Local Anesthetics. 2-Diethylamino-2',6'-acylxylidides

Sigmund M. Waraszkiewicz, William O. Foye,*

Massachusetts College of Pharmacy, Boston, Massachusetts 02115

H. Jack Adams, and Bertil H. Takman

Astra Pharmaceutical Products, Inc., Worcester, Massachusetts 01606. *Received June 27, 1975*

A series of C-alkylated derivatives of lidocaine has been synthesized, and the local anesthetic potencies were determined. Activity reached a maximum with the butyroxylidide (α-ethyl group), but toxicity increased regularly with the number of carbons in the side chain. Spectral data showed the compounds to exist as associated H-bonded structures, the free base most likely as intramolecularly bonded trans amides and the hydrochlorides most likely as associated cis amides.

A variety of structural modifications of the effective local anesthetic lidocaine has been made, most of them involving either substitution on the aromatic ring or alteration of the diethylamino group. Relatively few modifications have been made of the intermediate chain; the effects of increasing the distance between the amino function and the anilide group of lidocaine have been observed,[1] and the chain length of trimecaine (the 4'-methyl derivative)[2] has been increased. 2-Diethylamino-2',6'-propionoxylidide has also been prepared by Löfgren and Lundquist.[3] Systematic introduction of simple alkyl groups on the α-carbon of the intermediate chain does not appear to have been carried out previously; the synthesis and local anesthetic activity of compounds of this type are reported here. It was also hoped that study of these compounds, which should provide more sterically hindered derivatives of lidocaine, might aid in explaining some of the unusual physical properties of lidocaine, such as its absorption spectra and pK_a. In addition, further information regarding the possible existence of cis and trans amide isomers of the aminoacylxylidides might be obtained and their relative effects on local anesthetic properties determined.

Chemistry. The 2-diethylaminoacylxylidides were prepared by treating 2-haloacylxylidides with diethylamine in anhydrous benzene. The 2-haloacylxylidides were obtained using the method of Löfgren,[4] in which 2,6-xylidine is treated rapidly with a 2-haloacyl halide in glacial acetic acid–sodium acetate. Both the free bases and their hydrochlorides were isolated.

The ir and ^1H NMR spectra were recorded for both the free bases and the hydrochlorides of lidocaine, the α-alkyl derivatives, β- and γ-amino analogs of lidocaine, and a quaternary analog of lidocaine. Previously, Neville and Cook[5] had concluded that lidocaine base existed as a dimeric cis amide structure (1), on the basis of an amide II frequency at 1490 cm^{-1} and an NH stretching band at 3312 cm^{-1} in CCl_4 that showed no shift on dilution. The amide II frequency is characteristic of trans amides at approximately 1550 cm^{-1} and of cis amides at approximately 1485 cm^{-1}.[6] Trans amides capable of intramolecular association have been found[7] to give amide II bands at approximately 1500 cm^{-1}, close to those for cis amides, thereby making conformational assignments with the amide II band very questionable. Sharp bands near 3400 cm^{-1} are observed for the NH stretch of unassociated trans amides.[6,8] Broad absorption bands near 3300 and 3200 cm^{-1} are observed for the NH stretch of associated trans and cis amides, respectively.[3,6] On the basis of these observations, Lumley-Jones[9] concluded that lidocaine base exists as a five-membered intramolecular hydrogen-bonded trans amide structure (2).

Rao et al.[8] observed the NMR absorption due to the NH protons in lactams, which exist exclusively as cis or trans amides depending on ring size, and have concluded that due to anisotropic deshielding, the NH absorption of the cis amide is shifted downfield approximately 1.3 ppm relative to that observed for the trans amide.

Ir absorption in $CHCl_3$ of lidocaine base was found at 3280 cm^{-1} (broad) for the NH stretch and at 1495 cm^{-1} for the amide II band (Table I). The amide II absorption can be interpreted as either unassociated cis or associated trans, but the NH stretching band indicates the intramolecular hydrogen-bonded trans amide. Protonation of the amino group, which would prevent trans intramolecular bonding, shifted the NH band to 3170 cm^{-1}, characteristic of an associated cis amide. The amide II band shifted to 1530 cm^{-1}, intermediate to the cis and trans forms. The NMR absorption of the amide proton in lidocaine base was observed at 8.5 ppm and that of lidocaine hydrochloride at 10.3 ppm, confirming that the lidocaine base exists as a trans intramolecular hydrogen-bonded amide and the hydrochloride as a cis amide. The α-methyl analog (4) and its hydrochloride (5) showed amide absorption similar to that observed for lidocaine and its hydrochloride.

