

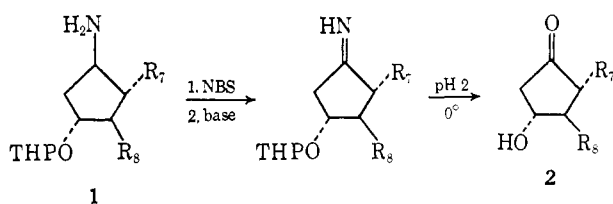
# A New Method for the Oxidation of Primary Amines to Ketones

E. J. Corey and Kazuo Achiwa

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. Received October 14, 1968

**Abstract:** A series of new selective reagents has been developed for the conversion of primary amines to ketones under mild conditions. These reagents combine with the amine,  $R_2CHNH_2$ , to form a Schiff base,  $R_2CHN=C<$ , which is rapidly transformed by prototropic rearrangement to an isomeric Schiff base. The latter base affords the desired ketone by hydrolysis in weakly acidic solution. 3,5-Di-*t*-butyl-1,2-benzoquinone (**5**), mesitylglyoxal (**8a**), and the nitro mesitylglyoxal derivatives **8b** and **8c** are shown to be highly effective reagents. With the advent of these reagents the biologically important "transamination" reaction becomes an efficient and generally useful synthetic tool.

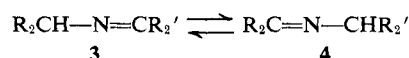
A key step in the two syntheses of prostaglandin  $E_1$  which have recently been reported from this laboratory<sup>1</sup> was the generation of the sensitive  $\beta$ -ketol system (**2**) from an  $\alpha,\gamma$ -amino alcohol derivative (**1**) by way of N-bromamine and -imine intermediates using the Ruschig method.<sup>2</sup> Concomitantly with this work a study was made to develop efficient new pro-



cedures for the conversion of primary amines to carbonyl compounds under extremely mild conditions, since it was not certain that the Ruschig process would be sufficiently gentle to permit the desired transformation.

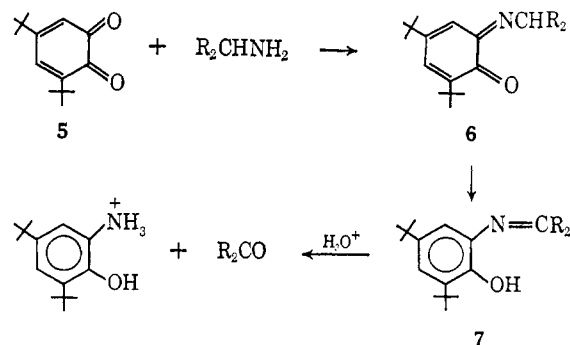
In contrast to the generation of carbonyl compounds by oxidation of primary and secondary alcohols, which is used with great frequency in synthesis and for which many selective reagents are known, the efficient oxidation of primary amines to carbonyl compounds has only been realized by the forementioned<sup>2</sup> process. Many of the standard selective oxidizing agents are totally unsatisfactory.<sup>3</sup> Most promising to date are various argentic ( $Ag^{II}$ ) salts which have recently been found to effect the conversion of amines to ketones under fairly mild conditions.<sup>4</sup> However, the yields obtained thus far have been only 30–60% in the most favorable cases. The biologically important conversion of primary amines to carbonyl compounds by

transamination involving prototropic interconversion of Schiff bases (**3**  $\rightarrow$  **4**) has not been applied as a



synthetic tool, since none of the reagents which have been studied to date are satisfactory. Ninhydrin, though suitable for oxidative decarboxylation of  $\alpha$ -amino acids, reacts with amines to give complex mixtures which afford only low yields of carbonyl compounds.<sup>5</sup> Various substituted benzaldehydes and isatins effect the oxidation of benzylamine to benzaldehyde (a very favorable case) in yields of only 50–80% and fail completely with amines such as cyclohexylamine, even under drastic conditions.<sup>6</sup> This paper reports the successful development of two types of reagents for selective oxidation of primary amines *via* the transamination pathway.

We shall discuss first the use of the readily available 3,5-di-*t*-butyl-1,2-benzoquinone (**5**)<sup>7</sup> as an extremely effective reagent for the conversion of primary amines to ketones under very mild conditions. Normally, primary amines react with quinones by conjugate addition to give *inter alia* amino hydroquinones. It is apparent that the substitution pattern in **5** is such as to obstruct nucleophilic approach by an amino group to all but C(1) of the aromatic ring, thereby favoring formation of the Schiff base **6**. Deprotonation of **6** to form the required intermediate for prototropic rearrangement to the desired isomeric Schiff base (**7**) should also be greatly facilitated in this system be-



(1) (a) E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3542 (1968); (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968).

