of ($k_H + k_F$) coefficients were calculated from eq 2 or 3 by plotting ln [$A_t - (A_\infty)_1$] or ln [$(A_\infty)_2 - A_t$] vs. time. Standard deviations from the observed straight lines were usually less than 0.5% of the logarithm range. In most cases a slow increase of absorbance was observed before and after the water-concentration jump as the result of a moisture contamination. Appropriate linear corrections were introduced to determine the $(A_\infty)_1$ and $(A_\infty)_2$ values at the water-concentration jump time used in rate-coefficient calculations.

Registry No. 4-$OCH_3C_6H_4COCH_3$, 100-06-1; 4-$CH_3C_6H_4COCH_3$, 122-00-9; $C_6H_5COCH_3$, 98-86-2; 4-$FC_6H_4COCH_3$, 403-42-9; 4-$ClC_6H_4COCH_3$, 99-91-2; 3-$ClC_6H_4COCH_3$, 99-02-5; 3-$CF_3C_6H_4COCH_3$, 349-76-8; 3-$NO_2C_6H_4COCH_3$, 121-89-1; 4-$OCH_3C_6H_4C(OH)_2CH_3$, 27150-99-8; 4-$CH_3C_6H_4C(OH)_2CH_3$, 53578-01-1; $C_6H_5C(OH)_2CH_3$, 4316-35-2; 4-$FC_6H_4C(OH)_2CH_3$, 73585-52-1; 4-$ClC_6H_4C(OH)_2CH_3$, 72360-69-1; 3-$ClC_6H_4C(OH)_2CH_3$, 73585-53-2; 3-$CF_3C_6H_4C(OH)_2CH_3$, 73589-85-2; 3-$NO_2C_6H_4C(OH)_2CH_3$, 73585-54-3.

Direct Synthesis of Benzo[*c*]phenanthridines and Benzo[*c*]phenanthridones via $S_{RN}1$ Reactions[1]

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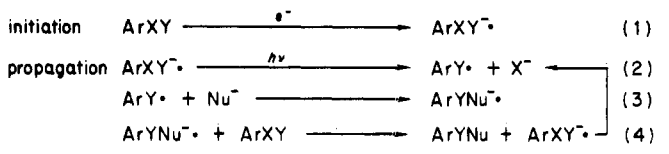
A straightforward and high-yield route to the 11,12-dihydrobenzo[*c*]phenanthridine (**3**) and 11,12-dihydrobenzo[*c*]phenanthridone (**14**) ring systems is based upon an $S_{RN}1$ reaction between 2-halobenzylamines **1** or 2-halobenzoic acids **11** and enolates derived from tetralones **2**. The efficient dehydrogenation of **3** or **14** gives the benzo[*c*]phenanthridines **4** or benzo[*c*]phenanthridones **15**. Use of properly substituted reactants leads to nitidine, avicine, and fagaronine and to analogues of those natural products.

Benzo[*c*]phenanthridines and benzo[*c*]phenanthridones are an important class of the isoquinoline alkaloid family. Synthetic studies started half a century ago,[3a] and since then, workers in this field were very active.[3b-d] In the recent period, targets of special interest were some alkaloids that had shown initial promise as antitumor agents.[4] This fact, together with scarcity from natural source and the need for analogues had led to the synthesis of nitidine,[5-8,24] avicine,[7,9] and fagaronine.[10,11] The multistep syntheses so far reported are of linear type and give overall yields ranging from good to very low. We report now a new and more direct route to these alkaloids and to various analogues.

The extended $S_{RN}1$ reaction (eq 1–4, Scheme I) developed in our laboratory[12] is the key step in the synthesis of isoquinolones[13,14] and isoquinolines[15a,b] from 2-halobenzamides or 2-halobenzylamines and nucleophiles derived from linear ketones (CH_3COR, R = CH_3, *i*-C_3H_7, *t*-C_4H_9). We have now applied this method to the synthesis of a series of benzo[*c*]phenanthridines by reaction of substituted iodobenzylamines with substituted tetralones (Scheme II).

Scheme I. The $S_{RN}1$ Extended Reaction



Scheme II. Synthesis of Benzo[*c*]phenanthridines

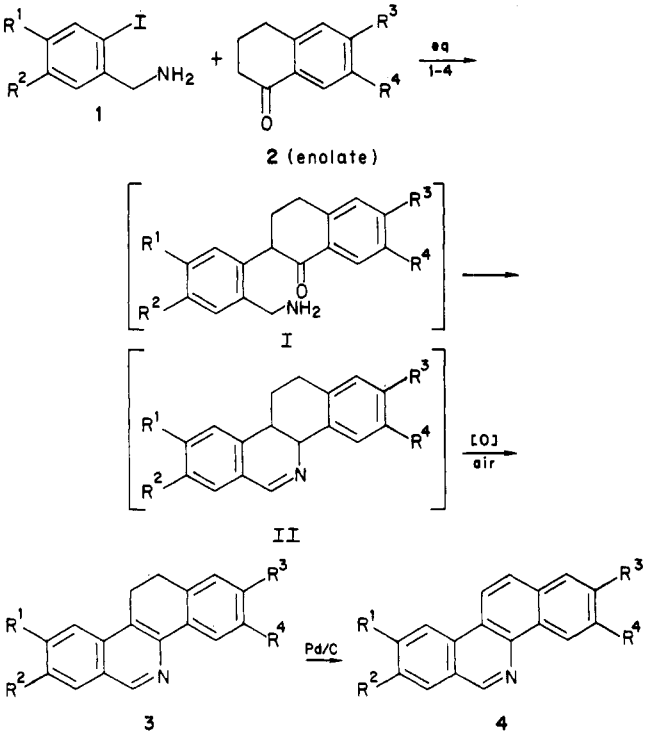


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Table I. Synthesis of Benzo[c]phenanthridines

