$FeCl_3$ and sodium acetylacetonate in a aqueous solution. The dark red product was extracted with $HCCl_3$. The extract was washed with H_2O three times and the solvent evaporated. The solid was then recrystallized from ethanol–water mixture which was vacuum dried. A 77% yield of $Fe(acac)_3$, mp 184°C dec, was obtained.

Electrodes. The nickel and copper electrodes were cleaned by thoroughly scouring them with steel wool and placing them in a solution of DMF and TEAB in which a potential of 5–10 V was applied across the electrodes for ≤1 min. After this procedure they were immediately transferred to the reaction flask. While all reactions followed a curve similar to that shown in Figure 2. cleaning the electrodes resulted in higher initial currents. Generally, currents ranged from 10 mA (initial) to as high as 80 mA (maximum) during the reaction.

The aluminum electrodes have, in more recent experiments, been cleaned by placing them in 3 *M* HCl for 15 min and rinsing thoroughly with H_2O and dried by rinsing them in organic solvents.

The standard calomel electrode which was periodically inserted into the reaction (≈1 min) to monitor the working electrode voltage probably led to some contamination by water. However, it did not affect product formation.

Since the anode dissolved during the reaction, current density measurements were not made. Likewise, electrochemical yields were not determined.

Electrolysis Reaction. In a typical reaction, to 60 ml of DMF in a 100-ml Berzelius beaker were added $Fe(acac)_3$ (4.4 g, 12.46 mmol), triphenylphosphine (1.5 g, 5.66 mmol), $Et_4N^+Br^-$ (0.802 g, 3.81 mmol), and 1-octyl bromide (8.6 ml, 49.78 mmol). A rubber stopper fitted with cleaned aluminum electrodes was used to seal the beaker. Nitrogen was bubbled through the stirred solution until solutes dissolved. An applied potential of 1.5 V was established and held until the current profile, as indicated in Figure 2, was completed.

Octane and octene were removed from the electrolyzed solution by vacuum distillation and analyzed by gas chromatography. An 8-ft column packed with 20% Carbowax 20M on 80–100 mesh Chromosorb W was used to separate octane from octene and a 6-ft column of 3% SE-30 80–100 mesh Chromosorb W was used to separate 1-octyl bromide from DMF.

The pot residue was treated with 100 ml of distilled H_2O and extracted with five 50-ml aliquots of ether. This ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated by rotoevaporator. Liquid chromatography on a 46 × 2 cm column of activated acidic aluminum oxide eluted with hexane was used to separate hexadecane and unreacted 1-octyl bromide from other residues contained in the ether extract. After solvent evaporation on a rotoevaporator, these products were analyzed by GLC on the same columns mentioned above.

The precent yields were based on the amount of 1-octyl bromide which had reacted and are reported in the text. The percent conversion (amount of product divided by amount of 1-octyl bromide) ranged from 70 to 98. The important factor in the percent conversion number is the concentration of starting halide or, more directly, the concentration of products. If the product concentration was too high, it began to oil out on the top of the DMF solution. This oil layer would then attract the 1-octyl bromide thereby reducing reactant in the bulk electrolysis solution. Thus it is essential for highest conversion to maintain a homogeneous solution.

Benzyl and Aryl Halides. While the general procedure for electrolysis with these substrates was identical with that described for the 1-octyl bromide, the work-up was slightly different. There was no vacuum distillation. The raw electrolysis mixture was diluted with 100 ml of water and extracted with five 50-ml aliquots of ether. The ether extract was dried, filtered, and reduced in volume by rotoevaporation. This material was then passed through an alumina column using hexane as the eluting solvent. The coupled products, bibenzyl or biphenyl, were thence isolated, sublimed, and weighed.

