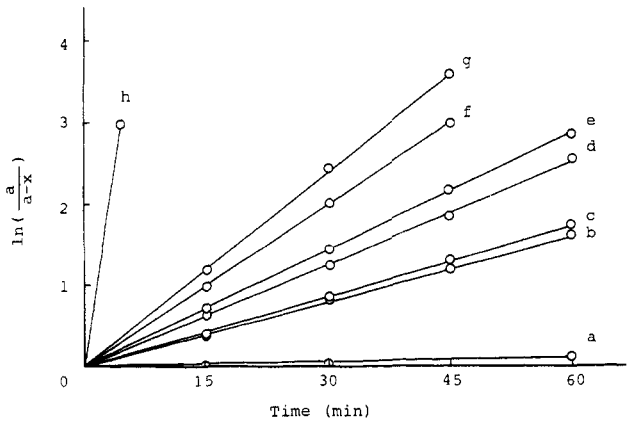

Figure 2. A plot of ln $[a/(a - x)]$ for the reaction of IVa with alcohols ([alcohol]/[IVa] = 10): (a) methanol; (b) ethanol; (c) 1-propanol; (d) 1-hexanol; (e) 3-hexanol; (f) 3-pentanol; (g) 2-propanol; (h) benzyl alcohol.

1). In this oxidation, no other products were detected. As shown in Figure 1, the oxidation rates for secondary alcohols were faster than those of primary alcohols. Then, excesses of various alcohols were treated with IVa and the consumption of IVa was followed by iodometric titration. As shown in Figure 2, various alcohols were oxidized and the rates demonstrates pseudo-first-order kinetics (eq 3).

$$-\mathrm{d[IVa]}/\mathrm{d}t = k[\mathrm{IVa}] \quad (3)$$

The relative rates of oxidation of alcohols, referenced to methanol, are shown in Table II. For primary alcohols, bulky alcohols are oxidized rapidly by IVa. Secondary alcohols are oxidized faster than primary alcohols by IVa.

On the other hand, primary alcohols are oxidized faster than secondary alcohols with IVb. Oxidations with IVb were so rapid that the rate of oxidation could not be measured by the same method as described above. Equimolar 1-hexanol and 3-hexanol were oxidized by IVb in one pot. Hexanal was obtained in a 1.7-times excess over 3-hexanone. When the oxidation was carried out by use of IVa in the same method, 3-hexanone was obtained in a 3.6-times excess over hexanal. This result shows that the relative rate of oxidation of primary and secondary alcohols is very dependent on the counter anion of the oxoaminium salt.

We investigated the selective oxidation of alcohols by use of an oxoaminium salt. This reaction proceeds cleanly under mild condition with a satisfactory yield of carbonyl compounds uncomplicated by the presence of side products.

Experimental Section

4-Methoxy-2,2,6,6-tetramethylpiperidinyl-1-oxy (III). To a stirred solution of 17.2 g (100 mmol) of 4-hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxy (II)[7] in 150 mL of anhydrous DMF was added 3.6 g (150 mmol) of NaH. After this suspension was stirred under nitrogen, 9.34 mL (150 mmol) of methyl iodide, dissolved in 34 mL of DMF, was added dropwise to the solution at 0 °C. The reaction mixture stood at room temperature for 5 h. After filtration of NaI, 500 mL of ether was added. The resulting mixture was washed with water and separated, and the ether layer was dried with anhydrous magnesium sulfate. The ether solution was concentrated in vacuo to give a viscous red liquid. *n*-Hexane was added and the mixture was stored at −20 °C. A total of 16.5 g of red needle crystals of III were obtained: 89% yield, mp 35–36 °C; mass spectrum, *m/e* 186; IR (KBr) 2980, 2940, 2820, 1470, 1390, 1360, 1350, 1315, 1180, 1100 cm^{-1}. Anal. Calcd for $C_{10}H_{20}NO_2$: C, 64.48; H, 10.28; N, 7.52. Found: C, 64.11; H, 10.59; N, 7.64.