A quaternary analog, 2-trimethylammonium-2',6'-acetoxylidide chloride[10] (6), where trans intramolecular association is impossible, showed ir absorption at 3160 cm^{-1} and NMR absorption at 10 ppm, indicating an associated cis amide.

A β-amino analog of lidocaine, 3-diethylamino-2',6'-butyroxylidide[11] (7), showed ir absorption at 3145 cm^{-1} and NMR absorption at 10.3 ppm, indicating that the compound, as the base, exists as an associated cis amide and not as a six-membered intramolecular hydrogen-bonded trans amide. The hydrochloride of this compound (8) again indicated an associated cis amide by the absorption at 3220 cm^{-1} and 9.5 ppm.

A γ-amino analog of lidocaine, 4-diethylamino-2',6'-butyroxylidide[12] (9), showed a sharp band in the ir at 3410 cm^{-1} for the NH stretch and a band at 1555 cm^{-1} for the amide II band. Both of these bands suggest an unassociated trans amide, a fact supported by the NMR absorption at 8.6 ppm. The trans amide in this case is not intramolecularly hydrogen bonded because this would require the improbable formation of a seven-membered ring. The hydrochloride of this compound (10) showed the presence of a minor amount of the trans amide but was predominantly an associated cis amide.

It may be concluded from these observations that the free bases of lidocaine and the α-alkyl derivatives are most likely the intramolecular hydrogen-bonded trans forms (2) as concluded by Lumley-Jones,[9] while the hydrochlorides are associated cis forms. The associated cis forms of the salts may be dimers (1) as suggested by Neville and Cook[5] or possibly an intramolecular species as shown by 3. The differences in amide conformation between the base and the salt in the α-, β-, and γ-amino compounds may have some interesting biologic implications, but further study

Table I. Spectral Data

No.	Compound	Ir[a] Amide II band, cm^{-1}	Ir[a] NH stretch band, cm^{-1}	NMR,[b] NH, ppm
	Lidocaine	1495	3280	8.5
	Lidocaine hydrochloride hydrate	1530	3170	10.3[a]
4	2-Diethylamino-2',6'-propionoxylidide	1490	3300	8.6
5	2-Diethylamino-2',6'-propionoxylidide hydrochloride	1530	3170	10.3[a]
6	2-Trimethylammonium-2',6'-acetoxylidide chloride	1535	3160	10 (br)
7	3-Diethylamino-2',6'-propionoxylidide	1525	3145	10.3
8	3-Diethylamino-2',6'-propionoxylidide hydrochloride	1525	3220	9.5
9	4-Diethylamino-2',6'-butyroxylidide	1555	3410 (sharp)	8.6
10	4-Diethylamino-2',6'-butyroxylidide hydrochloride	1520	3400 (minor), 3220 (major)	10.2

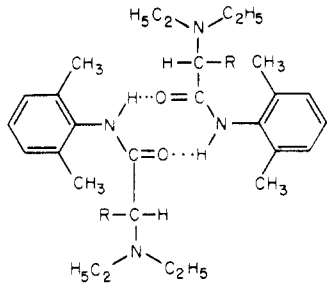
[a] Solvent, $CHCl_3$; concentration, 5%. [b] Solvent—CCl_4 for bases, D_2O for hydrochlorides; concentration, 5%.