	1			2			3			4		
entry		R^1	R^2		R^3	R^4		mp, °C	yield, %		mp, °C	yield, %
1	1a	H	H	2a	H	H	3a	120-122	38	4a	133-136[a]	90
2	1a	H	H	2b	OCH_3	H	3b	99-100	79	4b	200	98
3	1a	H	H	2c	OCH_2O		3c	119	65	4c	201-204	89
4	1a	H	H	2d	OCH_3	OCH_3	3d	138-140	35	4d	171-173	82
5	1a	H	H	2e	OC_3H_7-*i*	OCH_3	3e	89-91	39	4e	129-130	84
6	1b	OCH_3	OCH_3	2a	H	H	3f	164-166	45	4f	231-232	96
7	1b	OCH_3	OCH_3	2b	OCH_3	H	3q	198-200	56	4q	298	89
8	1c	OCH_2O		2a	H	H	3h	207-209	76	4h	240-242	94
9	1c	OCH_2O		2b	OCH_3	H	3i	186-187	52	4i	280	79
10	1b	OCH_3	OCH_3	2c	OCH_2O		3j	218-220	48	4j	281-282	96
11	1b	OCH_3	OCH_3	2e	OC_3H_7-*i*	OCH_3	3k	164-166	42	4k	268-270	96
12	1c	OCH_2O		2c	OCH_2O		3l	288	38	4l	320-323 dec[b]	63
13	1c	OCH_2O		2d	OCH_3	OCH_3	3m	231-232	72	4m	278-279	75
14	1b	OCH_3	OCH_3	2d	OCH_3	OCH_3	3n	220	68	4n	305-308	68
15	1c	OCH_2O		2e	OC_3H_7-*i*	OCH_3	3o	171-173	48	4o	278-280	67
16	1d	OC_3H_7-*i*	OCH_3	2f	OCH_3	OC_3H_7-*i*	3p	150-152	65	4p	200-204	89

[a] Lit.[33] mp 134 °C. [b] Lit.[34] mp 325-327 °C dec.

Access to benzo[c]phenanthridine and benzo[c]-phenanthridone alkaloids appeared to be possible if the tetralone enolates were good nucleophiles in reactions with 2-halobenzylamines or 2-halobenzamides and if the substituents on both the substrate (dimethoxy, methylenedioxy) and the nucleophile (methoxy, hydroxy, methylenedioxy) were stable under $S_{RN}1$ reaction conditions.

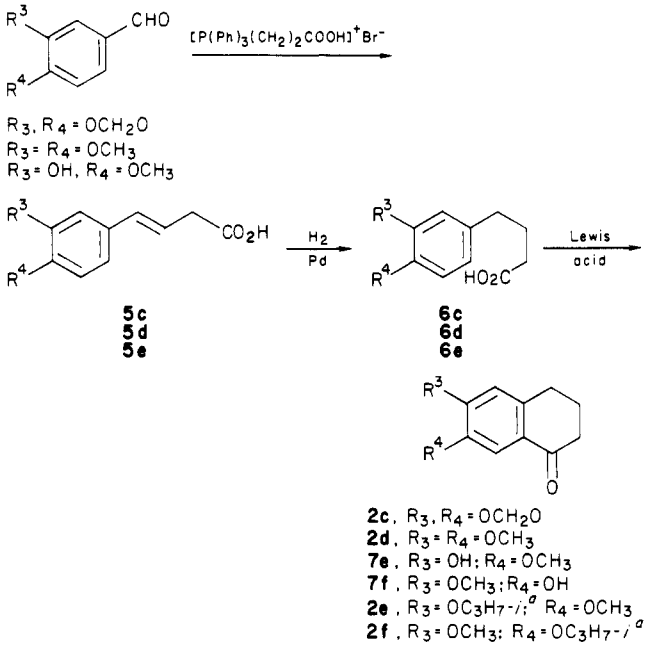
2-Iodo-4,5-dimethoxybenzylamine **1b** was prepared from veratrylamine by acetylation, and treatment with $Hg(OAc)_2/NaCl$[16] and then with iodine. The acetomercuration reaction was not effective for the preparation of **1c** because of lability of the methylenedioxy group, and the classical Sandmeyer reaction was not effective either. However, the silver trifluoroacetate/iodine method,[17] although slow and incomplete gave **1c** in adequate yield. The sequence of reactions used for the preparation of **1b** yielded **1d** when applied to 4-isopropoxy-5-methoxybenzylamine, prepared from vanillin by etherification with isopropyl bromide, oximation, and reduction with $LiAlH_4$.

The substituted tetralones **2c–f** were required to provide the desired substituents on the alkaloids. Reported syntheses based on the cyclization of substituted phenylbutanoic acids are known for **2c**, starting from the corresponding phenylbutenoic acid[5] (yield 16%) or from safrole[18] (yield 30%), and for **2d**, starting from veratrole[19] (yield 40%), while partial demethylation of **2d** is reported[20] to give **7e** (yield 4%). As it was crucial to secure these tetralones in substantial amounts, we devised the method outlined in Scheme III. The key step is a Wittig reaction between the bromopropionic acid phosphonium salt[21,22] and piperonylaldehyde, veratraldehyde, or isovanillin. Subsequent reactions gave the desired tetralones **2c** (60%), **2d** (55%), and **7e** (50%). This sequence applied to vanillin could give **7f**, but the monodemethylation of **2d** was found to be more direct.

$S_{RN}1$ Reactions between 1a and Tetralones. Although the $S_{RN}1$ reaction is now well documented[12,23a,b] we first explored the reaction of 2-iodobenzylamine (**1a**) with several tetralones to determine the nucleophilic behavior of the latter under our conditions. Treatment of **1a** with the enolate derived from **2a** under $S_{RN}1$ conditions (Table I, entry 1) consumed all the **1a** after 80 min and gave a moderate yield (38%) of the tetracyclic ring system **3a** together with an intractable mixture of byproducts. Neither the primary intermediate I nor the 1,2-dehydro derivative II was obtained, in accordance with our previous results on isoquinoline synthesis.[15a,b] A striking difference from those results is the clean and spontaneous aromatization of II by air oxidation during the workup to give **3a** directly, thus forming the heterocyclic ring in a one-pot reaction.

The reaction between **1a** and the enolate of 6-methoxy-1-tetralone (**2b**) (entry 2) was faster (60 min) and the yield (79%) was twice as high. The electron-releasing

Scheme III. Synthesis of Substituted Tetralones



[a] Prepared from the hydroxytetralone by reaction with *i*-C_3H_7Br.

