Kinetics of Decomposition of Certain Benzhydryl Nitrosobenzamides. Evidence for a Rearrangement Step

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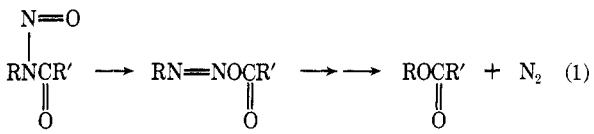
N-Benzhydryl-*N*-nitrosobenzamide and the 4-chloro- and 4-methoxybenzhydryl analogs were prepared and decomposed in benzene, acetonitrile, and acetic acid solvents. The rates of decomposition were all fairly similar, suggesting that a direct ionization to give benzhydryl carbonium ions is not occurring. Instead, these nitrosoamides appear to react by the normal pathway involving a rearrangement to the corresponding diazo ester in the first step.

N-Nitrosoamides of primary amines (1) decompose in both polar and nonpolar solvents to yield the corresponding esters (eq 1).[1,2] Various studies have shown that, for

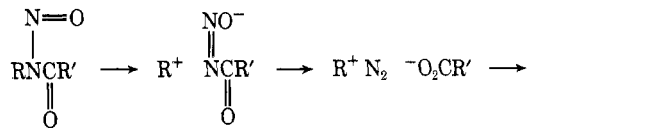


(1)

1 2

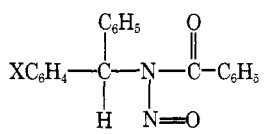
nitrosoamides of simple alkylamines (1, R = alkyl, benzyl, etc.), the first step in the reaction is a rearrangement of 1 into an isomer, the diazo ester **2**; subsequent reactions lead to the corresponding ester (eq 1).[1,2] The rate-determining step, the rearrangement,[2] has a relatively nonpolar transition state as shown by the following observations: (1) the nitrosoamide reaction of simple alkylamines proceeds readily in nonpolar solvents such as hexane,[1,2] (2) only a small solvent effect has been noted,[3] and (3) only a small electronic effect of substituents on the rates of decomposition has been observed.[4]

The purpose of the present work was to investigate the possibility that a direct ionization mode of decomposition (eq 2) might be competitive under certain circumstances.



(2)

Alkyl groups, R, that form stable carbonium ions could conceivably change the course of the decomposition to favor an SN1 mode of reaction (eq 2). The benzhydryl system was chosen for the present study in this context because it has been used in studies relating the deamination reaction to solvolysis,[5] and because the benzhydryl carbonium ion is the most stable of the carbonium ions studied in an alkyl nitrosoamide decomposition to date[2] (the triphenylmethyl system has not yet been examined). This paper covers the preparation of the nitrosobenzamides of benzhydrylamine (**3a**) and the 4-chloro (**3b**) and 4-methoxy (**3c**) derivatives, and the measurement of their rates



3a, X = H
b, X = 4-Cl
c, X = 4-CH_3O

of decomposition. The reactions were followed in benzene, acetonitrile, and acetic acid, and the results show that these nitrosoamides also follow the pathway outlined in eq 1.

Results

N-Benzhydryl-, *N*-(4-chlorobenzhydryl)-, and *N*-(4-methoxybenzhydryl)benzamides were nitrosated with dinitrogen tetroxide[6] to yield compounds **3a-c**. These nitrosoamides were not subjected to purification procedures because of their instability. The changes in the infrared spectra on nitrosation are large,[6,7] however, and the most reasonable impurities can be readily detected. The nitrosoamides used in the rate studies were pure as shown by their infrared spectra; these showed no detectable amounts of the starting amides or the product esters. The rates of decomposition were followed by the decrease in intensity of the visible absorption band of the nitroso group at ~425 nm.[7,8] A concentration of 10^{-2} *M* was chosen to give a convenient optical density for a cell of 1-cm path length. A commercial Haake circulator and temperature controller was used as a constant-temperature bath. With this apparatus it was possible to maintain a given temperature in the bath to within 0.01°; the thermometer could be read to 0.1° and estimated to within 0.01°. All runs were conducted at 25 ± 0.01°. For each run, the cell and the solvent were equilibrated at 25° in the constant-temperature bath, the nitrosoamide was quickly dissolved in the solvent of choice, and the spectra were taken on a Cary spectrometer Model 14, the cell chamber of which was connected to the Haake circulator. The initial optical density A_0 was obtained by extrapolation of the optical densities to time zero.