Divided Cell. An H cell design was used with a salt bridge mixture containing methyl cellulose (10.23 g), DMF (80 ml), and TEAB (4.4 g). Each half of the cell contained 60 ml of DMF, 0.8 g of TEAB, 1.50 g of Ph_3P, and 8.6 ml of 1-octyl bromide. The cathode compartment contained 4.4 g of $Fe(acac)_3$. After 366 hr, at an applied potential of 1.5 V and low currents (as expected), the reaction was stopped. Also the red color, due to $Fe(acac)_3$ diffusion, was hallfway across the salt bridge.

Although the yield was low owing to low currents, octane, octene, and hexadecane were isolated from the cathode compartment and analyzed by gas chromatography.

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Registry No.—$Fe(acac)_3$, 14024-18-1; $Ni(acac)_2$, 3264-82-2; $NiCl_2$, 7718-54-9; $FeCl_3$, 7705-08-0; acetylacetone, 123-54-6; sodium acetylacetonate, 15435-71-9.

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(10) It is not known why this curve is "bell" shaped at this time. However, it is felt that the initial rise in current flow could be due to (a) increased surface area on the electrodes owing to pitting and (b) also possibly from a drop in the cell resistance owing to an increase in ionic substances in solution. The latter part of the curve is more typical and is a function of $time^{-1}$.
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A New Stereospecific Synthesis of the *E* Isomers of 2-Phenyl-4-arylmethylene-2-oxazolin-5-ones*

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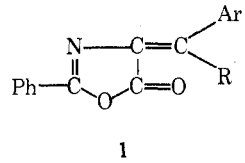
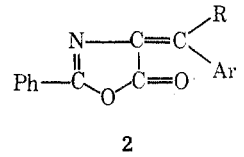
The Erlenmeyer azlactone synthesis,[1] a well-known reaction that is widely employed for the preparation of 2-aryl- (or alkyl-) 4-arylmethylene-2-oxazolin-5-ones, consists of heating aromatic aldehydes with hippuric or aceturic acids in the presence of acetic anhydride and sodium acetate and usually gives the thermodynamically stable isomers 1 (R = H).



1

(*Z*)



2

(*E*)

* Reactions in Polyphosphoric Acid. I.

Table I
Azlactones 2

Compd	R	Ar	Mp, °C	% yield	$\nu_{C=O}$ ($CHCl_3$)	τ ($CDCl_3$)	Formula	Anal., % Calcd C	Calcd H	Found C	Found H
2	H	C_6H_5	146–147	90[a]	1780	1.87 (m) 2.4–2.8 (m)					
5	H	4-ClC_6H_4	185	85	1790	1.65 (m) 2.4 (m)	$C_{16}H_{10}ClNO_2$	67.9	3.51	67.72	3.49
6	H	4-$CH_3OC_6H_4$	132	90	1780	1.7 (m) 2.4–2.8 (m) 6.1 (s)	$C_{17}H_{13}NO_3$	73.1	4.66	73.0	4.62
7	H	4-$CH_3C_6H_4$	117	80	1760	1.9 (m) 2.5–2.8 (m) 7.65 (s)	$C_{17}H_{13}NO_2$	77.5	4.95	77.2	4.9
8	H	3,4-$(MeO)_2C_6H_3$	141	82[a]	1775						
9	H	4-HOC_6H_4	109	80	1780		$C_{16}H_{11}NO_3$	72.5	4.15	72.3	4.1
10	H	2-HOC_6H_4	163	70	1720		$C_{16}H_{11}NO_3$	72.5	4.15	72.29	4.17
11	CH_3	C_6H_5	183	80	1770	1.87 (m) 2.4–2.8 (m) 7.4 (s)	$C_{17}H_{13}NO_2$	77.5	4.95	77.7	4.92
12	CH_3	4-ClC_6H_4	185	52	1780		$C_{17}H_{12}ClNO_2$	68.5	4.03	68.7	4.1
13	CH_3	4-$MeOC_6H_4$	169	50	1775	2.0 (m) 2.5–2.9 (m) 6.2 (m), 7.3 (s)	$C_{18}H_{15}NO_3$	73.7	5.09	73.8	5.1
14	CH_3	4-$O_2NC_6H_4$	180	88	1780		$C_{17}H_{12}N_2O_4$	66.4	3.9	66.5	3.87
15	CH_3	4-$CH_3C_6H_4$	160	70	1770	2.0 (m) 2.5–3.0 (m) 7.3 (s), 7.6 (s)	$C_{18}H_{15}NO_2$	78.0	5.4	78.2	5.3
16	H	4-$O_2NC_6H_4$	245	100	1795		$C_{16}H_{10}N_2O_4$	65.4	3.4	65.2	3.5
17	H	2,4-$Cl_2C_6H_3$	183	100	1790		$C_{16}H_9Cl_2NO_2$	60.2	2.82	60.3	2.79
18	H	2,6-$(MeO)_2C_6H_3$	168	100[a]	1780						
19	H	1-$C_{10}H_7$	160	100[a]	1775						
20	H	2-$CH_3OC_6H_4$	154	100[a]	1785						