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Table II. Synthesis of Benzo[c]phenanthridones

11		2			12		13			14			15		
	$R^1 = R^2 = R^5$		R^3	R^4		yield, %		mp, °C	yield, %		mp, °C	yield, %		mp, °C	yield, %
11a	H	**2b**	OCH_3	H	**12a**	75	**13a**	147	65	**14a**	188–190	95	**15a**		
11b	OCH_3	**2b**	OCH_3	H	**12b**	60	**13b**	188–190	72	**14b**	164–166	65	**15b**	193–196	83
11c	OCH_3	**2e**	OC_3H_7-*i*	OCH_3	**12c**	75	**13c**	166–168	70	**14c**	155–158	60	**15c**	182–185	96

group para to the carbonyl group of **2b** not only increased the nucleophilicity of the enolate but also made the second radical anion more easily oxidized by **1a** (eq 4).

Dehydrogenation, the last step necessary to get the fully aromatic benzo[c]phenanthridine, was unsuccessful when attempted by standard methods (heating in various solvents with DDQ or 10% Pd on charcoal). Finally, high yields of **4a** (90%) and **4b** (98%) were obtained by heating **3a** or **3b** without solvent at 250 °C for 4 h in the presence of 30% Pd charcoal.[5]

Similar reactions of **1a** with enolates of **2c** (Table I, entry 3) or **2d** (entry 4) led to the fully aromatic tetracyclic compounds **4c** or **4d** which possess rings A, B, and C of nitidine, avicine, or allonitidine. The phenolic function in **7e** made its enolate an unsuitable nucleophile for the $S_{RN}1$ reaction. Accordingly, **7e** was converted to the isopropyl ether **2e**, which was stable under the alkaline conditions of the $S_{RN}1$ reaction leading to **4e**. The isopropoxy group was selectively removed in the presence of the methoxy group[10a,11] to give ring A of fagaronine.

Reactions of Substituted Iodobenzylamines with Substituted Tetralones. The benzo[c]phenanthridine alkaloids are substituted on ring D by methylenedioxy or methoxy groups, thus the halobenzylamines needed for the $S_{RN}1$ reaction have to carry those substituents. Our second set of experiments was designed to explore the reactivity of the substituted 2-halobenzylamines **1b,c** with nucleophiles derived from substituted tetralones.

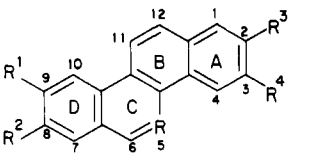
Treatment of **1b** with enolates of **2a** or **2b** gave the expected tetracyclic products **4f** or **4g**, containing ring D of nitidine and fagaronine, in satisfactory yields (Table I, entries 6, 7). Similarly, **4h** and **4i**, containing ring D of avicine, were obtained (Table I, entries 8, 9).

Since benzo[c]phenanthridines with the desired substituents on ring A or D were successfully obtained, it appeared probable that the desired alkaloids could be synthesized from the substrates **1c,d** and the nucleophiles **2c,e**.

Synthesis of Benzo[c]phenanthridine Alkaloids. Reaction of **1b** with the enolate of **2c** gave **4j**, nornitidine (entry 10). Quaternization with dimethyl sulfate followed by salt exchange gave nitidine chloride (**8**), mp 283 °C (lit.[24] mp 282–286 °C). Similarly, **4k** (entry 11), after quantitative acidic removal of the isopropoxy group, gave norfagaronine, **4l** (entry 12) is noravicine, and neither of the latter was quaternized (Chart I).

The overall yields, calculated upon the starting materials used for preparing the substrates and the nucleophiles, were 25% for nornitidine, 16% for norfagaronine, and 7% for noravicine. These compare well in most cases with the overall yields of the previous linear and longer syntheses. Moreover, the convergent approach makes our method versatile, and it was possible to obtain other natural products and analogues from different combinations of tetralones and substrates. Thus, norallonitidine (**4m**), a precursor of allonitidine, was obtained from **2d** and **1c** in 16% overall yield (entry 13), comparing well with that (9%) of the multistep linear synthesis.[25] Similarly, **4n**,

Chart I. Benzo[c]phenanthridines



		R^1	R^2	R^3	R^4	R
8	nitidine	OCH_3	OCH_3	OCH_2O		$^+NCH_3$
9	fagaronine	OCH_3	OCH_3	OH	OCH_3	$^+NCH_3$
10	avicine	OCH_2O		OCH_2O		$^+NCH_3$
4j	nornitidine	OCH_3	OCH_3	OCH_2O		N
4k	norfagaronine	OCH_3	OCH_3	OH	OCH_3	N
4l	noravicine	OCH_2O		OCH_2O		N
4m	norallonitidine	OCH_2O		OCH_3	OCH_3	N
4n		OCH_3	OCH_3	OCH_3	OCH_3	N
4o		OCH_2O		OC_3H_7-*i*	OCH_3	N
4p		OC_3H_7-*i*	OCH_3	OCH_3	OC_3H_7-*i*	N

a nonnatural product that has been synthesized by two groups[10b,26] using the linear strategy, was obtained in 16% yield. Other new analogues obtained by the $S_{RN}1$ reaction approach were **4o** (overall yield 10%), which has the avicine A ring and the fagaronine D ring, and **4p** (yield 16.5%), which after double deprotection gave **4q**, a product possessing the isofagaronine A ring and a nonnatural D ring.

Synthesis of Benzo[c]phenanthridones. Exploratory studies aimed at synthesizing benzo[c]phenanthridones were performed by reacting 2-bromo- or 2-iodobenzamide with the enolate of 6-methoxy-1-tetralone (**2b**).[27] The experiments were long (5–7 h until consumption of the substrate) and gave no $S_{RN}1$ substitution product but gave only the reduction product, benzamide. These results were surprising in view of the successful $S_{RN}1$ reactions of **2b** with 2-iodobenzylamines (Table I, entries 2, 7, 9). The nature of the leaving halogen in the benzamide should have little effect on the formation of the first radical anion $ArXY^{-\cdot}$ (eq 1) and on the subsequent fragmentation giving rise to $\cdot ArY$ (eq 2).. The reduction of this radical by transfer of a second electron was a minor competitive reaction in the benzylamine series ($Y = CH_2NH_2$) but superseded the nucleophilic attack (eq 3) in the 2-halobenzamide series ($Y = CO_2NH_2$). The reduction of $\cdot C_6H_4CONH_2$ to $^-C_6H_4CONH_2$, precursor of $C_6H_5CO_2NH_2$, is a termination step,[28] so that the $S_{RN}1$ reaction is sluggish and not suitable for synthetic purposes.