(2) (a) H. Ruschig, W. Fritsch, J. Schmidt-Thomé, and W. Haede, *Ber.*, **88**, 883 (1955); (b) W. E. Bachmann, M. P. Cava, and A. S. Dreiding, *J. Am. Chem. Soc.*, **76**, 5554 (1954); (c) L. Lábler and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 2975 (1959).

(3) See P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, pp 47–51.

(4) (a) R. G. R. Bacon and D. Stewart, *J. Chem. Soc., C*, 1384 (1966); (b) R. G. R. Bacon, W. J. W. Hanna, and D. Stewart, *ibid.*, 1388 (1966); (c) R. G. R. Bacon and W. J. W. Hanna, *J. Chem. Soc.*, 4962 (1965).

(5) R. Moubasher and A. M. Othman, *J. Am. Chem. Soc.*, **72**, 2666 (1950).

(6) (a) F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, 209 (1954); (b) W. Traube, *Ber.*, **44**, 3145, (1911).

(7) W. Flaig, T. Ploetz, and H. Biergans, *Ann.*, **597**, 196 (1955).

**Table I.** Oxidation of  $R_2CHNH_2$  to  $R_2CO$  by 2,5-Di-*i*-butyl-1,2-benzoquinone (**5**)

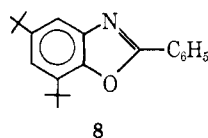
Substrate	Conditions for conversion to <b>7</b> <sup>a</sup>	Conditions for hydrolysis of <b>7</b> , <sup>b</sup> pH (time, hr)	Yield of ketone, %
Benzhydrylamine	I	2 (3)	90 <sup>c</sup>
$\alpha$ -Phenylethylamine	I	4 (1.5)	84 <sup>c</sup>
2- <i>exo</i> -Bornylamine	II	1 (25)	69 <sup>c</sup>
Cyclopentylamine	III	4 (1)	93 <sup>d</sup>
Cyclohexylamine	I	4 (1)	97 <sup>d</sup>
Cyclododecylamine	I	4 (1)	97 <sup>c</sup>

<sup>a</sup> Using 0.2 *M* amine and 0.2 *M* **5** for 20 min; I, at 23° in MeOH; II, at 23° in MeOH-THF, 6:1; III, at 0° in MeOH. <sup>b</sup> Using MeOH-THF-H<sub>2</sub>O, 3:3:1, at 23°. <sup>c</sup> Yield of isolated product. <sup>d</sup> Yield determined by gas chromatography analysis.

cause of the stability of the intermediate anion.<sup>8</sup> There is also ample difference between the free energies of **6** and **7** to force the conversion thermodynamically. For these and other reasons the quinone **5** appeared to be ideally suited for study.

A variety of primary amines have been successfully oxidized to ketones using the quinone reagent as is indicated in Table I. Most noteworthy are the extreme mildness of reaction conditions and the high yields which have been obtained. In general, equimolar amounts of the amine and **5** (ca. 0.2 *M*) were allowed to react in methanol at 23° for 20–30 min to form the desired Schiff base **7**, after which the reaction mixture was acidified to pH 2–4 and kept at 23° for a few hours to effect hydrolysis. In order to obtain optimum results, all reactants must be kept in solution. This necessitated the addition of a cosolvent, tetrahydrofuran, in certain cases.

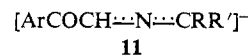
The quinone **5** does not appear to be a suitable reagent for the oxidation of amines of type  $RCH_2NH_2$  to aldehydes, since benzoxazolines and benzoxazoles are formed by further transformations of the desired Schiff bases. Thus, benzylamine after treatment with one equivalent of **5** in methanol at 23° for 30 min and hydrolysis at pH 4 in aqueous methanol at 23° for 30 min affords the benzoxazole **8** in 73% yield and benzaldehyde in only 9% yield.