4-Methoxy-1-oxo-2,2,6,6-tetramethylpiperidinium Bromide (IVa). To a stirred solution of 3.37 g (18.1 mmol) of III in 100 mL of *n*-hexane was added dropwise 1.45 g (9.1 mmol) of bromine which was dissolved in 20 mL of CCl_4 at room temperature. The dark-red precipitate appeared from the red solution. The precipitate was filtered and washed with CCl_4 to give 4.04 g (84%) of IVa: mp 206–207 °C dec; IR (KBr) 2940, 1620, 1460, 1370, 1320, 1240, 1160, 1100 cm^{-1}. Anal. Calcd for $C_{10}H_{20}NO_2Br$: C, 45.12; H, 7.57; N, 5.26; Br, 30.02. Found: C, 45.11; H, 7.45; N, 5.29; Br, 29.59.

4-Methoxy-1-oxo-2,2,6,6-tetramethylpiperidinium Chloride (IVb). Anhydrous chlorine was bubbled into the stirred solution of 2.0 g (10.7 mmol) of III in 100 mL of CCl_4. The orange precipitate appeared and it was filtered and washed with CCl_4 to give 2.1 g (9.5 mmol, 89%) of IVb: mp 121–123 °C dec; IR (KBr) 2951, 2897, 2827, 1616, 1466, 1446, 1388, 1377, 1219, 1161, 1106 cm^{-1}. Anal. Calcd for $C_{10}H_{20}NO_2Cl$: C, 54.17; H, 9.09; N, 6.32; Cl, 15.99. Found: C, 53.60; H, 9.22; N, 6.29; Cl, 16.88.

General Procedure for Oxidation of Alcohols by Use of IVa or IVb. To a solution of 15 mg (0.15 mmol) of 1-hexanol in 0.8 mL of anhydrous methylene chloride were added 40 mg (0.15 mmol) of IVa or 33 mg (0.15 mmol) of IVb. The reaction mixture was kept at room temperature until the oxoaminium salt (IVa or IVb) was no longer detectable. The product was determined by GLC and the yield was calculated. 2-Hexanol, 3-hexanol, crotyl alcohol, cinnamyl alcohol, benzyl alcohol, and benzhydrol were oxidized by the same method.

Oxidation of Benzoin by Use of IVa or IVb. To a solution of 49 mg (0.23 mmol) of benzoin in 1 mL of anhydrous methylene chloride were added 61 mg (0.23 mmol) of IVa or 52 mg (0.23 mmol) of IVb. After the dark-red color of oxoaminium salt disappeared, the reaction mixture was condensed in vacuo and the products were purified with silica gel column chromatography to give benzil: 6 mg (0.03 mmol, 13% by use of IVa), 22 mg (0.11 mmol, 45% by use of IVb). The physical and spectral data of the product agreed with those of an authentic sample of benzil.

Kinetic Method. The rate of consumption of the oxidizing agent (IVa) was followed by iodometric titration.[1]

To a solution of 37.5 mmol of the alcohol in 50 mL of anhydrous methylene chloride was added 1.0 g (3.75 mmol) of IVa. The reaction mixture was kept at room temperature. After 15, 30, 45, and 60 min, 5 mL of the solution was sampled and poured into 25 mL of acetic acid contained 5 mL of a 20% aqueous solution of potassium iodide. The mixture was left for 15 min in the dark. After 100 mL of water was added to the solution, the produced iodine was titrated with 0.1 N sodium thiosulfate solution.

Registry No. II, 2226-96-2; III, 95407-69-5; IVa, 90246-27-8; IVb, 95407-70-8; $CH_3(CH_2)_5OH$, 111-27-3; $CH_3(CH_2)_3CH(OH)CH_3$, 626-93-7; $CH_3(CH_2)_2CH(OH)CH_2CH_3$, 623-37-0; $CH_3CH{=}CHCH_2OH$, 6117-91-5; $PhCH{=}CHCH_2OH$, 104-54-1; $PhCH_2OH$, 100-51-6; PhCH(OH)Ph, 91-01-0; PhCH(OH)C(O)Ph, 119-53-9; $CH_3(CH_2)_4CHO$, 66-25-1; $CH_3(CH_2)_3C(O)CH_3$, 591-78-6; $CH_3(CH_2)_2C(O)CH_2CH_3$, 589-38-8; $CH_3CH{=}CHCHO$, 4170-30-3; $PhCH{=}CHCHO$, 104-55-2; PhCHO, 100-52-7; PhC(O)Ph, 119-61-9; PhC(O)C(O)Ph, 134-81-6; methanol, 67-56-1; ethanol, 64-17-5; 1-propanol, 71-23-8; 3-pentanol, 584-02-1; 2-propanol, 67-63-0.