We were thus led to explore an alternative convergent strategy based upon the $S_{RN}1$ reaction between a 2-iodobenzoic acid and a tetralone enolate, similar to our syn-

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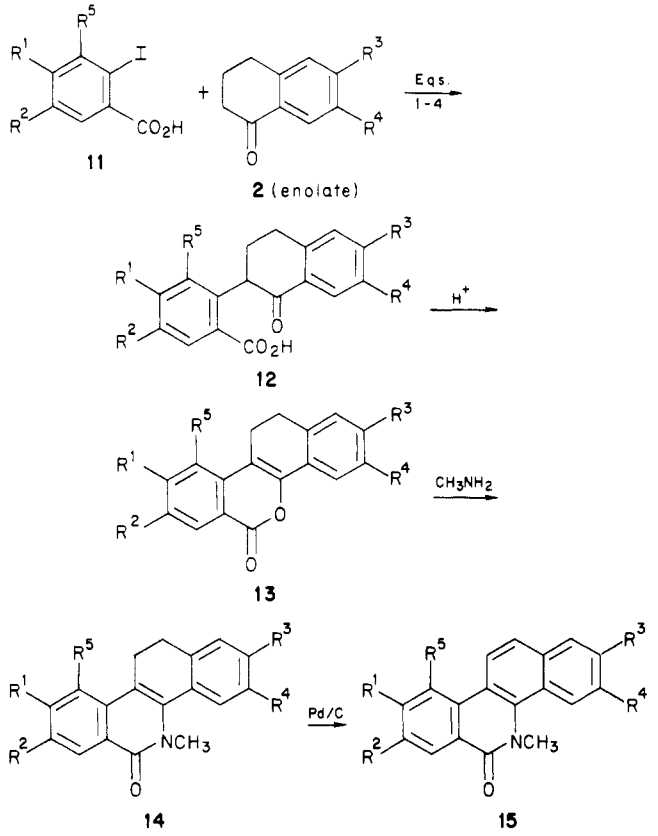
(27) Results from our laboratory (H. Ginsburg, unpublished), showing that 2-halobenzamides react with 4-methoxyacetophenone enolate to give the $S_{RN}1$ substitution products but give only benzamide with enolates of nucleophiles that lack an electron-releasing group, led us to select the enolate of **2b** rather than that of **2a**.

(28) A discussion of chain termination steps in $S_{RN}1$ reactions can be found in J. M. Saveant's review in: Saveant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323.

Scheme IV. Synthesis of Benzo[c]phenanthridones



thesis of isoquinolones via isocoumarones.[14] The $S_{RN}1$ reaction between 2-iodobenzoic acid or 2-iodo-3,4,5-trimethoxybenzoic acid (**11a** or **11b**) and **2b** or **2e** proceeded satisfactorily, and the subsequent reaction sequence shown in Scheme IV provided benzo[c]phenanthridones **15**. Removal of the isopropyl protecting group of **15c** gave **15d** ($R_1 = R_2 = R_4 = R_5 = OCH_3$; $R_3 = OH$) which has a ring A of fagaronine (Table II).

Experimental Section

General Procedures. Melting points are uncorrected and were measured on a Reichert melting point apparatus. Low-resolution mass spectra were obtained on an AEI MS 50 spectrometer; exact masses were determined by high-resolution mass spectroscopy on a Kratos MS 50 spectrometer. ^1H NMR spectra (in $CDCl_3$ unless otherwise indicated) were recorded on Varian T 60, Perkin-Elmer R 12, and Brucker WP 80 or WP 400 spectrometers; chemical shifts from tetramethylsilane are given in δ. Purifications were achieved by column chromatography (CC, elution) or by preparative thin-layer chromatography (PTLC, elution).

Materials. 2-Iodobenzylamine (Interchim, France) was purified (CC) before use. 2-Iodobenzoic acid (Aldrich) was used without purification. 1-Tetralone and 6-methoxy-1-tetralone (Aldrich) were purified (CC) before use.

4,5-Dimethoxy-2-iodobenzylamine (1b). *N*-Acetylveratrylamine, mp 103 °C, was prepared by acetylation of veratrylamine with acetic anhydride. This amide (6.98 g, 33.4 mmol) was treated with $Hg(OAc)_2/NaCl$[16] to give the chloromercuric derivative, which was refluxed in ethanol with iodine (8.48 g, 33.4 mmol) for 25 min. Workup with methylene chloride followed by washing with aqueous KI and sodium thiosulfate gave *N*-acetyl-4,5-dimethoxy-2-iodobenzylamine (8.3 g, 74%): mp 175 °C; ^1H NMR δ 2.0 (s, 3 H, $NHCOCH_3$), 3.84 (s, 6 H, OCH_3), 4.34–4.44 (d, 2 H, $CH_2NHCOCH_3$), 5.95 (s, 1 H, $NHCOCH_3$), 6.98 (s, 1 H, Ar), 7.23 (s, 1 H, Ar); mass spectrum, *m/e* 335 (M^+), 292. 208. Anal. Calcd for $C_{11}H_{14}INO_3$: C, 39.42; H, 4.21; N, 4.18; I, 37.87. Found: C, 39.50; H, 4.18; N, 4.16; I, 38.12. Hydrolysis of this compound (3 g, 8.9 mmol) by refluxing in 4 N methanolic HCl for 8 h and workup gave **1b** (2.5 g, 95%), as an unstable amorphous solid: ^1H NMR δ 1.45 (s, 2 H, CH_2NH_2), 3.78 (s, CH_2NH_2), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.92 (s, 1 H, Ar), 7.70 (s, 1 H, Ar); mass spectrum, *m/e* 293 (M^+), 227, 262, 166 ($M^+ - 127$).

