42031-38-9; **11**, 42031-39-0; **11** 2,4-DNP, 42031-40-3; **12**, 42031-41-4; **13** (X = ClO$_4$), 42031-42-5; **13** betaine, 42031-43-6; **14** (X = HSO$_4$), 42031-44-7; 1-(2-naphthylmethyl)-2-cyanopyridinium tetrafluoroborate, 42031-45-8; 1-(1-naphthylmethyl)-2-cyanopyridinium iodide, 42031-46-9; 1-(1-naphthylmethyl)-2-cyanopyridinium tetrafluoroborate, 42133-37-9; 11-acetamidoacridizinium perchlorate, 42031-47-0; 11-acetoxyacridizinium perchlorate, 42031-48-1.

Studies on the Synthesis of Benzo[*b*]quinolizinium Salts

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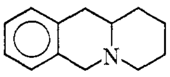
An improved procedure for the preparation of 8,9-dimethoxybenzo[*b*]quinolizinium bromide and a method for the preparation of selected 11-aminobenzo[*b*]quinolizinium bromides are described.

As a consequence of our work on derivatives of 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (**1**),[1] we became interested in the synthesis of derivatives of the parent aromatic system **2**.[2] These latter substances have been studied extensively by Bradsher and his coworkers,[3] but our findings differ significantly from those reported.



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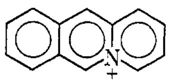
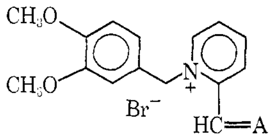
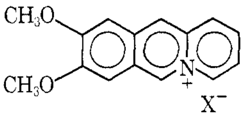


2

Bradsher and Dutta[4] reported that cyclization of the pyridinium salt **3a** in concentrated hydrochloric acid at 100°, followed by ion exchange, gave the quaternary chloride **4a**. However, in agreement with the report of Kupchan, Flouret, and Matuszak,[5] we found that the cyclization reaction was accompanied by demethylation, and that we were unable to obtain a pure product.



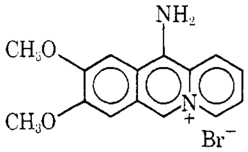
3a, A = O
b, A = NOH



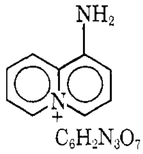
4a, X = Cl
b, X = Br

We decided to modify the procedure of Bradsher and Dutta[4] by using hydrobromic acid to avoid the necessity for ion exchange. We found that cyclization could be effected in 5 min at 75° in the concentrated acid. Pouring the reaction mixture into tetrahydrofuran precipitated the product **4b** as a yellow solid which could be obtained analytically pure after one recrystallization.

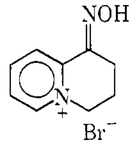
Bradsher has also advocated the preparation of benzo[*b*]quinolizinium salts by cyclization of the appropriate quaternary oxime,[6] and we attempted to prepare **4b** from **3b**. Conducting the reaction in hydrobromic acid as described above gave a product the nmr spectrum of which shows two equivalent exchangeable protons and only seven aromatic protons. Microanalysis indicated the presence of an additional nitrogen atom. These data suggested that the product is the 11-amino derivative **5**. This structure is analogous to that of the bicyclic primary amine picrate salt **6** prepared by Collicut and Jones[7] by treatment of the quaternary oxime **7** with acetic anhydride and concentrated sulfuric acid, followed by hydrolysis of the acetamide of **6**.