Runs varied from 2 to 3 half-lives and 7-14 points were used to establish the linearity of the first-order plots. The rate constants were determined from these by graphical methods.[9] The nitrosoamides proved not to be very soluble in acetic acid. In the acetic acid runs, they were first dissolved in a small amount of methylene chloride and then the acetic acid was added; the final concentration of methylene chloride in the acetic acid was 2-7%.

The data for a typical run are given in Table I. In all of the cases, linear plots of log A_0/A *vs* time were obtained and from these, the first-order rate constants were calculated; the data are given in Table II.

Discussion

In all of the solvents used, the 4-methoxybenzhydryl compound (**3c**) decomposed faster than the 4-chlorobenzhydryl analog (**3b**). The rate enhancement factor was 1.5 in benzene, 1.7 in acetonitrile, and 1.4 in acetic acid. This effect of the methoxy group is small relative to that to be expected if the reaction were to proceed *via* eq 2, however. For example, the rates of methanolysis of benzhydryl chlorides with the same suite of substituents increase in the order 4-Cl (0.47), 4-H (1.0), 4-CH_3O (~5000).[10] Further, the rate constants for the solvolysis of the corresponding benzhydryl 4-nitrobenzoates in 90% aqueous acetone fall in the order 0.5, 1.0, and >1300.[11]

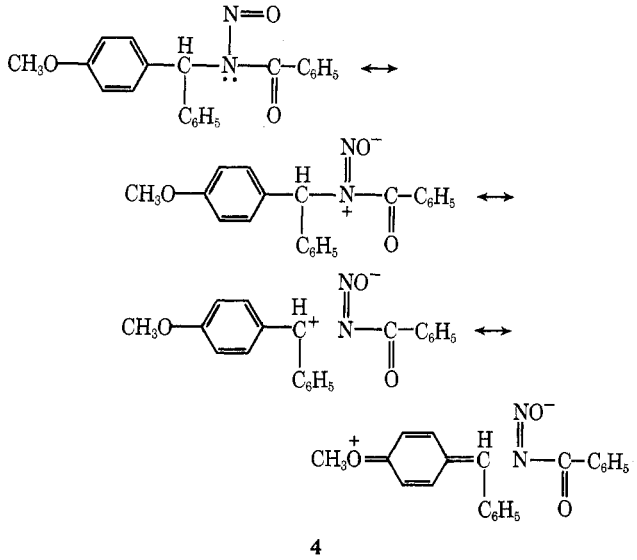
Table I
Decomposition of *N*-Nitroso-*N*-benzhydrylbenzamide (3a) in Benzene

Time, sec	A^a	Log A_0/A	k_1,[b] min^{-1}
0	0.720[c]	0.000	
235	0.620	0.065	3.8×10^{-2}
480	0.535	0.129	3.6×10^{-2}
710	0.470	0.185	3.4×10^{-2}
930	0.410	0.245	3.7×10^{-2}
1140	0.367	0.293	3.2×10^{-2}
1385	0.320	0.352	3.4×10^{-2}
1610	0.280	0.410	3.6×10^{-2}
1825	0.250	0.459	3.2×10^{-2}
2445	0.175	0.614	3.4×10^{-2}
3030	0.130	0.743	3.0×10^{-2}
			Av $3.4^4 \times 10^{-2}$

[a] A = optical density. [b] First-order rate constant calculated for each point. [c] Obtained by extrapolating the experimental points to time zero.

The small rate increase noted upon substitution of a methoxy group into a benzhydrylnitrosoamide shows that, even for benzhydryl groups, the nitrosoamide reaction is not diverted from the normal path outlined in eq 1 to the ionization mode outlined in eq 2. Of course, nitrosoamides bearing groups that would yield more stable carbonium ions (*e.g.*, **1**, R = triphenylmethyl) might follow eq 2. It appears, however, that all the nitrosoamides prepared to date decompose *via* the pathway outlined in eq 1.[12]

The small rate enhancement that was observed for series **3a–c** (Table II) is probably a result of inductive and resonance interactions (**4**) influencing the nucleophilicity of the oxygen atom in the nitroso group.



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Experimental Section

Instrumentation. Infrared spectra were obtained on a Perkin-Elmer Model 337 grating spectrophotometer. A Cary 14 recording spectrophotometer was used to obtain uv spectra. Proton magnetic resonance spectra were obtained with a Varian Model A-60. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Melting points, obtained on a Thomas-Hoover apparatus, were uncorrected.