Reaction of 2-Bromo-1,4-dimethoxybenzene with Various Nucleophiles via Aryne Reaction

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We have shown recently[1] that the reaction of 4-bromoveratrole (4-bromo-1,2-dimethoxybenzene, 1) with various primary and secondary aliphatic amines under aryne-

(1) Han, Y. X.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397.

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Table I. Reaction of 2-Bromo-1,4-dimethoxybenzene with Various Nitriles and Potassium Amide in Liquid Ammonia

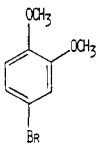
nitrile	yield,[a] %	bp, °C/torr
acetonitrile	83	95/0.3
propionitrile	81	118/0.45
butyronitrile	76	122/0.3
valeronitrile	64	138/0.3
phenylacetonitrile	56	172/0.15
1,7-dicyanoheptane	52	202/0.1

[a] Spectral data were consistent with proposed structure of product; satisfactory elemental analysis (C, H, N) was obtained.

Table II. Reaction of 2-Bromo-1,4-dimethoxybenzene with Various Primary and Secondary Amines and Potassium Amide

amine	yield, %	bp, °C/torr
n-propyl	94	116/0.3
iso-butyl	92	116/0.35
diethyl	87	93/0.25
dipropyl	85	121/0.3
dibutyl	86	124/0.3

forming conditions yields the corresponding 4-aminated veratrole product in good to excellent yields. However, treatment of 1 with certain aliphatic nitriles and potassium



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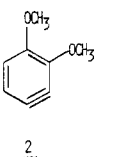
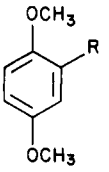


2

amide in liquid ammonia affords only 3,4-dimethoxyaniline. Apparently, the combined inductive effect of the two methoxy groups increases the reactivity of 3,4-dimethoxybenzyne (2) to such an extent that it undergoes nucleophilic addition with the less reactive but more abundant ammonia solvent molecule to the total exclusion of the more reactive but less abundant nitrile anion. The failure of nitriles to react with 1 under aryne-forming conditions is unfortunate since such a reaction would afford a series of nitriles which could be reduced to the