5

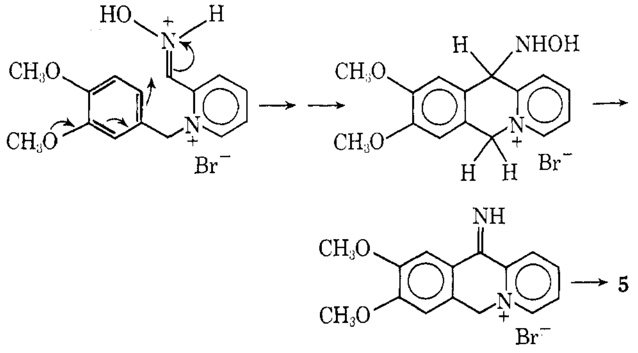


6



7

It is tempting to suggest that the conversion of **3b** to **5** proceeds by way of the nitrile,[8] but dehydration of an aldoxime with aqueous acid is unprecedented. Normally an oxime would be hydrolyzed under these conditions. In this case we suggest that instead of being attacked by water, the protonated oxime cyclizes. The resulting intermediate then dehydrates to the imine, which is a tautomer of **5**. Presumably such a dihydroaromatic hydroxylamine derivative is also involved in the acid-promoted conversion of 3,5-dimethylcyclohexenone oxime to 3,5-xylylamine,[9] and transformations similar to the above are involved in Semmler–Wolff aromatizations in general.[7,10]



The oximes **8a** and **8b** underwent cyclization to the 11-amino derivatives **9a** and **9b**, respectively. How-

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[1] J. W. H. Watthey and K. J. Doebel, U. S. Patent 3,484,443 (1969) [*Chem. Abstr.*, **72**, 3396f (1970)].

[2] K. J. Doebel and J. W. H. Watthey, S. African Patent 6,707,635 [*Chem. Abstr.*, **70**, 96652h (1969)].

[3] For a review see C. K. Bradsher, *Accounts Chem. Res.*, **2**, 181 (1969).

[4] C. K. Bradsher and N. L. Dutta, *J. Amer. Chem. Soc.*, **82**, 1145 (1960).

[5] S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

[6] C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

[7] A. R. Collicut and G. Jones, *J. Chem. Soc.*, 4101 (1960).

[8] Cyclization of analogous nitriles to 11-aminobenzo[*b*]quinolizinium salts is described in the accompanying paper: C. K. Bradsher and L. S. Davies, *J. Org. Chem.*, **38**, 4167 (1973).

[9] L. Wolff, *Justus Liebigs Ann. Chem.*, **322**, 351 (1902).

[10] M. V. Bhatt, *Experientia*, **13**, 70 (1957).

TABLE I

1-BENZYLPYRIDINIUM BROMIDES[a]

Compd	Yield, %	Mp, °C	Calcd, % C	H	Br	N	Found, % C	H	Br	N
3b	85	168–171.5	50.99	4.85	22.63	7.93	51.29	4.96	22.51	7.86
8a[b]	86	149–150	50.99	4.85	22.63	7.93	50.83	5.00		8.09
8b	68	155–157.5	52.32	5.22	21.76	7.63	52.32	5.22	21.49	7.63
8c	91	166.5–168	50.14	5.00	20.85	7.32	50.18	4.79	21.04	7.30

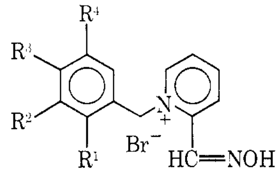
[a] The benzyl bromide starting materials were obtained as follows: 3,4-dimethoxy-, ref 13; 2,3-dimethoxy-, R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, **127,** 1437 (1925); 3,4-dimethoxy-2-methyl-, see below; 3,4,5-trimethoxybenzyl bromide was prepared by the method Haworth and Perkin used for the 2,3-dimethoxy compound and was used without purification. [b] Recrystallized from methanol–ethyl acetate.