The second type of reagent which has been developed for the conversion of primary amines to carbonyl compounds involving transamination *via* imines is characterized by the presence of the  $\alpha$ -keto aldehyde system in a structure which allows nucleophilic attack only at the formyl group. Mesitylglyoxal (**8a**) and its 3-nitro and 3,5-dinitro derivatives (**8b** and **8c**, respectively) are such structures. As in the case of the quinone **5**, internal steric shielding is utilized to control the site of electrophilic reactivity in the reagent. As expected, **8a–c** react under mild conditions with primary amines to form the corresponding Schiff bases **9a–c**.<sup>9</sup> Fur-

(8) Direct internal prototropic rearrangement of **6** to **7**, although conceivable, would appear to be stereoelectronically unfavorable.

ther, these Schiff bases undergo rapid prototropic rearrangement at 23° in the presence of bases such as tertiary amines or alkali metal alkoxides to give the isomeric Schiff bases **10a**, **10b**, and **10c**, although the isomerization **9**  $\rightarrow$  **10** is less facile than the analogous transformation of the *o*-quinone derived intermediates of structure **6**. The key experimental details for the transformation of **9a**, **9b**, and **9c** to **10a**, **10b**, and **10c**, respectively, are summarized in Tables II, III, and IV for a series of primary amines. It can be seen from the data in these tables that the efficiency with which primary amines are converted to carbonyl compounds is good in most cases and also that the conditions are relatively gentle. It is also clear that the electron-withdrawing mesityl group strongly facilitates the prototropic rearrangement of **9** to **10** as anticipated for a proton transfer route *via* an anion of structure **11**.



In addition, the ease of prototropic isomerization for the conversion **9a**  $\rightarrow$  **10a** has been found to vary with structure for a series of amines in a manner consistent with the rate-limiting formation of the anionic intermediate **11**. Decreasing ease of isomerization of the corresponding Schiff bases **9a** places these amines in the order: benzylamine, benzhydrylamine,  $\alpha$ -phenylethylamine, 2-*exo*-bornylamine, cyclopentylamine  $\cong$  *n*-dodecylamine, cyclohexylamine, and finally, cyclododecylamine.<sup>10</sup> The ease of prototropic isomerization **9**  $\rightarrow$  **10** also increases in going from the mesitylglyoxal series to the corresponding mono- and dinitro series.

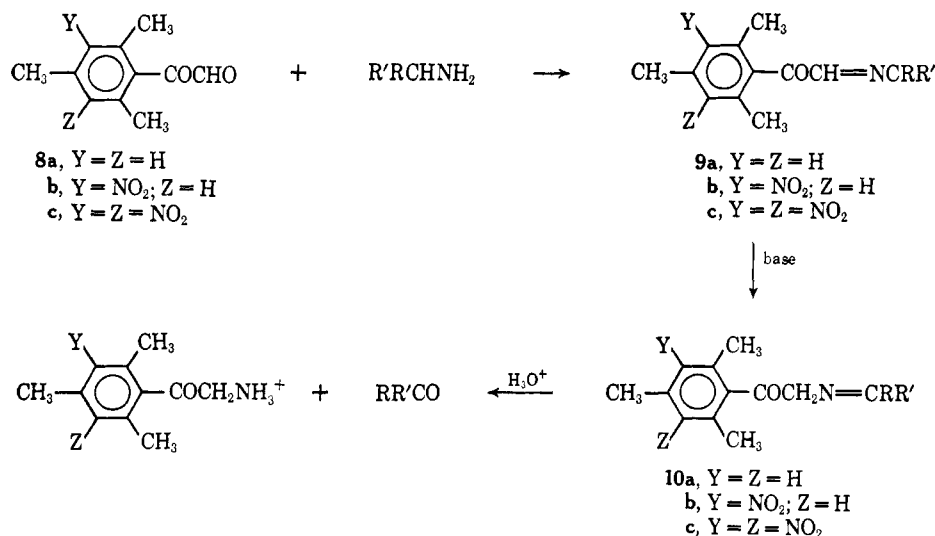
The yields cited in Tables II, III, and IV may not be optimum, especially in the cases in which aldehydes were produced. However, the reaction efficiencies are high enough to demonstrate utility of the reagents **8a–8c**. These may have a distinct advantage over the quinone **5** in cases where two bulky groups are attached to the  $CH-NH_2$  unit and where mildly basic conditions can be tolerated.

It is obviously possible to devise a number of other reagents which could serve the same purpose as the quinone and mesitylglyoxal derivatives discussed above. The principle to be used is simply that the reagent should possess a reactive carbonyl group to which is attached one or two powerfully  $\pi$ -electron-withdrawing groups, which must themselves be sterically protected against nucleophilic attack. Also, the anion produced by deprotonation of the Schiff base derived from the reagent and a primary amine clearly must be able to assume the optimum geometry for electron delocalization.