2-Iodo-4,5-(methylenedioxy)benzylamine (1c). (i) Acetylation. Piperonylamine (5 g, 0.036 mol) treated with Ac_2O gave the expected compound (6.1 g, 100%), mp 103 °C (lit.[29] mp 103 °C): ^1H NMR δ 2.0 (s, 3 H, $NHCOCH_3$), 6.25–6.35 (d, 2 H, $CH_2NHCOCH_3$), 5.95 (s, 2 H, OCH_2O), 6.77 (s, 3 H, Ar); mass spectrum, *m/e* 193 (M^+), 150 ($M^+ - 43$).

(ii) Iodination. To a solution of *N*-acetylpiperonylamine (3.0 g, 15 mmol) in chloroform (60 mL) were successively added silver trifluoroacetate (3.6 g, 16.3 mmol) and a chloroform solution of iodine (4.32 g, 17 mmol).[17] Workup (filtration, washing with aqueous solutions of sodium thiosulfate, sodium bicarbonate, and brine) gave a crude product shown (NMR) to contain some starting material (20%). Purification (CC, 98.5/1.5 methylene chloride/methanol) gave 2-iodo-4,5-(methylenedioxy)-*N*-acetylbenzylamine, crystallized from methylene chloride/hexane: mp 145 °C; ^1H NMR δ 2.0 (s, 3 H, $NHCOCH_3$), 4.30–4.40 (d, 2 H, $CH_2NHCOCH_3$), 5.95 (s, 2 H, OCH_2O), 6.91 (s, 1 H, Ar), 7.18 (s, 1 H, Ar); mass spectrum, *m/e* 319 (M^+), 276 ($M^+ - 43$), 261, 192 ($M^+ - 127$). Anal. Calcd for $C_{10}H_{10}INO_3$: C, 37.64; H, 3.16; N, 4.39; O, 15.04; I, 39.77. Found: C, 37.83; H, 3.24; N, 4.34; O, 14.95, I, 39.51.

(iii) Hydrolysis. Hydrolysis of the above product (1.50 g, 47 mmol) was carried out in methanolic hydrochloric acid solution (4 N) and gave **1c** (1.21 g, 93%), as an unstable amorphous solid: ^1H NMR δ 1.53 (br s, 2 H, NH_2), 3.76 (s, 2 H, CH_2NH_2), 5.95 (s, 2 H, OCH_2O), 6.91 (s, 1 H, Ar), 7.24 (s, 1 H, Ar).

2-Iodo-5-methoxy-4-isopropoxybenzylamine (1d). Vanillin (15 g, 9.87 mmol) treated with isopropyl bromide[10b] gave 3-methoxy-4-isopropoxybenzaldehyde (19.1 g, 100%), as a liquid. Treatment of the above product (17 g, 87 mmol) with hydroxylamine hydrochloride gave the oxime (18 g, 98%), crystallized from hexane: mp 98 °C; ^1H NMR δ 1.29–1.39 (d, 6 H, $OCH(CH_3)_2$), 3.90 (s, 3 H, OCH_3), 6.20–6.40 (m, 1 H, $OCH(CH_3)_2$), 6.90–7.40 (m, 3 H, CH_2NH_2 and 1 H Ar), 8.17 (s, 1 H, Ar), mass spectrum, *m/e* 209 (M^+), 167 ($M^+ - 42$), 124. Anal. Calcd for $C_{11}H_5NO_3$: C, 63.14; H, 7.22; N, 6.69; O, 22.94. Found: C, 63.39; H, 7.22; N, 6.70; O, 22.74.

A sample of the oxime (17.4 g, 83 mmol) was refluxed in tetrahydrofuran (150 mL) with lithium aluminum hydride (6.0 g, 0.16 mol). Alkaline workup (sodium hydroxide 6%, 35 mL; methylene chloride) gave 5-methoxy-4-isopropoxybenzylamine (15.9 g, 98%): ^1H NMR δ 1.29–1.39 (d, 6 H, $OCH(CH_3)_2$), 2.05 (br s, 2 H, CH_2NH_2), 3.75 (s, 2 H, CH_2NH_2), 2.80 (s, 3 H, OCH_3), 4.2–4.7 (m, 1 H, $OCH(CH_3)_2$), 6.80 (br s, 3 H, Ar).

This amine underwent the treatment already applied to piperonylamine and veratrylamine.

(i) Acetylation. Acetylation gave 5-methoxy-4-isopropoxy-*N*-acetylbenzylamine (91%): mp 85 °C (methylene chloride/hexane; ^1H NMR δ 1.29–1.39 (d, 6 H, $OCH(CH_3)_2$), 2.0 (s, 3 H, $NHCOCH_3$), 3.82 (s, 3 H, OCH_3), 6.80 (s, 3 H, Ar); mass spectrum, *m/e* 237 (M^+), 195 ($M^+ - 42$). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.70; H, 8.07; N, 5.90; O, 20.23. Found: C, 65.70; H, 8.23; N, 5.86; O, 20.14.

(ii) Iodination. Iodination gave 2-iodo-5-methoxy-4-isopropoxy-*N*-acetylbenzylamine (73%): mp 138 °C (methylene chloride/hexane); ^1H NMR δ 1.29–1.39 (d, 6 H, $OCH(CH_3)_2$), 2.0 (s, 3 H, $NHCOCH_3$), 3.82 (s, 3 H, OCH_3), 4.20–4.70 (m, 1 H, $OCH(CH_3)_2$), 6.1 (br s, 3 H), 6.96 (s, 1 H, Ar), 7.28 (s, 1 H, Ar); mass spectrum, *m/e* 363 (M^+), 279 ($M^+ - 84$), 236 ($M^+ - 127$). Anal. Calcd for $C_{13}H_{18}NO_3I$: C, 42.93; H, 5.00; N, 3.86; O, 13.21; I, 34.94. Found: C, 43.18; H, 5.07; N, 3.84; O, 13.32; I, 34.70.

(iii) Acid Hydrolysis. Acid hydrolysis gave 2-iodo-5-methoxy-4-isopropoxybenzylamine (**1d**) (95%), as an amorphous solid: ^1H NMR δ 1.29–1.39 (d, 6 H, $OCH(CH_3)_2$), 1.52 (s, 2 H, CH_2NH_2), 3.86 (s, 3 H, OCH_3), 4.2–4.7 (m, 1 H, $OCH(CH_3)_2$), 6.97 (s, 1 H, Ar), 7.32 (s, 1 H, Ar).