4-Methoxybenzophenone Oxime. 4-Methoxybenzophenone oxime was prepared on 70% yield from 4-methoxybenzophenone and hydroxylamine hydrochloride.[13] A mixture of syn and anti oximes was obtained: mp 115–139° (lit.[13a] mp 115–116° for anti and 137–138° for syn isomer); ir ($CDCl_3$) 3590, 3300 (broad), 2910, 1615, and 990 cm^{-1}; nmr (acetone-*d*) δ 3.32 and 3.37 (3 H, s, OCH_3), ~6.70 (9.1 H, m, C_6H_5 and C_6H_4), impurities at 1.6 (m), and 2.6 (s).

4-Methoxybenzhydrylamine Hydrochloride. Reduction of 6.0 g (26.4 mmol) of 4-methoxybenzophenone oxime with sodium in ethanol and formation of the hydrochloride yielded the salt:[14] 5.30 g (21.3 mmol, 82%); mp 218–220° (lit.[14a] mp 190°, lit.[15] mp 229°); ir (KBr) 2900 (broad), 1600, 1500, and 1030 cm^{-1}; nmr (DMSO-d_6) δ 3.35 (2.5 H, s, NH_3^+), 3.75 (3 H, s, OCH_3), 6.90 and 7.50 (10 H, m, C_6H_5, C_6H_4, CH).

Table II
First-Order Rate Constants for the Decomposition of the *N*-Nitrosobenzamides of Three Benzhydrylamines [3, RN(NO)COC_6H_5] at 25°

Solvent	R	Registry no.	k, min^{-1}	Half-life, min
Benzene	4-Chlorobenzhydryl	16469-42-4	2.7×10^{-2}	26
	Benzhydryl	16469-41-3	3.5×10^{-2}	20
	4-Methoxybenzhydryl	51271-73-9	3.9×10^{-2}	18
Acetonitrile	4-Chlorobenzhydryl		3.0×10^{-2}	23
	4-Methoxybenzhydryl		5.2×10^{-2}	13
Acetic Acid	4-Chlorobenzhydryl		3.8×10^{-2}	18
	4-Methoxybenzhydryl		5.4×10^{-2}	13

***N*-Benzhydrylbenzamides.** *N*-Benzhydrylbenzamide, *N*-4-chlorobenzhydrylbenzamide, and *N*-4-methoxybenzhydrylbenzamide were prepared from the corresponding amines and benzoyl chloride using pyridine as a solvent. The corresponding melting points follow: *N*-benzhydrylbenzamide, 174–175° (lit.[16] 172°); *N*-4-chlorobenzhydrylbenzamide, 178–180° (lit.[17] 180–181°); and *N*-4-methoxybenzhydrylbenzamide, 180–181° (lit.[18] 174°).

***N*-Nitroso-*N*-benzhydrylbenzamides.** *N*-Nitroso-*N*-benzhydrylbenzamide, *N*-nitroso-*N*-4-chlorobenzhydrylbenzamide, and *N*-nitroso-*N*-4-methoxybenzhydrylbenzamide were prepared by nitrosating the corresponding amides. A procedure slightly modified from that reported in the literature[6,17] was used. The amides were dissolved in methylene chloride, sodium acetate (~35-fold molar excess) was added and the mixture was cooled to −70°. Dinitrogen tetroxide (~20-fold molar excess with respect to the amide) was added and the temperature was raised to about −15 to −5°. The reaction mixture was stirred for about 2.5 hr and then worked up in a cold room. The final solution of the nitrosoamide in methylene chloride was washed with ice-cold 5% sodium carbonate solution and with saturated sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed at −10° (*ca.* 0.05 Torr). Because of their instability, the nitrosoamides were not purified. The course of the nitrosation could be readily followed in the ir by the loss of the amide carbonyl band at 1675 cm^{-1} and the growth of the nitrosoamide carbonyl band at 1710 cm^{-1} as well as the double-bond stretch of the nitroso group at 1510 cm^{-1}. The samples used for the kinetic studies were free of amide and the corresponding ester (formed on decomposition). Two absorptions in the uv are associated with the *N*-nitroso group: 405–409 (ϵ 70–73) and 423–426 nm (ϵ 71–75).[7,8]

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Registry No.—*syn*-4-Methoxybenzophenone oxime, 10147-61-2; *anti*-4-methoxybenzophenone oxime, 10147-60-1; 4-methoxybenzhydrylamine hydrochloride, 5427-61-2.