With the availability of the reagents **5**, **8a**, **8b**, and **8c** as synthetic tools for the conversion of primary amines to carbonyl compounds in addition to the Ruschig method<sup>2</sup> and the argentic salt method,<sup>4,11</sup> there is no reason why more use cannot be made in organic synthesis of the synthetic operation  $>CHNH_2 \rightarrow >C=O$ .

(9) The Schiff derivatives of 3,5-dinitromesitylglyoxal (**9c**) encountered in this study were uniformly crystalline solids (see Table IV) whereas the series of bases **9a** and **9b** were obtained as oils.

(10) The rates of isomerization were determined approximately by nmr measurements (directly on the reaction mixtures) of the intensity of the peak in **9** due to  $-CH=N-$  relative to an internal standard.



**Table II.** Oxidation of  $\text{RR}'\text{CHNH}_2$  to  $\text{RR}'\text{CO}$  by Mesitylglyoxal (**8a**)

Substrate	Conditions for conversion of <b>9a</b> to <b>10a</b> , <sup>a</sup> equiv of base (time, hr)	Conditions for hydrolysis of <b>10a</b> , pH (time, hr)	Yield of ketone, %
Benzhydramine	0.1 (0.33) <sup>b</sup>	3 (2 <sup>d</sup> )	83
$\alpha$ -Phenylethylamine	0.1 (0.33) <sup>b</sup>	3 (2 <sup>d</sup> )	84
2- <i>exo</i> -Bornylamine	1.0 (0.5 <sup>c</sup> )	1 (25 <sup>e</sup> )	70
Cyclopentylamine	0.1 (5 <sup>b</sup> )	3 (2 <sup>d</sup> )	90 <sup>f</sup>
Cyclohexylamine	1.0 (9 <sup>b</sup> )	3 (2 <sup>d</sup> )	87
Cyclododecylamine	1.0 (22 <sup>c</sup> )	3 (2 <sup>d</sup> )	86
Benzylamine	None (3 <sup>b</sup> )	4 (1 <sup>d</sup> )	55
<i>n</i> -Dodecylamine	0.1 (10.5 <sup>c</sup> )	4 (1 <sup>d</sup> )	38

<sup>a</sup> In each case the Schiff base **9a** was formed from equimolar amounts of mesitylglyoxal and the amine (*c* 0.1 *M*) in benzene at 23° for 30 min. <sup>b</sup> Using 1.0 *M* amine in dimethyl sulfoxide at 23° and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as base. <sup>c</sup> Using 1.0 *M* amine in 1:1 dimethyl sulfoxide-tetrahydrofuran at 23° and DBN as base. <sup>d</sup> Solvent, 8:1 MeOH-H<sub>2</sub>O. <sup>e</sup> Solvent, 4:4:1 MeOH-THF-H<sub>2</sub>O. <sup>f</sup> Yield determined by gas chromatography analysis; all other yields refer to isolated product.

**Table III.** Oxidation of  $\text{RR}'\text{CHNH}_2$  to  $\text{RR}'\text{CO}$  by 3-Nitromesitylglyoxal (**8b**)

Substrate	Conditions for conversion of <b>9b</b> to <b>10b</b> , <sup>a</sup> equiv of base (time, hr)	Conditions for hydrolysis of <b>10b</b> , <sup>d</sup> pH (time, hr)	Yield of ketone, %
Benzhydramine	0.5 Et <sub>3</sub> N (0.33 <sup>b</sup> )	2 (2)	91
$\alpha$ -Phenylethylamine	0.5 Et <sub>3</sub> N (0.33 <sup>b</sup> )	3 (2)	98
2- <i>exo</i> -Bornylamine	0.1 NaOMe (0.5 <sup>b</sup> )	1 (25)	73
Cyclopentylamine	0.1 NaOMe (0.5 <sup>b</sup> )	3 (1)	86 <sup>e</sup>
Cyclohexylamine	0.1 KO- <i>t</i> -Bu (0.7 <sup>b</sup> )	3 (1)	58
Cyclododecylamine	0.1 DBN (11.5 <sup>c</sup> )	3 (1)	75
Benzylamine	None (3.5 <sup>b</sup> )	3 (2)	63
<i>n</i> -Dodecylamine	0.1 NaOMe (0.5 <sup>b</sup> )	3 (1)	33