Table II. Local Anesthetic Activity. Rat Sciatic Nerve Block Method

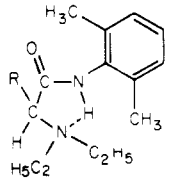
No.	Compound	Concn as base, %[a]	Frequency of block, %	Duration, min[b]	LD_{50}[c] ip in mice, mg/kg
	Lidocaine	0.25	100	102 ± 15	102 (73-142)
		0.50	100	123 ± 10	
		1.00	100	162 ± 39	
		2.00	100	185 ± 23	
4	2-Diethylamino-2',6'-propionoxylidide	0.125	100	82 ± 9	89 (76-110)
		0.25	100	92 ± 11	
		0.50	100	104 ± 10	
		1.00	100	114 ± 9	
		2.00	100	160 ± 18	
11	2-Diethylamino-2',6'-butyroxylidide	0.125	100	156 ± 32	54 (46-117)
		0.25	100	235 ± 12	
		0.50	100	297 ± 6	
		1.00	100	308 ± 5	
		2.00	100	318 ± 6	
12	2-Diethylamino-2',6'-valeroxylidide	0.125	100	117 ± 11	51 (41-58)
		0.25	100	123 ± 19	
		0.50	100	140 ± 12	
		1.00	100	179 ± 27	
		2.00	100	268 ± 36	
13	2-Diethylamino-2',6'-caproxylidide	0.125	80	92 ± 13	44 (38-49)
		0.25	60	111 ± 9	
		0.50	100	119 ± 24	
		1.00	100	196 ± 66	
		2.00	80	246	

[a] All solutions contained 1:100 000 epinephrine. [b] Mean ± standard deviation. [c] Mean and 95% confidence limits.

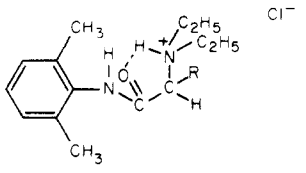
will be required before definite conclusions can be drawn.



1



2



3

Local Anesthetic Evaluation. Tests for local anesthetic activity were done by the rat sciatic nerve method[13] using lidocaine for comparison. This method determines duration of activity; testing data as well as toxicities (ip LD_{50} values) are shown in Table II. At the concentrations used in the test, all of the compounds gave 100% frequency of block except the caproxylidide derivative at some concentrations.

Table III. Ionization Constants, 23°

No.	Compound	pK_a[a]
	Lidocaine	7.86 ± 0.04
4	2-Diethylamino-2',6'-propionoxylidide	8.12 ± 0.04
11	2-Diethylamino-2',6'-butyroxylidide	7.91 ± 0.05
12	2-Diethylamino-2',6'-valeroxylidide	7.89 ± 0.07
13	2-Diethylamino-2',6'-caproxylidide	7.81

[a] Average ± scatter.

The testing results did not follow precisely the usual pattern reported for other local anesthetic series[1,2,14,15] where increasing the intermediate chain length has resulted in both increased activity and toxicity. As the number of carbons on the intermediate chain of our compounds increased, duration of activity declined, then increased to a maximum, and then declined. Activity reached a maximum with the α-ethyl substituent (11), and a minimum with the α-methyl derivative (4). Toxicity increased in a regular fashion with increasing number of carbons in the alkyl chain.

Ionization Constants. Ionization constants of the

compounds were determined (Table III) and were found to follow the usual pattern for an homologous series. The substitution of a methyl group on the intermediate chain caused a substantial increase in pK_a, but as the number of methylene groups in the side chain increased, the effect of the substituent became progressively less. With the propionyl and butyryl side chains, pK_a values differed very little from that of lidocaine.

The α-methyl derivative produced anesthesia of shorter duration than the other members of the series. The slightly higher pK_a value of this compound, 8.12, decreases the ratio between its base form and its ionic form at physiologic pH in comparison with the other compounds of the series which have pK_a values in the range of 7.81–7.91. If such an increase in pK_a were sufficiently large it could influence the penetrability of an agent adversely and prevent it from reaching its site of action in concentrations necessary to obtain durations of action comparable to those of agents of lower pK_a. In the present case, however, the differences in pK_a are not pronounced enough to explain the differences in duration times, particularly since the partition coefficients (lipid–water) in a homologous series like the present increase with increasing molecular weight, an increase that would facilitate penetration at least among the lower members of the series.

An explanation of the observed duration minimum may be found in the dual mechanisms of action proposed for agents of the amine type, e.g., lidocaine.[16] The ionic form of such agents has been suggested to act at a receptor-like structure at the axoplasmic side of the nerve membrane. The base form of the same agents acts independently at other parts of the membrane through a less specific mechanism, essentially as such uncharged molecules as alcohols and benzocaine.

If the lowest member of the present series acts predominantly at the receptor, and if the introduction of a side chain in the α position interferes with the fit of the agent to the receptor, a decrease in blocking efficacy should be expected as the side chain is enlarged. But if this same increase in bulkiness makes the higher homologues more efficient at the other sites where the base form may act, an increase in blocking efficacy could be expected instead. In this series it is conceivable that in going from the unsubstituted lidocaine to its α-methyl derivative more is lost in receptor fit than is gained by increased blocking efficacy of the base form.