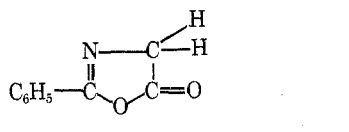
[a] Known compounds.

Although the existence of geometric isomers of azlactones with an exocyclic double bond in the 4 position had been predicted, it was through the pioneering work of Carter and co-workers[2] that the stable and labile isomers of 2-phenyl-4-ethylidene- and 2-phenyl-4-phenylmethylene-2-oxazolin-5-ones were prepared and characterized. Originally the Plöchl–Erlenmeyer azlactone,[3] 1 (Ar = Ph; R = H), had been assigned the *E* configuration[4] but recently it has been shown to have the *Z* configuration instead.[5] It is now generally accepted that *Z* isomers are obtained in Erlenmeyer synthesis.[4a] In a few cases the Erlenmeyer method does give a mixture of isomers,[6] which are separated by fractional crystallization. Niemann and co-workers[7] reported that the condensation of benzaldehyde with hippuric acid in 100% concentrated sulfuric acid gave a mixture of 1 and 2 (Ar = Ph; R = H) but the isomers could not be separated. In general, the *E* isomers 2 (R = H) are prepared by special methods,[2] by isomerization of the *Z* isomers in saturated hydrobromic acid,[4c,5c,8] by photochemical isomerization,[9] or from 2-phenyloxazolinonium perchlorate.[10] Of these, the hydrobromic acid method has been employed in the isomerization of a few azlactones [1, R = H; Ar = 1-$C_{10}H_7$, C_6H_5, 2-$CH_3OC_6H_4$, 2,6-$(CH_3O)_2C_6H_3$, 3,4-$(CH_3O)_2C_6H_3$] and has not worked in the case of others.[11] The photoisomerization method gives about 18% yield of the desired isomer. The perchlorate method of Boyd[10] was the first reported stereospecific synthesis of 2 (Ar = Ph; R = H) but the yield of 2 was low and the general applicability of the method has not been demonstrated.