<sup>a</sup> In each case Schiff base **9b** was formed from equimolar amounts of 3-nitromesitylglyoxal and the amine (*c* 0.1 *M*) in benzene at 23° for 30 min. <sup>b</sup> At 23° with 1.0 *M* reactants in dimethyl sulfoxide. <sup>c</sup> At 23° with 1.0 *M* reactants in 1:1 dimethyl sulfoxide-tetrahydrofuran. <sup>d</sup> Solvent, 6:6:1 MeOH-THF-H<sub>2</sub>O. <sup>e</sup> Yield determined by gas chromatography analysis; all other yields refer to isolated product.

**Table IV.** Oxidation of  $\text{RR}'\text{CHNH}_2$  to  $\text{RR}'\text{CO}$  by 3,5-Dinitromesitylglyoxal (**8c**)

Substrate	<b>9c</b> , mp, <sup>a</sup> °C	Conditions for conversion of <b>9c</b> to <b>10c</b> , <sup>b</sup> equiv of base (time, hr)	Conditions for hydrolysis of <b>10c</b> , <sup>c</sup> pH (time, hr)	Yield of ketone, %
Benzhydramine	165–166	0.1 Et <sub>3</sub> N (0.33)	2 (2)	91
$\alpha$ -Phenylethylamine	114–115	0.1 Et <sub>3</sub> N (0.5)	3 (2)	80
2- <i>exo</i> -Bornylamine	102–103	1.0 Et <sub>3</sub> N (19)	1 (25)	92
Cyclopentylamine	137.5–138	0.1 NaOCH <sub>3</sub> (0.33)	3 (1)	75 <sup>d</sup>
Cyclohexylamine	150.5–151	0.1 KO- <i>t</i> -Bu (0.33)	3 (1)	62
Cyclododecylamine	136–137	0.1 KO- <i>t</i> -Bu (0.5)	3 (1)	80
Benzylamine	112–113.5	None (6.5)	3 (2)	78
<i>n</i> -Dodecylamine	69–70	0.1 NaOCH <sub>3</sub> (0.5)	3 (1)	34

<sup>a</sup> Each Schiff base **9c** was formed from equimolar amounts of 3,5-dinitromesitylglyoxal and the amine (*c* 0.1 *M*) in benzene at 23° for 30 min and recrystallized from methanol; elemental analyses for C, H, and N were in each case in good agreement with the calculated values. <sup>b</sup> At 23° with 1.0 *M* reactant in 1:1 dimethyl sulfoxide-tetrahydrofuran. <sup>c</sup> Solvent 4:4:1 MeOH-THF-H<sub>2</sub>O. <sup>d</sup> Yield determined by gas chromatography analysis; all other yields refer to isolated product.

The general synthetic equivalence of these functions

(11) The argentic salt oxidation<sup>4</sup> appears to be more efficient for the formation of aldehydes than of ketones, in contrast to the methods described herein.

connects two manifolds of synthetically equivalent functional groups, the nitrogen series (e.g.,  $>\text{CHNO}_2$ ,  $>\text{CHN}_3$ ) and the oxygen series (e.g.,  $>\text{CHOH}$ ,  $>\text{C=O}$ ), which have complementary electronic and

synthetic properties.<sup>12</sup> The work cited at the outset<sup>1</sup> provides an example of the value of this approach.

## Experimental Section

**Reagents.** 3,5-Di-*t*-butyl-1,2-benzoquinone (**5**), red needles, mp 114–115°, was prepared by oxidation of 3,5-di-*t*-butylcatechol according to ref 7. Mesitylglyoxal (**8a**), bp 91° (0.9 mm), mp 34–36°, was prepared by selenium dioxide oxidation of acetomesitylene in dioxane at reflux according to Gray and Fuson.<sup>13</sup> Oxidation of 3-nitroacetomesitylene<sup>14</sup> was carried out with a 20% excess of selenium dioxide in acetic acid–water, 94:6, at 95–100° to give 3-nitromesitylglyoxal (**8b**), mp 104–105°, purified by chromatography on silica gel (6% ethyl acetate–benzene as solvent) and distillation (bp 129–132° (0.65 mm)). (*Anal.* Calcd: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.73; H, 5.17; N, 6.23). Oxidation of 3,5-dinitroacetomesitylene<sup>15</sup> with the same mixture gave the glyoxal **8c**, purified by chromatography on silica gel and sublimation, mp 149–150°. (*Anal.* Calcd: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.34; H, 3.86; N, 10.62).

