BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (10), 3097—3098 (1978)

The Bimolecular Reduction of Acridine and 9-Substituted Acridines by Sodium 1-Benzyl-1,4-dihydronicotinamide-4-sulfinate

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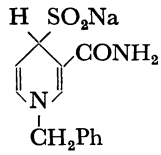
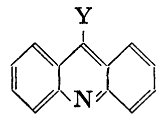
(Received May 11, 1978)

Synopsis. Sodium 1-benzyl-1,4-dihydronicotinamide-4-sulfinate is found to undergo the bimolecular reduction of acridine or 9-substituted acridines to the corresponding 9,9′-biacridans.

The reducing behavior of sodium 1-benzyl-1,4-dihydronicotinamide-4-sulfinate (BNA-SO_2Na)[1] has received little attention. Recently we have found that BNA-SO_2Na reacts with various halogen compounds through the cleavage of its carbon-sulfur bond to give sulfones, olefins, and reduction products.[2] In order to explore further the chemical reactivity of BNA-SO_2Na, the reactions of BNA-SO_2Na were carried out with acridine (**1**) and its derivatives (**2**—**4**), with a methoxy, chloro, or cyano group at the 9-position. Herein, we wish to report our findings on these reactions.

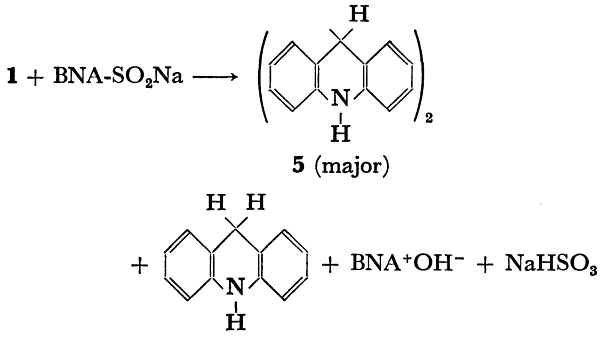


BNA-SO_2Na



Y=H (**1**), CH_3O (**2**), Cl (**3**) and CN (**4**)

As Table 1 shows, the reaction of **1** with BNA–SO_2Na in 80 vol % aqueous methanol at 25 °C afforded 9,9′-biacridan (**5**), together with a small amount of acridan (**6**). In this reaction, BNA-SO_2Na was converted to 1-benzylnicotinamide hydroxide (BNA^+OH^-) and a sulfite ion. The formation of **5** along with an equivalent amount of BNA^+OH^- constitutes the bimolecular reduction of **1** by BNA-SO_2Na. On the other hand, the reaction of **1** with 1-benzyl-1,4-dihydronicotinamide (BNAH) or sodium dithionite afforded only **6**, without the formation of any **5**. Sodium dithionite would undergo the reduction of **1**, probably *via* the intermediary formation of an adduct (**7**), followed by the decomposition of **7** by water to give **6**.[3] Similar phenomena were also found in the reaction of 10-methylacridium chloride (**8**) with BNA-SO_2Na (Table 1). Thus, it is concluded that BNA-SO_2Na shows a reducing behavior different from that of BNAH and sodium dithionite.



5 (major)

6 (minor)

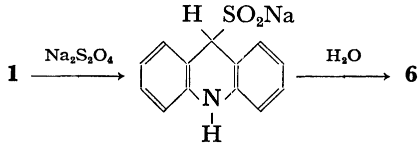


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Table 1. The reductions of **1** and **8** with BNA-SO_2Na or $Na_2S_2O_4$[a)]

Substrate	Reducing agent	Time h	Product, %[b)]			
			Biacridans	Acridans	BNA^+OH^-	SO_3^{2-}
1	BNA-SO_2Na	12	76	7	36	32
1	$Na_2S_2O_4$	2	0	75	—	—
8	BNA-SO_2Na	12	69	13	35	35
8	$Na_2S_2O_4$	2	12	41	—	—

a) Concentration of **1** and **8**: 6×10^{-2} mol/l. Solvent: 80 and 50 vol % $MeOH-H_2O$ for BNA-SO_2Na and $Na_2S_2O_4$ respectively. Reducing agent/substrate molar ratio: 1. b) Biacridans% = {2 × biacridans (mol)/substrate (mol)} × 100. Acridans, BNA^+OH^- and SO_3^{2-}% = {products (mol)/substrate (mol)} × 100.

