Potential Antiarthritic Agents. 2. Benzoylacetonitriles and β-Aminocinnamonitriles[1]

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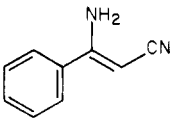
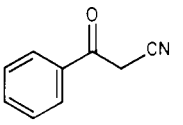
Benzoylacetonitrile and β-aminocinnamonitrile are shown to possess potent antiinflammatory activity in the rat adjuvant arthritis model. In a series of phenyl-substituted analogues, only *o*-, *m*-, and *p*-fluorobenzoylacetonitrile and *m*- and *p*-fluoro-β-aminocinnamonitrile retained activity. Additionally, β-amino-2- and β-amino-3-thiopheneacrylonitrile and β-oxo-2- and β-oxo-3-thiophenepropionitrile exhibited similar activity. These agents are not believed to be acting via prostaglandin synthetase inhibition. The metabolic profile of benzoylacetonitrile is also described.

The past decade has been witness to the development of many new chemical entities useful for the symptomatic treatment of rheumatoid arthritis. By and large, these agents share properties which relate not only to their molecular structure but to their mode of action as well:[2] (1) They are acidic compounds, usually arylacetic acid analogues. (2) They are effective by virtue of their ability to inhibit prostaglandin synthetase and, thus, are plagued by gastrointestinal side effects characteristic of aspirin-like compounds. (3) They are useful in the relief of joint pain and swelling but are ineffective in halting the progression of the disease state or in hastening repair to the damaged tissues.

We have discovered that both β-aminocinnamonitrile (**1a**) and benzoylacetonitrile (**2a**) exhibit a high degree of



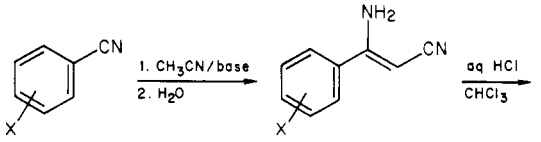
1a



2a

potency and efficacy in inhibiting the development of rat adjuvant arthritis. While **1a** does show activity in the rat carrageenin-induced edema assay,[3] **2a** does not show any activity, and neither compound shows strong activity in an in vitro prostaglandin synthetase inhibition assay. Clearly, the high efficacy observed in the adjuvant arthritis assay did not seem to be a consequence of only PG synthetase inhibition, and it was reasonable to presume that another mechanism was operative. Such a mechanism might indeed provide an agent with true antiarthritic properties. A series of analogues, therefore, was prepared for pharmacological evaluation.

Chemistry. β-Aminocinnamonitriles, **1**, were easily prepared by the condensation of acetonitrile anion with the appropriately substituted benzonitrile (eq 1)[3] and are



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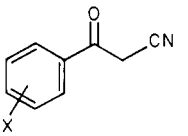
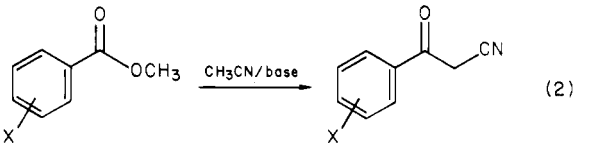


(1)

2

listed in Table I. Similarly, benzoylacetonitriles, **2**, were prepared as reported in the literature[4,5] (eq 2) or by the facile acid hydrolysis of β-aminocinnamonitriles (eq 1). These ketones are listed in Table II.

While sodium amide, sodium *tert*-butoxide, and sodium isopropoxide were commonly employed as bases in these reactions, the most useful method utilized 1 equiv of

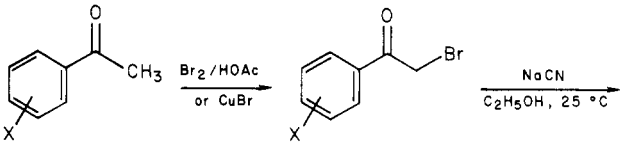


(2)

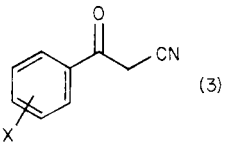
2

sodium hydride in ether containing a catalytic amount of *tert*-butyl alcohol. This technique avoided the displacement of certain substituents (e.g., fluorine and alkoxide) from the aromatic ring by nucleophilic bases.