Experimental Section

Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were done by Alfred Bernhardt Microanalytical Laboratory, Mulheim, West Germany. Infrared spectra were recorded on a Perkin-Elmer Model 257B spectrophotometer. NMR spectra were recorded on a Joel Model C-60H instrument with tetramethylsilane as internal standard and carbon tetrachloride, chloroform, or water as solvent. Gas chromatographs were obtained with a Varian Model 1700 dual column gas chromatograph with flame ionization detectors. Infrared spectra were consistent with proposed structures, and gas chromatographs showed the products to be pure.

2-Bromo-2',6'-propionoxylidide. This procedure is representative of the preparation of the 2-bromo-2',6'-acylxylidides. To a solution of 16.1 g (0.133 mol) of 2,6-xylidine in 110 ml of glacial acetic acid cooled to 10° was added quickly 25.0 g (0.146 mol) of 2-bromopropionyl chloride. A solution (210 ml) of sodium acetate trihydrate (330 g in 1380 ml of water) cooled to 10° was added quickly, resulting in precipitation of product. The suspension was shaken for 0.5 h, and the product was filtered, washed with distilled water, and dried, giving 27.2 g (80%): mp 153–157°. It was recrystallized twice from 95% ethanol: mp 163–167° (lit.[11] mp 162–164°).

2-Bromo-2',6'-butyroxylidide. This compound was obtained in 78% yield: mp 199–201°. Anal. ($C_{12}H_{16}BrNO$) C, H, Br.

2-Bromo-2',6'-valeroxylidide. This was obtained in 90% yield: mp 188–190°. Anal. ($C_{13}H_{18}BrNO$) C, H, Br.

2-Bromo-2',6'-caproxylidide. This was obtained in 85% yield: mp 169–172°. Anal. ($C_{14}H_{20}BrNO$) C, H, Br.

2-Diethylamino-2',6'-propionoxylidide Hydrochloride (5). A mixture of 5.0 g (0.0195 mol) of 2-bromo-2',6'-propionoxylidide, 4.28 g (0.0585 mol) of redistilled diethylamine, and 50 ml of anhydrous benzene was refluxed for 15 h. After the mixture was cooled, diethylamine hydrobromide was removed by filtration, and the benzene solution was extracted with three 25-ml portions of 1 N hydrochloric acid. The combined acid extracts were extracted with 25 ml of ether to remove unreacted starting material. The acid extracts were brought to a pH of 10 with 7 N sodium hydroxide solution, and the resulting suspension was extracted with four 25-ml portions of ether. The ether extracts were dried over anhydrous sodium sulfate and filtered, and the ether was evaporated under vacuum to give a yellow oil. This was dissolved in anhydrous ether and converted to the hydrochloride by the addition of hydrogen chloride in anhydrous ether. The solid was filtered and washed with ether, giving 3.67 g: mp 221–225° dec. It was recrystallized twice from absolute ethanol: mp 229.5–231° dec. A sample of the hydrochloride was converted to the free base: mp 60–63° (lit.[3] mp 54–55°).

2-Diethylamino-2',6'-butyroxylidide Hydrochloride (11). A mixture of 4.0 g (0.0148 mol) of 2-bromo-2',6'-butyroxylidide, 3.25 g (0.044 mol) of redistilled diethylamine, and 25 ml of anhydrous benzene was sealed in an autoclave and placed in an oven at 100° for 15 h. The reaction mixture was treated as described in the previous procedure, and a yield of 1.31 g (34%) was obtained of a waxy solid. This was converted to the hydrochloride and recrystallized three times from absolute ethanol–ether: mp 224–226° dec.[17] Anal. ($C_{16}H_{27}ClN_2O$) C, H, N.

2-Diethylamino-2',6'-valeroxylidide Hydrochloride (12). A mixture of 5.0 g (0.0176 mol) of 2-bromo-2',6'-valeroxylidide, 3.86 g (0.0528 mol) of redistilled diethylamine, and 25 ml of anhydrous benzene was sealed in an autoclave and placed in an oven at 100° for 18 h. The reaction mixture was treated in similar fashion to the foregoing, and 0.87 g (18%) of light tan solid was isolated. This was converted to the hydrochloride and recrystallized twice from absolute ethanol–ether: mp 204–205.5°.[17] Anal. ($C_{17}H_{29}ClN_2O$) C, H, N.