Table 2. The reductions of **2**, **3**, and **4** with BNA-SO_2Na[a)]

Substrate	Solvent	Time, h	Product (%)[b)]
2	80% $MeOH-H_2O$	20	**9** (41), Acridone(6), BNA^+OH^-(43)[c)]
3	EtOH	6	**10** (58), Acridone(37), BNA^+Cl^-(59)
4	DMF	3	**11** (91), BNA^+OH^-(100)

a) Concentration of **2**, **3**, and **4**: 6×10^{-2} mol/l. Reducing agent/substrate molar ratio = 1 (for **2** and **3**) and 2 (for **4**). b) **9** and **10**% = {2 × **9** and **10** (mol)/substrate (mol)} × 100. **11**, acridone, and BNA^+OH^- (Cl^-) % = {products (mol)/substrate (mol)} × 100. c) Recovery% of **2**: 45%.

The reactions of 9-substituted acridines with BNA–SO_2Na were affected by the nature of the substituents. The reaction of **2** or **3** with BNA-SO_2Na afforded 9,9′-dimethoxy-9,9′-biacridan (**9**) or 9,9′-biacridine (**10**) respectively as the reduction product, as Table 2 shows. In both reactions, however, acridone was obtained as another product. In addition, in the case of **2**, the **2** was recovered in considerable amounts. On the other hand, BNA-SO_2Na was converted to BNA^+OH^- (Cl^-) in larger amounts than those of **9** and **10**. Furthermore,

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the reduction of **2** with KBH_4 in 80 vol % aqueous methanol was found to afford acridone in a 40% yield, with a 45% recovery of **2**. These facts suggest that the 9,10-dihydro-compounds of **2** and **3**, which may be easily oxidized with air to acridone and the starting material, are produced in addition to **9** and **10**. In the reaction of **4** with BNA-SO$_2$Na, 9-cyanoacridan (**11**) was produced in a high yield, without the formation of any 9,9′-dicyano-9,9′-biacridan. Thus, the existence of an electron-withdrawing group, such as the cyano group, at the 9-position of the acridine ring favored the formation of a dihydro-compound by two-electron reduction.[4]

Experimental

Material. The BNA-SO$_2$Na was prepared according to the procedures described in our proceding paper.[2]

Reduction by BNA-SO$_2$Na. *Acridine (1)*: A solution of a mixture of 3.06 mmol of **1** and 3.05 mmol of BNA-SO$_2$Na in 50 cm^3 of 80 vol% aqueous methanol was stirred under nitrogen at 25 °C for 12 h. A white precipitate (0.42 g, 76%) of **5** was formed and recrystallized from DMSO under nitrogen: mp 260—262 °C (lit,[5] 260—261 °C). (Found: C, 86.72; H, 5.26; N, 7.73%. Calcd for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59; N, 7.77%). Its IR spectrum was identical with that of the authentic specimen. After the precipitate had been removed by filtration, 50 cm^3 of water was added to the filtrate to give 0.038 g (7%) of a white precipitate of **6** (mp 168—169 °C (lit,[5] 170 °C)). After the removal of **6** by filtration, the filtrate was acidified by concentrated hydrochloric acid to bring about the evolution of sulfur dioxide. The amount of sulfur dioxide evolved (32%) was determined by the method described previously.[2] The solution thus acidified was evaporated *in vacuo*, and the residue was treated by the procedures described previously to yield 0.28 g (36%) of BNA$^+$Cl$^-$ (mp 230—233 °C (lit,[2] 236 °C)). Similar procedures were used for the reactions of **1** or **8** with BNAH, sodium dithionite, or BNA-SO$_2$Na. 10,10′-Dimethyl-9,9′-biacridan (mp 271—273 °C (lit,[5] 272—274 °C)) was obtained in a 69% yield. (Found: C, 86.65; H, 6.15; N, 6.96%. Calcd for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21%).