Table III. ^{1}H NMR Data for Some 2-Substituted 1,4-Dimethoxybenzenes



		chemical shifts[a,b]					coupling constants, Hz			
no.	R	R	H_3	H_5	H_6	other	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$	other
1	Br		7.20	6.80	6.85	$(OCH_3)_1$, 3.84 $(OCH_3)_4$, 3.75	2.0		c	
2	$NHCH_2CH_2CH_3$ α β	α-CH_2, 3.19 β-CH_2, 1.77 CH_3, 1.09	6.32	6.23	6.73	$(OCH_3)_1$, 3.87 $(OCH_3)_4$, 3.84 NH, 4.20	3.5		8.5	
3	$NHCH_2CH(CH_3)_2$	CH_2, 3.03 CH, 2.04 CH_3, 1.10	6.27	6.20	6.74	$(OCH_3)_1$, 3.89 $(OCH_3)_4$, 3.84	3.0		8.5	
4	$N(CH_2CH_3)_2$	CH_2, 3.32 CH_3, 1.13	6.69	6.58	6.86	$(OCH_3)_1$, 3.92 $(OCH_3)_4$, 3.86	3.0		9.0	
5	$N(CH_2CH_2CH_3)_2$ α β	α-CH_2, 3.18 β-CH_2, 1.62 CH_3, 0.96	6.65	6.55	6.96	$(OCH_3)_1$, 3.90 $(OCH_3)_4$, 3.85	3.0		9.0	
6	$N(CH_2CH_2CH_2CH_3)_2$ α β γ	α-CH_2, 3.27 β-CH_2, 1.53 γ-CH_2, 1.48 CH_3, 1.00	6.71	6.60	6.92	$(OCH_3)_1$, 3.92 $(OCH_3)_4$, 3.89	3.0		9.5	
7	CH_2CN	CH_2, 4.23	6.76	6.90	6.68	$(OCH_3)_1$, 3.84 $(OCH_3)_4$, 3.78	0.5		2.0	
8	$CH(CN)CH_3$	CH, 4.22 CH_3, 1.57	6.80	6.98	6.78	$(OCH_3)_1$, 3.81 $(OCH_3)_4$, 3.78	0.5		2.0	
9	$CH(CN)CH_2CH_3$	CH, 4.25 CH_2, 2.02 CH_3, 1.20	6.97	7.11	6.94	$(OCH_3)_1$, 3.93 $(OCH_3)_4$, 3.81	0.5		2.0	
10	$CH(CN)CH_2CH_2CH_3$ α β	CH, 4.18 α-CH_2, 1.82 β-CH_2, 1.45 CH_3, 0.91	6.86	7.01	6.85	$(OCH_3)_1$, 3.82 $(OCH_3)_4$, 3.79	0.5		2.0	
11	$CH(CN)C_6H_5$	CH, 5.67 C_6H_5, 7.50	6.98	7.03	6.96	$(OCH_3)_1$, 3.93 $(OCH_3)_4$, 3.87	0.5		1.5	
12	$[CH(CN)CH_2CH_2]_2CH_2$[d] α β γ	CH, 4.20 α-CH_2, 2.47 β-CH_2, 1.93 γ-CH_2, 1.82	6.98	7.01	6.96	$(OCH_3)_1$, 3.93 $(OCH_3)_4$, 3.90	0.5 0.5		2.0 2.0	
13	$CH(CH_3)COCH_3$ α β	CH, 3.73 α-CH_3, 1.32 β-CH_3, 2.01	6.94	6.66	6.30	$(OCH_3)_1$, 3.78 $(OCH_3)_4$, 3.70	4.0		9.0	CH, 8.5

[a] Downfield from Me_4Si in ppm. [b] All spectra were recorded in $CDCl_3$ unless indicated otherwise. [c] Overlapping signals. [d] Dimer.

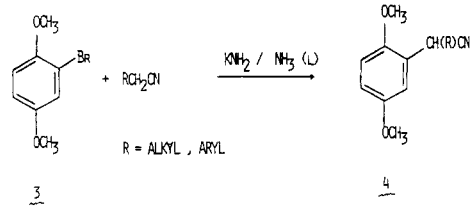
Table IV. Characteristic Infrared Bands for Some 2-Substituted 1,4-Dimethoxybenzenes (cm^{-1})[a]

no.	mol form	A	B_1	B_2	$B_{2'}$	C	D_1	E	F_1[d]	F_2[e]	D_2
2	$C_{11}H_{17}NO_2$	3445	3020	2980 2960	2895 2855		c	1625	1255 1230 1065 1040	1195 1185 1165	895[f] 835
3	$C_{12}H_{19}NO_2$	3445	3015	2980	2890 2845		c	1620	1260 1225 1065 1035	1195 1180 1165	895[f] 835
4	$C_{12}H_{19}NO_2$		g	2980 2955	2890 2855		c	1620 1600	1235 1215 1065 1040	1185 1130	860 800
5	$C_{14}H_{23}NO_2$		3015	2980 2955	2895 2855		c	1620 1600	1235 1220 1065 1040	1190 1135	860 800
6	$C_{16}H_{27}NO_2$		3015	2980 2955	2895 2855		c	1620 1600	1230 1215 1065 1040	1190 1135	860 800
7	$C_{10}H_{11}NO_2$		3020	2970 2940	2905[f] 2965	2270	c	1625 1605	1250 1230 1060 1040	1195 1175 1090	885 870 820
8	$C_{11}H_{13}NO_2$		3025 3015	2980 2960	2905[f] 2865	2270	c	1625 1605	1255 1230 1060 1035	1195 1175 1095	885 870 820
9	$C_{12}H_{15}NO_2$		3025	2995 2965	2905 2860	2265	c	1625 1605	1255 1230 1065 1040	1195 1175 1105	890 870 820
10	$C_{13}H_{17}NO_2$		3020	2990 2965	2900 2865	2270	c	1625 1605	1260 1240 1060 1040	1195 1175 1120	885 870 820
11	$C_{16}H_{15}NO_2$[h]		3040 3030	g	g	2260	i	1610	1250 1235 1050 1035	1195 1175 1120	875 840 825 740[j] 710[j]
12	$C_{17}H_{21}N_2O_2$		3030	2965	2895 2865	2270	c	1610	1260 1240 1060 1035	1195 1175 1135	885 870 820