2-Iodo-3,4,5-trimethoxybenzoic Acid (11c). A sample of 3,4,5-trimethoxybenzoic acid (2.2 g, 10.4 mmol) treated as described above (see **1b**) gave the 2-iodo derivative (2.65 g, 75%): mp 135–142 °C; ^1H NMR δ 3.93 (s, 3 H, OCH_3), 3.95 (s, 3 H,

(29) Malan, R. *J. Chem. Soc.* **1927**, 2655.

OCH_3), 3.98 (s, 3 H, OCH_3), 7.54 (s, 1 H, Ar); mass spectrum, *m/e* 338 (M^+), 323 ($M^+ - 15$), 308 ($M^+ - 30$), 211 ($M^+ - 127$).

6,7-(Methylenedioxy)-1-tetralone (2c). *trans*-4-[3,4-(Methylenedioxy)phenyl]but-3-enoic Acid (5c). Piperonaldehyde (11.26 g, 75 mmol) dissolved in a mixture (50/50) of tetrahydrofuran and dimethyl sulfoxide (150 mL) was reacted with 3-bromopropionic acid triphenylphosphonium salt[20] (31.12 g, 75 mmol) and sodium hydride (7.2 g, 0.15 mmol) at room temperature with mechanical stirring for 20 h. Acidic workup and purification (CC) gave the expected acid **5c** (8.4 g, 41%) crystallized from methylene chloride, mp 114 °C (lit.[18] mp 116–117 °C).

4-[3,4-(Methylenedioxy)phenyl]butanoic Acid (6c). Catalytic hydrogenation of **5c** (3.3 g, 14.4 mmol) gave **6c**, 100% crystallized from ether/pentane, mp 78 °C (lit.[4] mp 75–76 °C).

6,7-(Methylenedioxy)-1-tetralone (2c). A sample of **6c** (3.3 g, 14.4 mmol) was refluxed in benzene (60 mL) with oxalyl chloride (excess) for 120 min. Distillation of the solvent gave the corresponding acid chloride, which was refluxed in carbon disulfide (20 mL) with aluminum chloride (excess) for 3 h. Workup and purification (CC, florisil, 50/50 hexane/methylene chloride) gave **2c** (2 g, 65%), crystallized from hexane/ether, mp 75 °C (lit.[18] mp 75 °C).

6,7-Dimethoxy-1-tetralone (2d). *trans*-4-(3,4-Dimethoxyphenyl)but-3-enoic Acid (5d). Veratraldehyde (12.4 g, 75 mmol) was reacted with 3-bromopropionic acid phosphonium salt as described above and gave the acid **5d** (16.2 g, 95%), crystallized from ether/hexane: mp 65 °C; IR 3000, 2700–2500, 1700, 1600, 1580, 1500 cm^{-1}; ^1H NMR δ 3.26 (d, 2 H, CH_2COOH), 3.96 (s, 6 H, $OCH_3 \times 2$), 6.22 (t, 1 H, CH=$CH$$CH_2$), 6.35 (br s, 1 H, CH=$CH$Ar), 6.90 (m, 3 H, Ar); mass spectrum, *m/e* 222 (M^+), 178 ($M^+ - 44$). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.35; O, 28.01. Found: C, 64.98; H, 6.36; O, 28.35.

4-(3,4-Dimethoxyphenyl)butanoic Acid (6d). A sample of **5d** (10.0 g, 45 mmol) was hydrogenated to give the acid **6d** (9.65 g, 95%), crystallized from ether/hexane, mp 60 °C (lit.[19] mp 57–59 °C).

6,7-Dimethoxy-1-tetralone (2d). A sample of **15** (3.5 g, 16 mmol) was kept at 40 °C with polyphosphoric acid (25 g) for 4 h. Workup (methylene chloride) gave **2d** (3 g, 93%) crystallized from ether/hexane, mp 96 °C (lit.[30] mp 96 °C).

6-Isopropoxy-7-methoxy-1-tetralone (2e). *trans*-4-(3-Hydroxy-4-methoxyphenyl)but-3-enoic Acid (5e). Isovanillin (3-hydroxy-4-methoxybenzaldehyde) (15.2 g, 0.1 mol) was treated with 3-bromopropionic acid triphenylphosphonium salt (41.5 g, 0.1 mol) as above and, after purification (CC, silica, methylene chloride) gave **5e** (10 g, 48%), crystallized from methylene chloride: mp 145–146 °C; ^1H NMR δ 3.18 (d, 2 H, CH_2COOH), 3.90 (s, 3 H, OCH_3), 6.22 (t, 1 H, CH=$CH$$CH_2$), 6.29 (br s, 1 H, CH=$CH$Ar), 6.9 (m, 3 H, Ar); mass spectrum, *m/e* 208 (M^+), 164 ($M^+ - 44$). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.80; O, 30.76. Found: C, 63.27; H, 6.07; O, 30.50.

4-(3-Hydroxy-4-methoxyphenyl)butanoic Acid (6e). Catalytic hydrogenation of **5e** (2.6 g, 12.3 mmol) gave a quantitative yield of **6e**, mp 95 °C (lit.[31] mp 87–90 °C).

6-Hydroxy-7-methoxy-1-tetralone (7e). A sample of **6e** (2.6 g, 12.3 mmol) was heated at 40 °C with polyphosphoric acid (26 g) and chloroform (0.5 mL). Workup, purification, and crystallization led to **7e** (1.6 g, 67%), mp 116 °C (lit.[20] mp 117–119.5 °C).

6-Isopropoxy-7-methoxy-1-tetralone (2e). A sample of **7e** (3.1 g, 16 mmol) refluxed in dimethylformamide (8 mL) with isopropyl bromide (8 mL) and potassium carbonate according to a known procedure[10a] gave **2e** (3.8 g, 100%), crystallized from methylene chloride/hexane: mp 101 °C; ^1H NMR δ 1.37 (d, 6 H, $OCH(CH_3)_2$), 2.12 (m, 2 H, $COCH_2$), 2.57 (t, 2 H), 2.87 (t, 2 H), 3.87 (s, 3 H, OCH_3), 4.57 (sept, 1 H, $OCH(CH_3)_2$), 6.62 (s, 1 H, Ar), 7.50 (s, 1 H, Ar). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.96; H, 7.76; O, 20.36.