9-Methoxyacridine (2): To a solution of 1.49 mmol of **2** in 25 cm^3 of 80 vol% aqueous methanol, we added 1.5 mmol of BNA-SO$_2$Na. The solution was stirred under nitrogen at 25 °C for 20 h. A pale yellow precipitate which was thus deposited (0.13 g) was removed by filtration, washed under nitrogen with 80 vol% aqueous methanol, and dried *in vacuo*: mp>260 °C (The color turned to brown at 172 °C). The elementary analysis of the precipitate was carried out without purification, since it was oxidized easily with air in an organic solvent.

Found: C, 79.67; H, 5.60; N, 6.78%. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.97; H, 5.75; N, 6.66%.

The pattern of its IR spectrum was similar to that of **5**. Its UV spectrum (CHCl$_3$) showed a peak at 280 nm, thus being similar to that of **5**. In contact with air, however, the UV spectrum changed completely to that of **2**, which had two peaks at 256 and 354 nm (ε: 1.4×10^5 and 8.3×10^3). Based on these facts, it was identified as **9**. Yield: 41%. On the other hand, the filtrate was concentrated to one-fifth of its original volume, and the orange precipitate thus deposited (0.31 g) was removed by filtration, washed with water, and dried *in vacuo*. The precipitate was chromatographed on silica gel. Elution with chloroform gave 0.14 g (45%) of **2** and 0.016 g (6%) of acridone. The combined filtrate was developed on an anion-exchange resin (Amberlite IRA-400) to yield 0.16 g (43%) of BNA$^+$Cl$^-$.

9-Chloroacridine (3): To a solution of 2.89 mmol of **3** in 50 cm^3 of ethanol, we added 3.11 mmol of BNA-SO$_2$Na. The mixture was stirred under nitrogen at 25 °C for 6 h. A pale yellow precipitate (**10**) thus deposited was removed by filtration, washed successively with ethanol and water, dried *in vacuo*, and recrystallized from toluene; mp>360 °C. Yield: 58%. Its IR spectrum was similar to that of **1**. (Found: C, 87.77; H, 4.83; H, 8.03%. Calcd for $C_{26}H_{16}N_2$: C, 87.61; H, 4.53; N, 7.86%). The filtrate was concentrated to one-fifth of its original volume, and 50 cm^3 of water was added. Extraction with dichloromethane gave 0.21 g (37%) of acridone. The aqueous layer was treated by a method similar to that used in the case of **1** to yield 0.42 g (59%) of BNA$^+$Cl$^-$.

9-Cyanoacridine (4): A solution of a mixture of 2.94 mmol of **4** and 6.01 mmol of BNA-SO$_4$Na in 50 cm^3 of DMF was stirred under nitrogen at 25 °C for 3 h. The solution immediately showed a red color, and then it turned orange. The reaction mixture was added to 200 cm^3 of water to give 0.55 g (91%) of a white precipitate of **11** (mp 146—147 °C (lit,[5] 146 °C)). Its IR spectrum was identical with that of the authentic specimen. After the removal of **11** by filtration, the filtrate was treated by a method similar to that used in the case of **1** to yield 0.73 g (100%) of BNA$^+$Cl$^-$.

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5) Ref. 3, Chaps. 5 and 6, and the references cited therein; H. Goth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965); F. Mader and V. Zanker, *Chem. Ber.*, **94**, 2418 (1964).