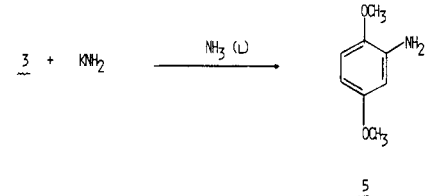
[a] A = nitrogen–hydrogen stretching vibrations. B_1 = aromatic C–H stretching absorptions. B_2 = aliphatic C–H stretching vibrations. C = CN stretching absorption. D_1 = bands of the aromatic overtone region. E = aromatic C=C vibrations. F = C–O–C and C–N stretching vibrations. D_2 = C–H out-of-plane bending bands. [b] O–C–H stretching vibrations of methoxy groups. [c] Weak absorptions at 1880, 1820, and 1770 cm^{-1}. [d] C–O stretching. [e] C–N stretching. [f] Weak. [g] Overlapping of bands. [h] Nujol mull—all others as neat liquids. [i] Multiple set of band overtones. [j] Monosubstituted phenyl group.

biologically important 1,2-dimethoxy-4-phenethylamines.

We report herein that 2-bromo-1,4-dimethoxybenzene (**3**) does react with nitriles (eq 1) in the presence of potassium amide in liquid ammonia to yield predominantly 2-(α-cyanoalkyl)-1,4-dimethoxybenzenes **4** in 56–83% (Table I). A small quantity of 2,5-dimethoxyaniline (**5**) was isolated in each of these reactions. In a separate reaction, **5** was formed in 62% yield from the reaction of **3** with potassium amide in liquid ammonia (eq 2). The products were identified on the basis of ^1H NMR (Table III), ^{13}C NMR,[2] and IR spectroscopy (Table IV). GC analysis of the nitrile reaction extract revealed only one peak indicating the absence of other isomeric products.



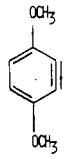
3 4 (1)



5 (2)

The greater selectivity of the aryne intermediate in this reaction, i.e., 3,6-dimethoxybenzyne (**6**), as compared to 3,4-dimethoxybenzyne (**2**) probably reflects the absence of polarization of the "triple bond" in aryne **6**; the inductive effect of the two methoxy groups are canceled in this symmetrically substituted aryne intermediate. Subsequent nucleophilic addition of nitrile anions to **3** yields, of course, only a single product.

(2) Jovanovic, M. V.; Biehl, E. R. *Org. Magn. Reson.*, submitted for publication.



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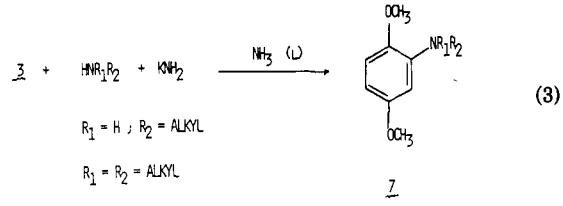
The nitrile products 4 should serve as valuable precursors to biogenic amines possessing both a phenethylamino side chain and 2,5-dimethoxy-substituted benzene ring. The physiological properties of compounds of this type have not been studied as extensively as those which contain a 3,4-dihydroxy-substituted aromatic ring, e.g., epinephrine and norepinephrine derivatives. However, 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane has been reported to be 80–100 times more active than mescaline on a dose–response basis[3] and 3-amino-1-(2,5-dimethoxy-4-methylphenyl)butane shows promise as antidepressant agent.[4]

The reaction of 3 with several primary and secondary amines was found also to give the corresponding 2,5-di-



(3)

7

methoxyanilines (7) in excellent yields (85–94%). These results are listed in Table II. The products were also identified on the basis of ^{1}H NMR (Table III), ^{13}C NMR,[2] and IR (Table IV) spectroscopy.