TABLE II

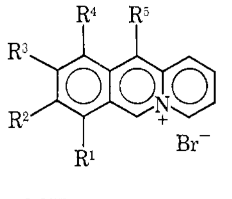
BENZO[*b*]QUINOLIZINIUM BROMIDES

Compd	Yield, %	Mp, °C	Calcd, % C	H	Br	N	Found, % C	H	Br	N
5[a]	89	267–267.5	53.75	4.51	23.84	8.36	53.85	4.45	23.67	8.66
9a	66	252–255	53.75	4.51	23.84	8.36	54.02	4.60	23.70	8.64
9b	70	223–223.5	52.61	4.69	21.88	7.67	52.53	4.90	21.75	7.62
9c[b]	62	228–231	57.49	4.83	23.92	4.18	57.19	4.66	23.73	4.49
9e	72	258–260	56.27	4.41	24.96	4.38	56.46	4.51	25.13	4.33

[a] Recrystallized from methanol–ethanol. [b] The mother liquor yielded a small amount of the 11-NH_2 derivative **9d**, mp 259.5–260°. *Anal.* Calcd: C, 55.02; H, 4.91; Br, 22.88; N, 8.02. Found: C, 54.82; H, 4.88; Br, 22.90; N, 7.86.



8a, $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$
b, $R^1 = H$; $R^2 = R^3 = R^4 = OCH_3$
c, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = H$
d, $R^1 = R^4 = OCH_3$; $R^2 = R^3 = H$



9a, $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$; $R^5 = NH_2$
b, $R^1 = H$; $R^2 = R^3 = R^4 = OCH_3$; $R^5 = NH_2$
c, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = R^5 = H$
d, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = H$; $R^5 = NH_2$
e, $R^1 = R^4 = OCH_3$; $R^2 = R^3 = R^5 = H$
f, $R^1 = R^4 = OH$; $R^2 = R^3 = R^5 = H$

ever, cyclization of the oxime **8c** gave almost exclusively **9c**, although a small quantity of the amine **9d** was isolated in a pure state.

Cyclization of **8d**[11] gave exclusively the substance lacking the amino group **9e**. Bradsher and Barker[11] obtained this substance as the mixed salt with hydroxylamine hydrobromide. Ion exchange of the picrate gave the bromide salt; we obtained the bromide directly—one recrystallization gave the pure salt.

Those substances which cyclize to give only the amino derivative have a methoxy group para to the site of cyclization, flanked by a methoxy group and a hydrogen atom. Those substances which gave little or no amino compound presumably react more slowly, enabling oxime hydrolysis to occur. In **8c** the steric requirements of the methyl group will reduce the resonance effect of the adjacent methoxy group. In the case of **8d** the results can be rationalized by consideration of the steric effects of the methoxy group ortho to the site of cyclization.

In contrast to an earlier report,[11] demethylation of **9e** was found to proceed normally in concentrated hydrobromic acid, to give the known hydroquinone derivative **9f**.[12]

Experimental Section

All melting points (uncorrected) were determined on a Thomas-Hoover Uni-melt capillary melting point apparatus. Nmr spectra were obtained on a Varian A-60A spectrometer (Me_4Si).

1-(3,4-Dimethoxybenzyl)-2-formylpyridinium Bromide (3a).[4]—A solution of 3,4-dimethoxybenzyl bromide[13] (65 g) and freshly distilled 2-picolinaldehyde (31 g) in dimethylformamide (10 ml) was maintained at 30° for 18 hr. The solid was slurried in ethyl acetate (250 ml), filtered, and dried, giving 81 g of **3a**, mp 118–128°.

Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.08; H, 5.07; N, 4.37.

8,9-Dimethoxybenzo[*b*]quinolizinium Bromide (4b)—**3a** (10 g) was finely ground and added to 48% hydrobromic acid (25 ml) previously heated to 75°. After 5 min at 75° the solution was poured into tetrahydrofuran (400 ml) with stirring. The yellow solid was recrystallized from methanol-ethanol to give 6.3 g of **4b**: mp 247–250°; nmr (DMSO-d_6) δ 10.13 (s, 1), 9.21 (m, 1) 8.81 (s, 1), 8.36 (m, 1), 7.82 (m, 2), 7.64 (s, 2), 4.08 (s, 3), 4.03 (s, 3).

Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27: H, 4.41; Br, 24.96; N, 4.38. Found: C, 56.01; H, 4.56; Br, 24.81; N, 4.34.

The 1-benzylpyridinium bromides 3b and **8a–c** were obtained by the method used by Bradsher and Barker[11] for the preparation of **8d**. Details are given in Table I. Reaction time was 18 hr at 30°; recrystallization was from methanol.

The benzo[*b*]quinolizinium bromides 5 and **9a–c,e** were obtained from **3b** and **8a–d**, respectively, using the general method employed for the conversion of **3a** to **4b**. Details are given in Table II. Recrystallization was from ethanol.

7,10-Dihydroxybenzo[*b*]quinolizinium Bromide (9f).[12]—A solution of 6.4 g of **9e** in 25 ml of 48% hydrobromic acid was refluxed for 3 hr. The reaction mixture was cooled and the product was recrystallized twice from 48% hydrobromic acid, extracted exhaustively with methanol in a Soxhlet apparatus (leaving a small

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[11] C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **29**, 61 (1964).

[12] D. F. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **30**, 252 (1965).

[13] L. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem Soc.*, **127** 1445 (1925).

amount of a black, insoluble substance), and finally recrystallized from methanol to give 2.3 g of **9f**, mp 315–318° dec.

Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.44; H, 3.46; Br, 27.36; N, 4.80. Found: C, 53.37; H, 3.50; Br, 27.30; N, 4.84.

3,4-Dimethoxy-2-methylbenzyl Bromide.—A mixture of 2,3-dimethoxytoluene (80 g), bromomethyl methyl ether (137 g), and glacial acetic acid (88 ml) was maintained at 30° for 8 hr. The reaction mixture was poured into ice–water and the solid was recrystallized from hexane to give 73 g of the benzyl bromide, mp 66–68°. Structural assignment was by analogy with the corresponding chloro compound.[14]

Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35; Br, 32.39. Found: C, 48.97; H, 5.40; Br, 32.39.

Acknowledgments.—We thank Dr. V. Boekelheide for useful discussions, and the Analytical Research Department for analyses and spectral data.

Registry No.—**3a**, 42031-49-2; **3b**, 21852-33-5; **4b**, 24403-47-2; **5**, 21852-31-3; **8a**, 42031-53-8; **8b**, 21852-51-7; **8c**, 21831-11-8; **9a**, 42031-56-1; **9b**, 21852-49-3; **9c**, 21831-08-3; **9d**, 21852-24-4; **9e**, 42031-60-7; **9f**, 3919-24-2; 3,4-dimethoxy-2-methylbenzyl bromide, 21831-10-7; 2,3-dimethoxytoluene, 4463-33-6; bromomethyl methyl ether, 13057-17-5.

(14) E. D. Hornbaker and A. Burger, *J. Amer. Chem. Soc.*, **77**, 5314 (1955).

Kinetics in the Thermolysis of 1-Arylethyldimethylamine Oxides in Aqueous Media[1]