2-Diethylamino-2',6'-caproxylidide Hydrochloride (13). A mixture of 5.0 g (0.0168 mol) of 2-bromo-2',6'-caproxylidide, 3.68 g (0.0504 mol) of redistilled diethylamine, and 25 ml of anhydrous benzene was sealed in an autoclave and placed in an oven at 100° for 22 h. The reaction mixture was treated in similar fashion to the foregoing, and 2.10 g (43%) of light tan solid was obtained. This was converted to the hydrochloride and recrystallized twice from absolute ethanol–ether: mp 189–190.5°. Anal. ($C_{18}H_{31}ClN_2O$) C, H, N.

Ionization Constants. The purified hydrochlorides were dissolved in CO_2-free distilled water at 23° to give a concentration of 0.001 M. The pH of the solutions was determined with a Radiometer Model PHM 26C and titrated automatically using a Radiometer Model TTT 11 titration apparatus (Copenhagen, Denmark). The volume of NaOH (0.02 N) added and the pH of the solutions were determined by extrapolating to the axes on the titration curve. In the case of 2-diethylamino-2',6'-caproxylidide, precipitation occurred during the titration even after dilution to 200 ml. The degree of scatter was calculated by taking the antilogarithm of each pK_a value, averaging them, and recording the logarithm of the average as a pK_a. The largest deviation between this value and the determined values is the scatter.

Local Anesthetic Evaluation. Primary local anesthetic testing was done according to Camougis and Takman.[13] Each compound was tested at five concentrations, with 1:100000 epinephrine added to the test solutions. Precisely 0.2 ml of drug solution (pH 4.5–6.5) was injected into the midthigh region of a rat so that it deposited around the sciatic nerve trunk. Five animals were used at each concentration, and both thighs were injected on each animal. Animals were then examined at frequent intervals for frequency and duration of motor block.

Acute Toxicity. Acute toxicity was determined according to Adams et al.[18] using female CRCD mice, weighing about 20–25 g. Test compounds were dissolved in isotonic saline or distilled

water and administered ip. Three to five dose levels were used for each LD_{50} value, and there were ten animals at each dose level. Control animals received vehicle at a dose volume comparable to the highest dose volume of test compound. The LD_{50} values and 95% confidence limits were calculated by the minimum logit χ^2 method.[19]

Acknowledgment. The authors wish to thank Mrs. M. P. Hogan for analyzing the testing data and Drs. E. Meymaris, W. McKenzie, and E. Byrnes for helpful discussions.

References and Notes

(1) P. Koelzer and K. Wehr, *Arzneim.-Forsch.*, **8**, 544 (1958).
(2) R. Dofek, A. Sekera, and C. Vrba, *J. Pharm. Sci.*, **50**, 161 (1961).
(3) N. Löfgren and B. Lundquist, U.S. Patent 2,441,498 (1948).
(4) N. Löfgren, *Ark. Kemi, Mineral. Geol.*, **22A**, No. 18 (1946).
(5) G. A. Neville and D. Cook, *J. Pharm. Sci.*, **58**, 636 (1969).
(6) I. Suzuki, M. Tsuboi, T. Shimanouchi, and S. Mizushima, *Spectrochim. Acta*, **16**, 471 (1960).
(7) R. A. Nyquist, *Spectrochim. Acta*, **19**, 509 (1963); R. D. McLachlan and R. A. Nyquist, *ibid.*, **20**, 1397 (1964).
(8) C. N. R. Rao, K. G. Rao, A. Goel, and D. Balasubramanian, *J. Chem. Soc. A*, 3077 (1971).
(9) R. Lumley-Jones, *J. Pharm. Sci.*, **63**, 1170 (1974).
(10) R. Dahlbom, A. Misiorny, and A. P. Truant, *Acta Pharm. Suecica*, **2**, 213 (1965).
(11) N. Löfgren and B. Lundquist, *Sven. Kem. Tidskr.*, **58**, 206 (1946).
(12) A. B. Steinbach, *J. Gen. Physiol.*, **52**, 144 (1968).
(13) G. Camougis and B. H. Takman, *Methods Pharmacol.*, **1**, 1-40 (1971).
(14) H. F. Yipf, *Pharm. Acta Helv.*, **42**, 480 (1967).
(15) W. L. McKenzie and W. O. Foye, *J. Med. Chem.*, **15**, 291 (1972).
(16) B. H. Takman, *Br. J. Anaesth.*, **47**, 183 (1975).
(17) H. J. F. Adams, G. H. Kronberg, and B. H. Takman, U.S. Patent 3,812,147 (1974).
(18) H. J. Adams, G. H. Kronberg, and B. H. Takman, *J. Pharm. Sci.*, **62**, 1677 (1973).
(19) A. Berkson, *J. Am. Stat. Assoc.*, **48**, 565 (1953).