**Oxidation of Amines by 3,5-Di-*t*-butyl-1,2-benzoquinone (**5**).** The reaction of quinone **5** with amine was carried out under nitrogen according to the conditions summarized in Table I, then tetrahydrofuran–water or water was added and the pH of the resulting solution was adjusted by the addition of crystalline oxalic acid dihydrate, and the reaction mixture was stirred until hydrolysis was complete. Isolation of the carbonyl compound was accomplished by dilution with water and extraction with pentane–ether. An aliquot of the extracts was subjected to quantitative gc analysis after drying over sodium sulfate using a structurally related ketone differing in formula by CH<sub>2</sub> or C<sub>2</sub>H<sub>4</sub> as internal standard. Pure ketones were isolated by careful distillation or as the crystalline 2,4-dinitrophenylhydrazone derivatives in some cases. All products were compared rigorously (infrared and nmr spectra, melting point and mixture melting point, gas chromatography retention times) with authentic reference samples.

The procedures used for oxidation of amines using the mesitylglyoxals **8a–8c** were modified according to the details given in Tables II, III, and IV, and similar techniques were used for isolation, identification, and analysis.

(12) For a discussion of synthetically equivalent functional groups, see E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(13) A. R. Gray and R. C. Fuson, *J. Am. Chem. Soc.*, **56**, 739 (1934).

(14) R. Adams and A. Ferretti, *ibid.*, **83**, 2559 (1961).

(15) R. C. Fuson and J. T. Walker, *ibid.*, **52**, 3269 (1930).

The following procedures illustrate two specific preparative experiments in detail.

**Cyclododecanone. A. Oxidation of Cyclododecylamine by 3,5-Di-*t*-butyl-1,2-benzoquinone (**5**).** To a solution of 183.3 mg (1 mmol) of cyclododecylamine in 3 ml of methanol at 23° was added with stirring under nitrogen 220.3 mg (1 mmol) of 3,5-di-*t*-butyl-1,2-benzoquinone in 3 ml of methanol. Stirring was continued for 20 min, during which time the color of the reaction mixture changed from red to dark yellow after 5 min and then to violet after 20 min. Tetrahydrofuran (6 ml) and water (2 ml) were added to the reaction mixture, and the pH was adjusted to 4 by addition of crystalline oxalic acid dihydrate. After 1 hr at 23° the hydrolysis mixture was diluted with 80 ml of water, the product was extracted with pentane–ether (1:1) (four 20-ml portions), and the extract was washed with saturated sodium chloride solution and dried over sodium sulfate. Vpc analysis (using a 6 ft × 0.125 in. diameter column containing 10% SE-30 silicone on 80–100 mesh Diatoport S at 170°) was performed on an aliquot of the dried pentane–ether solution, to which had been added a weighed amount of cyclododecanone as an internal standard, and indicated 100 ± 2% yield of cyclododecanone. Product isolation was accomplished by careful concentration, followed by bulb-to-bulb distillation. Cyclododecanone, bp 120–130° (bath temperature) (0.5 mm), mp 57–59°, was obtained in 97% yield. The melting point was undepressed upon mixture with an authentic commercial sample (mp 59–60°), and the infrared and nmr spectra were identical.

**B. Oxidation of Cyclododecylamine by Mesitylglyoxal (**8a**).** To a solution of cyclododecylamine (183.3 mg) in benzene (5 ml) was added a solution of mesitylglyoxal (176 mg) in benzene (5 ml) at 23°, and stirring was continued for 30 min under nitrogen. After removal of the solvent, the resulting Schiff base (**9a**) was dissolved in a solution of 0.1 mmol of DBN in 1 ml of dimethyl sulfoxide–tetrahydrofuran (1:1). The reaction was allowed to proceed for 10.5 hr under nitrogen, and then the reaction mixture was submitted to hydrolysis at pH 3 for 2 hr with stirring at 23° after addition of 8 ml of methanol–tetrahydrofuran (1:1) and crystalline oxalic acid dihydrate. Product isolation was performed as in the above experiment. The cyclododecanone, mp 56–59°, so obtained (86% yield) exhibited infrared and nmr spectra which were identical with those of an authentic sample.

**Acknowledgment.** We are grateful to the National Institutes of Health, the National Science Foundation, and the Hoffmann-La Roche & Co. for financial assistance.