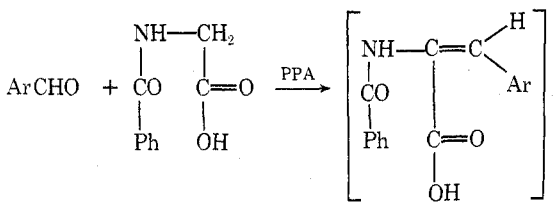
We now report here a new and simple method for the direct synthesis of the *E* isomers of azlactones. Aromatic aldehydes condense with hippuric acid when heated in polyphosphoric acid (PPA) at 80–100° to give 80–90% yields of 2. One may alter this method by using the expedient of heating the stable isomers in polyphosphoric acid medium to get the same products (Table I). Polyphosphoric acid has been employed in a series of cyclodehydration reactions but not as a medium for the synthesis of azlactones from aldehydes and hippuric acid.[12] However, Kaneko and co-workers[12d] isomerized the azlactone of indole-3-aldehyde in PPA. By the PPA method, we have been able to synthesize some previously known *E* azlactones (2, R = H) and also some *E* isomers which had not previously been obtained. Salicylaldehyde and 4-hydroxybenzaldehyde, both of which give 4-(acetoxyphenyl)methylene oxazolones under Erlenmeyer conditions, condense with hippuric acid in PPA to give the corresponding hydroxy derivatives, 2 (Ar = 2-HOC_6H_4, 4-HOC_6H_4; R = H).[13] It is well known that ketones such as acetone, cyclohexanone, and fluorenone condense with hippuric acid to give the corresponding oxazolones.[14] Although Lure and co-workers[15] reported that 3- and 4-nitroacetophenonones condense with hippuric acid in the presence of anhydrous potassium carbonate to give α-arylethylidene azlactones in 13–28% yields, acetophenone and substituted acetophenones do not condense with hippuric acid. In PPA medium, these compounds react with hippuric acid to give α-arylethylidene azlactones 2 (R = CH_3) in good yields. Benzophenone does not, however, react under these conditions. The configuration of α-arylethylidene azlactones is tentatively assumed to be *E* at the present time, since our compounds differ in melting points from those prepared by Bernabe and co-workers[16a] by the C-alkylation of 1 (R = H) with diazomethane, products to which Burger and Pages[16b,c] assigned the *Z* structure. The configurations of the oxazolinones 2 (R = H), prepared by the PPA method, are shown to be *E* by spectral data and their ready conversion to the stable isomers by treatment with pyridine[2] or by melting and recrystalli-

zation of the molten products. In NMR spectra of these compounds, the ethylenic proton is masked by aromatic protons, whereas in the NMR spectra of the corresponding *Z* isomers, this proton appears as a singlet at τ 2.7–2.8.[5a,c,d,16d,18] These compounds show carbonyl absorption around 1770–1790 cm^{-1}.

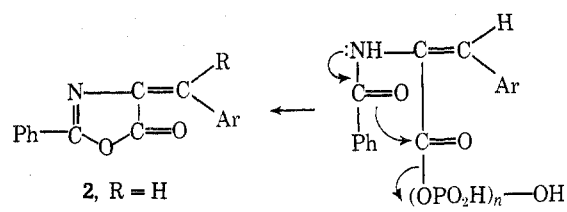
It is generally accepted that 2-phenyl-2-oxazolin-5-one (**3**) is an intermediate in the Erlenmeyer reaction[1c-e,17] and that **3** condenses with aldehydes to give **1**. It may be pointed out that hippuric acid is not converted to **3** in PPA but both the isomers of 2-benzamidocinnamic acids,[2c,5e,19] **4a** and **4b**, both of which are obtained by the alkaline hydrolysis of **1** and **2** (R = H; Ar = C_6H_5), respectively, and are hence assumed to have configurational identities, are converted to **2** (R = H; Ar = Ph) in PPA. Thus it is likely that aldehydes condense with hippuric acid in PPA to give **4b** which then cyclizes to give **2**. The following mechanism is suggested for the azlactone formation.



3



4b, Ar = C_6H_5



2, R = H

Other condensation reactions in PPA are currently under study and will be reported later.

Experimental Section

Melting points were determined on a Fisher-Johns block and are reported uncorrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer in $CHCl_3$ or CCl_4 solutions. NMR spectra were determined on a Varian A-60 instrument with tetramethylsilane as the internal standard with $CDCl_3$ as the solvent.

2-Phenyl-4-phenylmethylene-2-oxazolin-5-one (2). To a sample of polyphosphoric acid,[20] prepared from phosphoric acid (20 ml, d^{20} 1.7) and phosphoric anhydride (32 g), was added benzaldehyde (5.3 g, 50 mmol) and hippuric acid (8.95 g, 50 mmol). The mixture was then heated on a steam bath (80–95°) for 90 min and was then poured into water. The resultant solid product was collected and repeatedly washed with water. The oxazolone was recrystallized from a mixture of benzene–Skellysolve B: mp 146–147° (12.0 g, 90% yield); ir $\nu_{C=O}$ ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) τ 1.87 (4 ortho H), 2.4–2.8 (7 H).