6-Methoxy-7-isopropoxy-1-tetralone (2f). 6-Methoxy-7-hydroxy-1-tetralone (7f). A sample of **2d** (1 g, 5 mmol), treated with hydrobromic acid according to a reported method,[20] gave after purification (CC, 80/20 benzene/ethyl acetate) **7f** (0.384 g, 40%), crystallized from methylene chloride: mp 152 °C (lit.[21] mp 149–152 °C). Further elution gave 6,7-dihydroxytetralone (0.2 g, 22%) mp 190–192 °C (lit.[20] 192–195 °C), and 6-hydroxy-7-methoxy-1-tetralone (0.03 g, 3%), mp 118–120 °C (lit.[20] mp 117–119.5 °C).

6-Methoxy-7-isopropoxy-1-tetralone (2f). A sample of **7f** (0.50 g, 2.6 mmol) treated with isopropyl bromide as above gave **2f** (0.60 g, 97%), crystallized from methylene chloride/hexane: mp 99–100 °C; ^1H NMR δ 1.37 (d, 6 H, $OCH(CH_3)_2$), 2.10 (m, 2 H, $COCH_2$), 2.57 (t, 2 H), 2.88 (t, 2 H), 3.89 (s, 3 H, OCH_3), 4.57 (sept, 1 H, $OCH(CH_3)_2$), 6.60 (s, 1 H, Ar), 7.48 (s, 1 H, Ar). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.75; H, 7.73; O, 20.48. Found: C, 71.67; H, 7.61; O, 20.79.

Synthesis of 3. General Procedure. To liquid ammonia (200 mL) under argon in a 500-mL three-necked Pyrex flask fitted with a dry ice condenser were added the ketone (1.5 mmol), freshly sublimed t-C_4H_9OK (2 mmol), and the substrate (0.5 mmol). The flask was illuminated for 40–80 min in a Rayonet apparatus (S.O. New England Co.) equipped with four R.U.L. 3000 tubes. The course of the reaction was monitored by analyzing aliquots (TLC or GLC) and after consumption of the substrate was quenched by adding NH_4Cl. After evaporation of the solvent, water (50 mL) was added, and the crude product was extracted with methylene chloride (3 × 20 mL). Workup and purification gave **3**. Melting points are given in Table I. High-resolution mass spectra were within 0.001 mass number of the calculated values.

Synthesis of 4. General Procedure. Samples of **3** were heated at 250 °C without solvent under nitrogen with 30% Pd/charcoal (25% by weight) for 4 h. Addition of methylene chloride, filtration, and purification gave **4**. Melting points are listed in Table I. High-resolution mass spectra were within 0.001 mass number of the calculated values.

2-Hydroxy-3,8,9-trimethoxybenzo[c]phenanthridine (4k', Chart I). A sample of **4k** (0.076 g, 0.22 mmol) was heated in acetic acid (5 mL) with 48% HBr (0.3 mL) at 100 °C for 180 min.[10a] Workup at pH 8 gave norfagaronine (0.068 g, 90%): mp 271–273 °C (lit.[32] mp 274–276 °C); mass spectrum, *m/e* 335 (M^+), 334, 320, 306, 292; exact mass calcd for $C_{20}H_{17}NO_4$ 335.1157, found 335.1161.

3,9-Dihydroxy-2,8-dimethoxybenzo[c]phenanthridine (4q). A sample of **4p** (0.03 g, 0.07 mmol) was similarly hydrolyzed with 48% HBr to give the dihydroxy compound (0.01 g, 44%): mp 288–290 °C; ^1H NMR (Me_2SO) δ 3.95 (2 s, 6 H, OCH_3), 7.41 (s, 1 H, H-1), 7.42 (s, 1 H, H-7), 7.73 (s, 1 H, H-10), 7.76 (d, J = 9 Hz, 1 H, H-12), 8.13 (d, J = 9 Hz, 1 H, H-11), 8.55 (s, 1 H, H-4), 9.05 (s, 1 H, H-6); mass spectrum, *m/e* 321 (M^+), 306, 278, 263, 235; exact mass calcd for $C_{19}H_{15}NO_4$ 322.0001, found 321.0984.

Synthesis of 12 and 13. General Procedure. A mixture of the tetralone enolate (3 mmol) and the iodobenzoic acid (1 mmol) was irradiated for 75 min with a Hanau QS 100 lamp. The crude **12** obtained after acidic workup contained 25–30% of the dehalogenated benzoic acid (^1H NMR). This mixture was dissolved in 5–6 mL of benzene containing 0.015 g of *p*-toluenesulfonic acid and refluxed for 75–180 min. Workup with $NaHCO_3$ and purification by PTLC gave **13** (yields and melting points listed in Table II).

Synthesis of 14. A sample of **13** (0.5–1 mmol), a slight excess of a 40% aqueous solution of methylamine, and 5–7 mL of dioxane were placed in a thick-walled glass tube equipped with a screw cap and heated at 100 °C for 150 min with magnetic stirring. The solvent and reagent were removed under vacuum, and the product was refluxed in benzene for 45 min to give **14**, which was purified by PTLC and recrystallized. Yields and melting points are listed in Table II. The mass spectra of **14b,c** were within 0.001 mass number of the calculated values.

Synthesis of 15b,c. Aromatization of **14b,c** (0.15 mmol) was carried out by heating with 30% Pd/charcoal to give **15b,c**. Yields and melting points are given in Table II.

2-Hydroxy-3,8,9,10-tetramethoxy-5-methylbenzo[c]phenanthridin-6-one (15d). A sample of **15c** (0.25 g, 0.6 mmol) was treated with polyphosphoric acid for 24 h at room temper-

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ature. Workup gave the product (0.02 g, 100%): mp 200–204 °C (methylene chloride); ^{1}H NMR δ 3.93 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.03 (s, 3 H, NCH_3), 4.03 (s, 3 H, OCH_3), 7.20 (s, 1 H, H-1), 7.48 (s, 1 H, H-4), 7.50 (s, J = 10 Hz, 1 H, H-12), 7.85 (s, 1 H, H-7), 9.90 (d, J = 10 Hz, 1 H, H-11); mass spectrum, m/e 395 (M^+), 380, 364, 337, 266; exact mass calcd for $C_{22}H_{21}NO_4$ 395.1294, found 395.1331.