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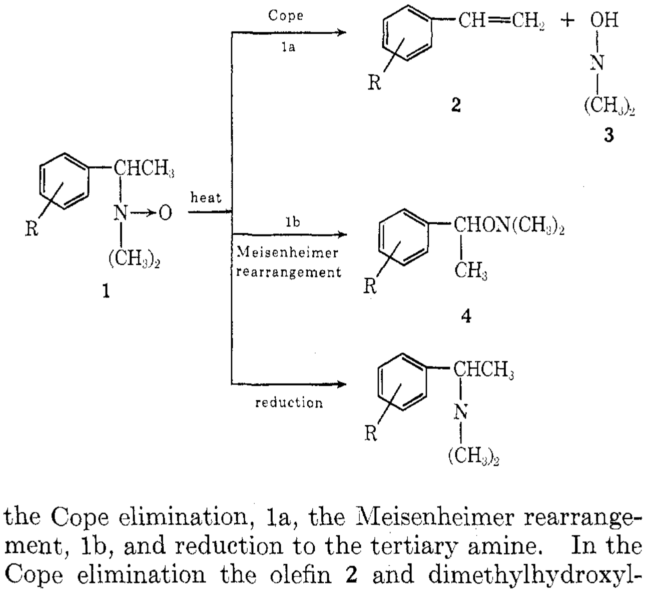
The kinetics of the thermolysis of unsubstituted and 1-(*p*-methoxy, *o*-methoxy, *p*-methyl, *o*-methyl, *p*-chloro, and *p*-nitro)phenylethyldimethylamine oxides, 1, at 94° in aqueous media have been determined by nuclear magnetic resonance spectroscopy. Essentially only the Cope elimination reaction occurred with all amine oxides except in the last two cases, those containing *p*-Cl and *p*-NO_2 substituents. With amine oxides possessing electron-withdrawing substituents, the Meisenheimer rearrangement and the formation of the free tertiary amine complicated the evaluation of the rate of the Cope elimination reaction. Good agreement was obtained between log k/k_0 with Hammett's σ constants for the amine oxides possessing electron-donating substituents which showed a ρ of -6.5. Activation parameters for the *p*-OMe derivative in the Cope thermolysis are E_a = 39.6 kcal/mol and $\Delta S^\ddagger$ = 32 eu. Mechanistic implications of the Cope reaction are discussed in light of these data.

Several studies have shown that during the thermolysis of benzyl tertiary amine oxides **1** there are at least three main competing reactions occurring (Scheme I), the Cope elimination, 1a, the Meisenheimer rearrangement, 1b, and reduction to the tertiary amine. In the Cope elimination the olefin **2** and dimethylhydroxylamine **3** are formed. The Meisenheimer rearrangement involves a migration of benzyl group from nitrogen to oxygen yielding **4**.[2a]

SCHEME I



The competition between these three reactions is markedly affected by the nature of the groups on the tertiary amine oxides. Essentially, only the Cope reaction occurs unless benzyl or allyl groups are involved. In cases where the Cope elimination reaction cannot occur, it has been shown that the electron-withdrawing groups on the benzyl group (*e.g.*, NO_2) enhance the Meisenheimer reaction.[2b] No reports, however, have appeared of a substituent effect study where the two reactions compete from the same starting material.

This study has been directed to the kinetics of the Cope reaction, a Hammett $\rho\sigma$ study, a determination of Arrhenius activation parameters, effects of water on the reaction rate constants, and proximity effects in the Cope reaction. These aspects of the Cope reaction have not been reported. Also reported is additional esr evidence for a radical intermediate in the Meisenheimer rearrangement.

Results

Aqueous Media.—The thermolysis of the tertiary amine oxides was carried out in aqueous media for various reasons. Amine oxides are difficult to obtain pure, since they readily form hydrates. The removal of the water from the hydrate is difficult without partial decomposition of the amine oxide, even at reduced pressure.[3] Lepley, Cook, and Willard[3b] attempted to remove all water from the oxide of *N,N*-dimethylbenzylamine by a freeze-drying process at 0.01 Torr. The hydroscopic, free-flowing white powder proved to be the monohydrate with an nmr ($CHCl_3$) peak at δ 5.03. This is also the position found for the water

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(1) This paper was presented in part at the 28th Annual Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June 1973, Abstract ORGN, 26.

(2) (a) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3929 (1949); (b) U. Schöllkopf, U. Ludwig, M. Patsch, and W. Franken, *Justus Liebigs Ann. Chem.*, **703**, 77 (1967).

(3) (a) G. P. Shulman, P. Ellgen, and M. Connor, *Can. J. Chem.*, **43**, 3459 (1965); (b) A. R. Lepley, P. M. Cook, and G. F. Willard, *J. Amer. Chem. Soc.*, **92**, 1101 (1970).