Compounds **5–15** (Table I) were prepared by the condensation of the appropriate carbonyl compounds with hippuric acid in PPA.

Isomerization of 2-Phenyl-4-phenylmethylene-2-oxazolin-5-one (1). To a sample of **1** (Ar = Ph; R = H; 5 g) was added polyphosphoric acid (50 g). The mixture was heated on a steam bath for 90 min. The product was isolated as above, mp 146–147° (5.0 g). A mixture melting point with the above sample showed no depression.

Compounds **2**, **5–8**, and **16–20** were prepared similarly by isomerization of the stable isomer in PPA.

Conversion of 2 to 1 (Ar = Ph; R = H). A sample of **2** (1 g) was dissolved in 10 ml of pyridine at room temperature. After 5 min, the mixture was poured on excess concentrated hydrochloric acid on crushed ice. The precipitate was filtered, washed with water, and recrystallized from ethanol, mp 166° (yield 98%, 0.98 g).

Reaction of Hippuric Acid in PPA. Hippuric acid (1 g) in PPA (10 g) was heated for 90 min on a steam bath. The product was isolated as above, and turned out to be the starting material (yield 90%, 0.9 g, mp 189°).

Reaction of 2-Benzamidocinnamic Acid 4a.[5e] A sample of **4a**, mp 231–232° (1 g), was heated in 10 g of PPA on a steam bath for 90 min. The product isolated, as usual, turned out to be **2** (Ar = Ph; R = H), mp 147° (yield 97%, 0.97 g).

Reaction of 2-Benzamidocinnamic Acid 4b.[5e] A sample of **4b**, mp 201–202° (1 g), was treated as above. The final product **2** melted at 147°, identical in all respects with the *E* isomer above (yield 87%, 0.87 g).

Registry No.—**1** (R = H; Ar = C_6H_5), 17606-70-1; **1** (R = H; Ar = 4-ClC_6H_4), 57427-77-7; **1** (R = H; Ar = 4-$CH_3OC_6H_4$), 57427-78-8; **1** (R = H; Ar = 4-$CH_3C_6H_4$), 57427-79-9; **1** (R = H; Ar = 3,4-$(MeO)_2C_6H_3$), 25349-37-5; **1** (R = H; Ar = 4-$O_2NC_6H_4$), 57427-80-2; **1** (R = H; Ar = 2,4-$Cl_2C_6H_3$), 57427-81-3; **1** (R = H; Ar = 2,6-$(MeO)_2C_6H_3$), 57427-82-4; **1** (R = H; Ar = 1-$C_{10}H_7$), 57427-83-5; **1** (R = H; Ar = 2-$CH_3OC_6H_4$), 57427-84-6; **2**, 15732-43-1; **4a**, 26348-47-0; **4b**, 57427-85-7; **5**, 57427-86-8; **6**, 57427-87-9; **7**, 57427-88-0; **8**, 25349-38-6; **9**, 57427-89-1; **10**, 57427-90-4; **11**, 57427-91-5; **12**, 57427-92-6; **13**, 57427-93-7; **14**, 57427-94-8; **15**, 57427-95-9; **16**, 57427-96-0; **17**, 57427-97-1; **18**, 57427-98-2; **19**, 57427-99-3; **20**, 57428-00-9; hippuric acid, 495-69-2; polyphosphoric acid, 8017-16-1; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 4-methoxybenzaldehyde, 123-11-5; 4-methylbenzaldehyde, 104-87-0; 3,4-dimethoxylbenzaldehyde, 120-14-9; 4-hydroxybenzaldehyde, 123-08-0; 2-hydroxybenzaldehyde, 90-02-8; acetophenone, 98-86-2; 4′-chloroacetophenone, 99-91-2; 4′-methoxyacetophenone, 100-06-1; 4′-nitroacetophenone, 100-19-6; 4′-methylacetophenone, 122-00-9.