Experimental Section

GLC analyses were performed on a Gow Mac Series 550 instrument with a thermal conductivity detector using a 6 ft × $^1/_8$ in. 10% SP-2100 column.

Proton NMR spectra were measured in $CDCl_3$ solutions on a Perkin-Elmer R32 spectrometer at 90 MHz. Carbon NMR spectra were recorded in $CDCl_3$ in 10-mm tubes on a WP 200-SY Bruker spectrometer at 50.327 MHz. Chemical shifts are reported as parts per million (δ) relative to internal standard Me_4Si. Infrared (IR) spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer.

Starting Materials. The amines and nitriles were purchased from Aldrich Chemical Co. and were dried and distilled prior to use. 2-Bromo-1,4-dimethoxybenzene (3) was prepared by bromination of 1,4-dimethoxybenzene with pyridinium bromide perbromide in chloroform.

General Reaction of 3 with Nitriles. Potassium amide (0.2 mol) was prepared by adding potassium (0.2 mol) to 150 mL of liquid ammonia containing 0.01 g of ferric nitrate. The discharge of the initial blue color of the solution to gray indicated the conversion of potassium to potassium amide. The appropriate nitrile (0.5 mol) was added over a period of 5 min and the solution was stirred for 10 min at which time 3 (0.05 mol) was added dropwise and the resulting solution was stirred for 1 h. Then the ammonia was evaporated by heating on a steam bath, and the residue was dissolved in ether and extracted with two 200-mL portions of 6 N HCl. The ether was dried (Na_2SO_4) and the residue distilled to yield the nitrile product.

General Procedure for the Reaction of 3 with Primary and Secondary Amines. A solution of potassium amide (0.1 mol) in 150 mL of liquid ammonia was prepared in the same manner as described above in the general reaction of 3 with nitriles. The appropriate amine (150 mL) was added, and the ammonia was evaporated by heating with a steam bath and under a gentle flow of nitrogen. Compound 3 was added then and the reaction stirred for 1 h. The amine product was obtained by passing the reaction mixture through a column packed with silica G, concentrating the appropriate fraction (rotary evaporator), and then distilling the residue under vacuum.

Acknowledgment is made to the Robert A. Welch Foundation, Houston, TX, for partial support of this research (Grant N-118).

Registry No. 2-Bromo-1,4-dimethoxybenzene, 25245-34-5; 1,4-dimethoxy-2-(*N*-propylamino)benzene, 95514-69-5; 1,4-dimethoxy-2-(*N*-isobutylamino)benzene, 95514-70-8; 1,4-dimethoxy-2-(*N*,*N*-diethylamino)benzene, 2628-49-1; 1,4-dimethoxy-2-(*N*,*N*-dipropylamino)benzene, 95514-71-9; 1,4-dimethoxy-2-(*N*,*N*-dibutylamino)benzene, 84311-83-1; 2-(cyanomethyl)-1,4-dimethoxybenzene, 18086-24-3; 2-(1-cyanoethyl)-1,4-dimethoxybenzene, 62115-72-4; 2-(1-cyanopropyl)-1,4-dimethoxybenzene, 95514-72-0; 2-(1-cyanobutyl)-1,4-dimethoxybenzene, 95514-73-1; 2-(cyano(phenyl)methyl)-1,4-dimethoxybenzene, 95514-74-2; 1,7-dicyano-1,7-bis(2,5-dimethoxyphenyl)heptane, 95514-75-3; 2,5-dimethoxyaniline, 102-56-7; propylamine, 107-10-8; isobutylamine, 78-81-9; diethylamine, 109-89-7; dipropylamine, 142-84-7; dibutylamine, 111-92-2; acetonitrile, 75-05-8; propionitrile, 107-12-0; butyronitrile, 109-74-0; valeronitrile, 110-59-8; phenylacetonitrile, 140-29-4; 1,7-dicyanoheptane, 1675-69-0.

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