechanism, the azoniaazulene chemistry including hydride reduction, and scope and limitation of these processes is at present in progress.



Scheme

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References and Notes

1. Whaley, W. M.; Govindachari, T. R. *Organic Reactions*, vol 6; Adams, R. Ed.; John-Wiley and Sons: New York, 1951; pp 74-150.
2. Ishii, H.; Ichikawa, Y.-I.; Kawanabe, E.; Ishikawa, M.; Ishikawa, T.; Kuretani, K.; Inomata, M.; Hoshi, A. *Chem. Pharm. Bull.*, **1985**, *33*, 4139-4151. Recently it was reported that nitidine (8, 9-dimethoxy-5-

methyl-2, 3-methylenedioxybenzo[*c*]phenanthridinium) inhibited DNA topoisomerase I [Fang, S. -D.; Wang, L. K.; Hecht, S. M. *J. Org. Chem.*, **1993**, *58*, 5025-5027].

3. Ishii, H.; Ishikawa, T.; Watanabe, T.; Ichikawa, Y.-I.; Kawanabe, E. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 2283-2289.
4. Synthesized from the corresponding benzaldehyde and acetopiperone according to the reported method.[2] The preparation will be reported elswhere.
5. Use of a solvent such as acetonitrile[3] resulted in formation of a complex mixture.
6. All new compounds were fully characterized by spectroscopic data and combustion analyses.
7. In **2a** the signals due to aromatic protons and methylenedioxy groups were observed as follows: δ ($CDCl_3$) 5.97 and 6.08 (each 2H, s, OCH_2O), 6.58 (2H, s, 3'- and 6'-H), 7.07 (1H, s, 8-H), 7.19 (1H, s, 5-H), 7.22 (1H, d, *J*=8.3 Hz, 3-H), and 7.68 (1H, d, *J*=8.3 Hz, 4-H).
8. Although the decomposition was observed even after treatment of commercial $CDCl_3$ with K_2CO_3, each signal was reasonably assignable. Use of C_6D_6 in place of $CDCl_3$ gave simple NMR spectra.
9. Crystal data for **4a**: rhombohedral (hexagonal axes), space group $R\bar{3}$ (No. 148); *a*=26.668 (3) Å, *c*=13.755 (4) Å; *V*=8472 (3) $Å^3$; *Z*=18; d_{calc}=1.29 g cm^{-3}; μ (CuKα)=6.8 cm^{-1}. A total of 2984 symmetry-independent reflections ($2\theta_{max}$=128.0°) were recorded on a MAC Science MXC18 diffractometer. Of these, 2206 unique reflections with $I>3.0\sigma(I)$ were used for the structure solution and refinement (303 parameters) using the CRYSTAN-GM program system (Version 6. 1. 1). An E map revealed all the non-H atoms. Cycles of refinement and difference Fourier syntheses showed all the H atoms in the structure. All H atoms were placed in positions found in the difference Fourier map. The positions of eleven H atoms were fixed. Anisotropic block-matrix refinement for non-H atoms and isotropic for H atoms converged to a standard agreement factor, *R*=0.060. The supplementary materials have been deposited at the Cambridge Crystallographic Data Centre.
10. **3a**: λ_{max} (MeOH) 244 nm (log ε 4.40), 261 (4.65), 347 (4.43), and 419 (3.98). **1a**: λ_{max} (MeOH) 232 nm (log ε 4.47), 280 (4.36), 341 (4.14), and 351 (4.11).
11. In **3a** the signals due to aromatic protons were observed as follows: δ (CD_3OD) 7.35 (1H, s, 4-H), 7.69 (1H, d, *J*=9 Hz, 5-H), 7.85 (1H, s, 8-H), 7.93 (1H, s, 1-H), 8.24 (1H, s, 11-H), and 8.47 (1H, d, *J*=9 Hz, 6-H).
12. Trial to prepare a crystal for X-ray analysis has been unsuccessful until now.
13. Slavik, J.; Slavikova, L. *Coll. Czech. Chem. Commun.*, **1955**, *20*, 356-361; Our synthetic work for **1b** will be reported elsewhere.
14. Sha, C.-K.; Young, J.-J.; Yeh, C.-P.; Cheng, S.-C.; Wang, S.-L. *J. Org. Chem.*, **1991**, *56*, 2694-2696.

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