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(20) Polyphosphoric acid from Matheson Coleman and Bell was used. A ratio of 1:10 of the reactants to PPA gave the best results. In a few cases (6–10) the reaction proceeded at room temperature itself and heating only led to darkening of the product.

N-Methylation of Amides, Lactams, and Ureas

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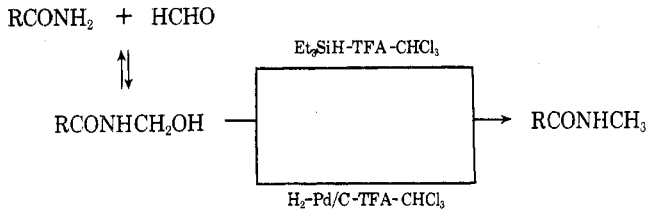
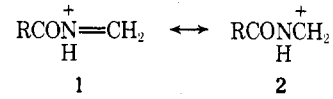
Few satisfactory methods are currently available for the N-methylation of amides and related compounds.[2] One of the more promising existing methods for amide alkylation was reported by Johnson and Crosby,[2c] who reduced a mixture of a primary amide and an acetal by catalytic hydrogenation in the presence of concentrated sulfuric acid. We now describe a milder and more versatile two-step procedure which consistently affords high isolated yields of mono-N-methylated products from the corresponding unsubstituted compounds.

Scheme I



It is well known[3] that various amides and related compounds react reversibly with formaldehyde, usually at neutral or slightly basic pH, to produce methylol derivatives (Scheme I). The equilibrium for this reaction lies to the methylol side at most pH's to the extent of about 5 kcal/mol. Many such methylols have been reported and usually are easily prepared and isolated. These methylols have found wide synthetic use in amidomethylation at carbon.[3] We have discovered that methylols derived from amides are reduced to the corresponding N-methylated product, usually at room temperature, by triethylsilane–trifluoroacetic acid, as well as by catalytic hydrogenation at atmospheric pressure in the presence of trifluoroacetic acid. A number of representative examples are shown in Table I.

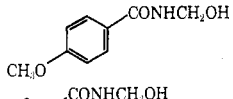
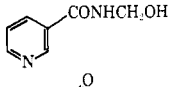
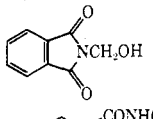
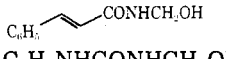
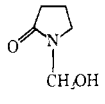
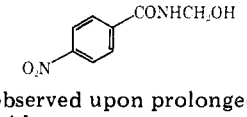
Triethylsilane has previously been shown to be effective for the reduction of many types of electrophilic species, particularly carbonium ions.[4] Treatment of an amide methylol with trifluoroacetic acid presumably produces an electrophilic acyliminium ion (**1** ↔ **2**)[3] which is then reduced to



1 **2**

the *N*-methyl compound by hydride transfer from silicon to carbon. It is likely that the catalytic reduction route, also utilizing trifluoroacetic acid, proceeds via the same acyliminium ion (**1** ↔ **2**).

Table I
Reduction of Methylols to *N*-Methyl Compounds

Registry no.	Methylol	Isolated yield of N-methylated product, %	
		Et_3SiH–TFA	H_2–5% Pd/C–TFA
57428-71-4	$C_5H_{11}CONHCH_2OH$	86	97
6282-02-6	$C_6H_5CONHCH_2OH$	94	97
57428-72-5		91	84
3569-99-1		88	93
118-29-6		No reaction[a]	No reaction
6043-65-8		85	79[b]
20779-63-9	$C_6H_5NHCONHCH_2OH$	85	80
57428-73-6	$(CH_3CH_2)_2NCONHCH_2OH$	57	65
15438-71-8		84	84
40478-12-4		92	66[c]

[a] No reduction product was observed upon prolonged heating. [b] The product is *N*-methylhydrocinnamamide. [c] The product is *p*-amino-*N*-methylbenzamide.