Notes

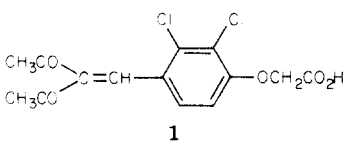
(Vinylaryloxy)acetic Acids. A New Class of Diuretic Agents. 2.[1] [4-(3-Oxo-1-alkenyl)phenoxy]acetic Acids

John B. Bicking,* Charles M. Robb, L. Sherman Watson, and Edward J. Cragoe, Jr.

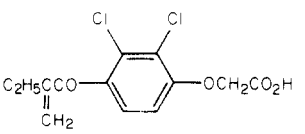
Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received August 27, 1975*

A series of (*E*)-[4-(3-oxo-1-alkenyl)phenoxy]acetic acids was synthesized and tested in dogs for saluretic and diuretic properties. Several compounds exhibited noteworthy activity, e.g., (*E*)-[2,3-dichloro-4-(3-oxo-1-butenyl)phenoxy]acetic acid (**3a**). While possessing only half of the dose potency of ethacrynic acid (**2**), the active compounds act similarly to this diuretic in causing a prompt increase in the excretion of water and in the excretion of sodium and chloride ions in approximately equimolar amounts. Potassium ion excretion is increased but less markedly than sodium excretion.

The initial paper in this series described the saluretic and diuretic properties of [(diacylvinyl)aryloxy]acetic acids[1] including the highly active diacetylvinyl compound 1. The presence of the double bond activated toward nucleophilic attack is critical to the high potency of these compounds. In this regard and in general structure, they are related to the prototypical ethacrynic acid[2] (**2**) which they also resemble in profile of action on electrolyte and water excretion.

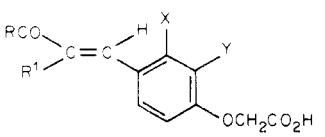


1



2

This report discloses synthesis and renotropic properties of a series of [4-(3-oxo-1-alkenyl)phenoxy]acetic acids of general structure 3 which, like ethacrynic acid, incorporate a double bond activated by a single conjugated carbonyl group (Table I).



3

Chemistry. Three synthetic routes to the compounds 3 have been followed; all involve aldol condensations between substituted benzaldehydes and aliphatic or alicyclic ketones or aldehydes.

In the first route (Scheme I), a 4-hydroxybenzaldehyde (4) is condensed with a ketone to yield a 4-(3-oxo-1-alkenyl)phenol (**5**). Strongly basic Claisen–Schmidt conditions were employed in condensations with acetone, cyclobutanone, and cyclopentanone. The use of acid catalysis in reactions with 2-butanone typically[3] effected condensation at the methylene group of this ketone, as is clearly shown by the NMR spectra of **5e** and **5f**. Phenols **5** were alkylated with ethyl bromoacetate and the resulting crude esters hydrolyzed in acid to yield products **3a–f**.

In a second route (Scheme II), hydroxybenzaldehydes (4) are alkylated with ethyl bromoacetate and the resulting esters hydrolyzed to yield the formylphenoxyacetic acids **6**, which then are condensed in dilute NaOH solutions with the appropriate ketones or propionaldehyde to give the products **3g–j**. Under these conditions, condensation with 2-butanone occurs at the 1-methyl group (yielding **3i**).

Cyclohexanone failed to give isolable 1:1 condensation products with hydroxybenzaldehydes or formylphenoxyacetic acids according to Schemes I or II. However, the morpholine enamine of cyclohexanone did react satisfactorily with ethyl (2,3-dichloro-4-formylphenoxy)acetate (**7**) according to the procedure of Birkofer, Kim, and