Registry No. **1a**, 39959-51-8; **1b**, 98799-33-8; **1c**, 98799-35-0; **1d**, 98799-40-7; **2a**, 529-34-0; **2b**, 1078-19-9; **2c**, 41303-45-1; **2d**, 13575-75-2; **2e**, 98799-45-2; **2f**, 98799-46-3; **3a**, 98799-47-4; **3b**, 98799-48-5; **3c**, 98799-49-6; **3d**, 98799-50-9; **3e**, 98799-51-0; **3f**, 98799-52-1; **3g**, 98799-53-2; **3h**, 98799-54-3; **3i**, 98799-55-4; **3j**, 54022-61-6; **3k**, 98799-56-5; **3l**, 94656-27-6; **3m**, 98799-57-6; **3n**, 98799-58-7; **3o**, 98799-59-8; **3p**, 98799-60-1; **4a**, 218-38-2; **4b**, 98799-61-2; **4c**, 214-09-5; **4d**, 56517-13-6; **4e**, 98799-62-3; **4f**, 56517-12-5; **4g**, 98799-63-4; **4h**, 214-06-2; **4i**, 98799-64-5; **4j**, 18034-03-2; **4k**, 52259-71-9; **4k'**, 52259-72-0; **4l**, 217-52-7; **4m**, 51116-29-1; **4n**, 15462-10-9; **4o**, 98799-65-6; **4p**, 98799-66-7; **4q**, 98799-77-0; **5c**, 62848-88-8; **5d**, 98799-43-0; **5e**, 98799-44-1; **6c**, 41303-44-0; **6c** (acid chloride), 98799-42-9; **6d**, 13575-74-1; **6e**, 57596-01-7; **7e**, 15288-02-5; **7f**, 15288-01-4; **11a**, 88-67-5; **11c**, 98799-41-8; **12a**, 98799-76-9; **12b**, 98799-67-8; **12c**, 98799-68-9; **13a**, 55377-55-4; **13b**, 98799-69-0; **13c**, 98799-70-3; **14a**, 98799-71-4; **14b**, 98799-72-5; **14c**, 98799-73-6; **15b**, 98838-09-6; **15c**, 98799-75-8; **15d**, 98799-74-7; $Ph_3P^+(CH_2)_2CO_2H\cdot Br^-$, 51114-94-4; *N*-acetylveratrylamine, 65609-25-8; veratrylamine, 5763-61-1; piperonylamine, 2620-50-0; *N*-acetylpiperonylamine, 59682-83-6; 6-iodo-*N*-acetylpiperonylamine, 98799-34-9; vanillin, 121-33-5; 4-isopropoxybenzaldehyde, 2538-98-9; 3-methoxy-4-isopropoxybenzaldoxime, 98799-36-1; 3-methoxy-4-isopropoxybenzylamine, 98799-37-2; 3-methoxy-4-isopropoxy-*N*-acetylbenzylamine, 98799-38-3; 2-iodo-5-methoxy-4-isopropoxy-*N*-acetylbenzylamine, 98799-39-4; 3,4,5-trimethoxybenzoic acid, 118-41-2; piperonaldehyde, 120-57-0; veratraldehyde, 120-14-9; isovanillin, 621-59-0.

Supplementary Material Available: ^{1}H NMR spectral data for **3a–p**, **4a–p**, **13a,c**, **14a–c**, and **15a–c** (8 pages). Ordering information is given on any current masthead page.

Copper(II)-Promoted Aqueous Decomposition of Aldicarb

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The copper(II)-promoted decomposition of aldicarb, 2-methyl-2-(methylthio)propanal *O*-[(methylamino)carbonyl]oxime, was investigated over the pH region 2.91 to 5.51. The products are 2-methyl-2-(methylthio)propionitrile (82%) and 2-methyl-2-(methylthio)propanal (18%). Thus in contrast to many acyl compounds Cu^{2+} promotes the same reaction as that observed in acid rather than the base-catalyzed process. From the effects of Cu^{2+} concentration and temperature upon the rate of reaction a scheme is proposed. Cu^{2+} complexation leads to a β-thioiminium ion whose special stability provides fragmentation as the predominant pathway.

Aldicarb, 2-methyl-2(methylthio)propanal *O*-[(methylamino)carbonyl)] oxime (I), is a widely used systemic pesticide which acts on the central nervous system. Both aldicarb and its toxic metabolites contaminate the aquifers in various parts of the United States,[1] and in many instances levels in drinking water wells exceed the current federal guideline of 10 ppb.[2] Recent studies in our lab-

$$CH_3SC(CH_3)_2CH{=}CNOC(O)NHCH_3$$
I

oratory[3] and by others[4,5] have determined the effects of pH and temperature on the hydrolysis rate and the reaction products of aldicarb. At pH values above 7.0 a characteristic base-catalyzed carbamate decomposition via methyl isocyanate dominates, and the principal products are the oxime (II) of 2-methyl-2-(methylthio)propanal (III), methylamine, dimethylurea, and carbon dioxide.[3] At pH

$$CH_3SC(CH_3)_2CH{=}NOH$$
II

values below 5.0 an unusual acid-catalyzed reaction occurs, leading principally to 2-methyl-2-(methylthio)propionitrile (IV) and methylamine.[3] The acid-catalyzed process is peculiar since most *N*-methylcarbamates react orders of magnitude more slowly in acid media than in basic media.[6] Minor products in both reactions come in part from the small amount (~9%) of the *Z* isomer present in I.

The characterization of the acid-catalyzed component in the hydrolysis of aldicarb (I)[3] led us to speculate on the interesting possibility of catalysis by divalent metal ions. Multivalent ions, acting as Lewis acids,[7-9] catalyze a variety of organic reactions and have several advantages over the proton in assisting reaction.[8] For example, the metal often carries more than a single positive charge, and in solutions near neutrality the concentration of divalent metal can usually be brought to 10^{-2} M, some 4 to 5 orders of magnitude greater than the hydronium ion concentration. More complex mechanisms for metal ion catalysis have been reported for hydrolysis of acyl derivatives, such as esters, amides, and anhydrides.[10-19] These studies provide

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