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Syntheses of Some 1,2,3,4-Tetrahydropyrazino[1,2-a]benzimidazoles

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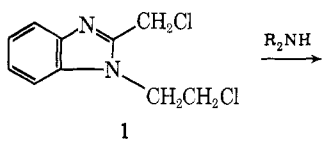
A general and convenient method for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles has been developed. Evidence is presented for the existence of the 1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole system.

It was the purpose of this work to develop a general and convenient synthetic route to 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole and its derivatives. Saunders[1] prepared *N*-carbethoxy-1,2,3,4-tetrahydropyrazino-[1,2-a]benzimidazole in low yield by pyrolyzing 2-(4′-carbethoxypiperazine)phenyl azide. This method has been improved and extended by Garner, Garner, and Suschitzky.[2] Schmutz and Kunzle[3] prepared the ring system by treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with secondary amines. When one of the alkyl groups was



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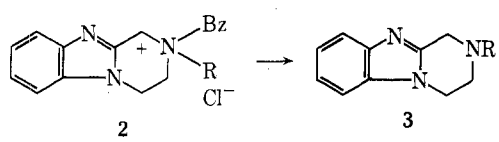

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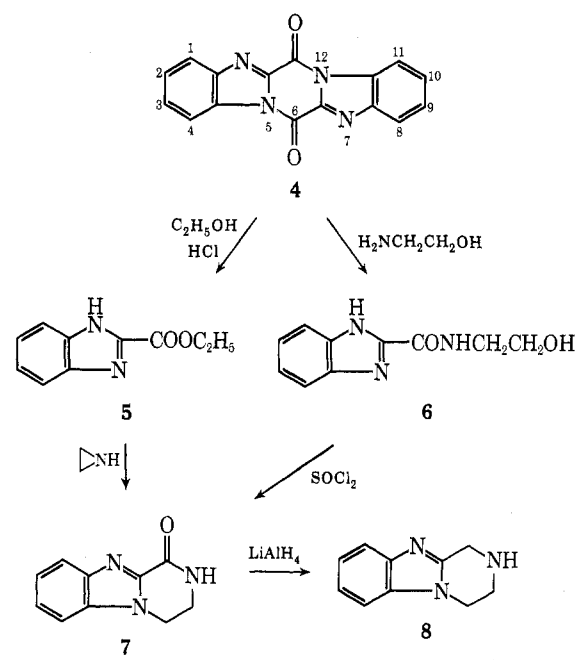
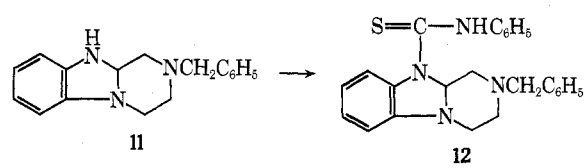
benzyl, hydrogenolysis gave the corresponding 2-alkyl derivative. A similar but more direct synthesis involved treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with primary amines. This leads directly to the 2-alkyl derivative.[4]

Freedman[5] explored a new synthetic pathway to this ring system which is shown in Scheme I. In this work,[5] difficulties were encountered in the conversion of **7** into **8**. This scheme, at this stage, was not very efficient. It appeared, however, to have one advantage, namely ease of procurement of starting materials. It was decided therefore to restudy the procedure, with special emphasis on the conversion of **7** into **8**. This has now been completed and we now have a convenient general method for the preparation of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles in good yields.

The starting compound, dibenzimidazo[1,2-a,1′,2′-a]tetrahydropyrazine-6,13-dione (**4**), was prepared by a known method.[6] We found that the conversion of **6** into **7** proceeded in higher yield than the conversion of **5** into **7**. Initially the reduction of **7** with lithium aluminum hydride gave air-sensitive products from which only small amounts of 8 could be isolated. Suspecting the overreduction of **7**, we investigated the $LiAlH_4$ reduction of the more easily reducible 2-benzyl-1,2,3,4-tetrahydropyrazino-[1,2-a]benzimidazol-1-one (**10**). Compound **10** was prepared by the synthesis outlined in Scheme I, using 2-benzylaminoethanol in place of 2-aminoethanol. An analytical sample of the reduction product could not be obtained because of its instability. The product was shown to be 2-benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (**11**). The nmr and ir assignments agreed with this structure, and the product formed a stable thiourea derivative (**12**) in high yield when **10** was treated with phenyl isothiocyanate.

Scheme I





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