An alternate route to benzoylacetonitrile analogues involved cyanide displacement upon the substituted phenacyl bromides[6] (eq 3). All acetophenones employed



3 **4**



(3)

1

were commercially available, except for the three difluoroacetophenones leading to compounds **2p–r**. These intermediates (**3**, X = F_2) were easily prepared via Friedel–Crafts acylation of the requisite difluorobenzenes and were assigned structures by analogy to the corresponding dichlorobenzene isomers.[7,8] Structures also were substantiated by 100-MHz proton NMR, whereby the side-chain $-COCH_3$ signals showed long-range coupling (J = 6 Hz) for those isomers containing an *o*-fluoro substituent.[9]

In reactions analogous to those of eq 1, the thiophene analogues of **1** and **2** were prepared and are complied in Table III. The fluoro analogues **5c** and **6c** were obtained from 2-cyano-5-fluorothiophene, prepared by the method of Gronowitz.[10]

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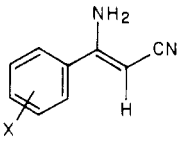
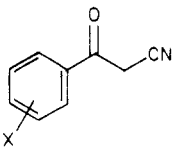
Table I. β-Aminocinnamonitrile Analogues



no.	X	yield, %	mp, °C	formula	anal.
1a	H	*a*	84-81	$C_9H_8N_2$	*a*
1b	2-F	19	64.5-66	$C_9H_7N_2F$	C, H, N, F
1c	3-F	24	67-69	$C_9H_7N_2F$	C, H, N, F
1d	4-F	20	98-100[b]	$C_9H_7N_2F$	C, H, N, F
1e	4-Cl	85	138-140[c]	$C_9H_7N_2Cl$	C, H, N, Cl
1f	2-Br	25	98-100	$C_9H_7N_2Br$	C, H, N, F
1g	4-Br	37	144-147	$C_9H_7N_2Br$	C, H, N, F
1h	3-CF_3	43	81-83	$C_{10}H_7N_2F_3$	C, H, N, F
1i	4-CF_3	59	136-138	$C_{10}H_7N_2F_3$	C, H, N, F
1j	2-CH_3	38	87-91	$C_{10}H_{10}N_2$	C, H, N
1k	4-CH_3	52	104-107[d]	$C_{10}H_{10}N_2$	
1l	4-Ph	28	187-189[e]	$C_{15}H_{12}N_2$	
1m	3-CN	11	171-174	$C_{10}H_7N_3$	C, H, N
1n	2,6-Cl_2	22	146-151	$C_9H_6N_2Cl_2$	C, H, N, Cl
1o	3,4-$(CH_3)_2$	56	130-133	$C_{11}H_{12}N_2$	C, H, N

[a] Commercially available; see also ref. 3. [b] Lit.[3] mp 110-112 °C. [c] Lit.[11] mp 144-145 °C. [d] Lit.[3] mp 104-107 °C. [e] Lit.[3] mp 187-189 °C.

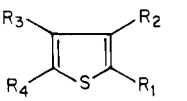
Table II. Benzoylacetonitrile Analogues[a]



no.	X	synth meth	yield, %	mp, °C	lit. mp, °C	ref
2a	H	*b*		79-80	80-81	4, 12
2b	2-F	I	87	53-54	53	13
2c	3-F	III	37	69-70		14
2d	4-F	I	80	78-80		14
2e	2-Cl	I	77	50-54	56-57	15
2f	3-Br	I	88	93-95	88-89	15
2g	4-Br	III	42	164-165	160-161	15
2h	3-CF_3	I	80	58-60		
2i	4-CF_3	I	91	44-45		
2j	2-OCH_3	III	34	90-91	87-88	13, 15
2k	4-OCH_3	III	42	132-133		16
2l	4-CN	II	35	126-129		
2m	4-OH[c]	III	38	168-172[d]	182-183	13, 15
2n	4-NO_2	III	44	122-123	122-123	15
2o	4-NH_2	*b*		157-158	157-158	15
2p	2,4-F_2	III	44	107-110		
2q	2,5-F_2	III	32	87-89		
2r	3,4-F_2	III	52	74-75		

[a] All new compounds were analyzed elementally and found to be acceptable to within ±0.4% for C, H, N, and halogen if present. [b] Commercially available. [c] Analysis acceptable for $C_9H_7NO_2 \cdot 0.25H_2O$. [d] Decomposition.

Table III. Thiophene Analogues

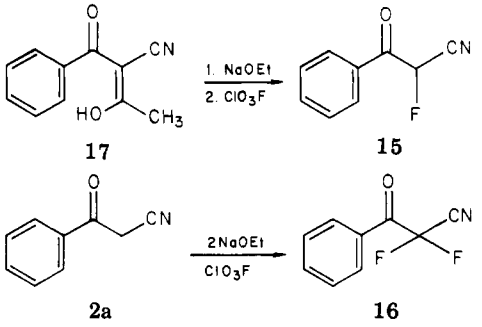


no.	R_1	R_2	R_3	R_4	synth meth	yield, %	mp, °C	formula	anal.
5a	$C(NH_2)=CHCN$	H	H	H	I	24	50-54	$C_7H_6N_2S$	C, H, N, S
5b	H	$C(NH_2)=CHCN$	H	H	I	17	67-69.5	$C_7H_6N_2S$	C, H, N, S
5c	$C(NH_2)=CHCN$	H	H	F	I	60	86-87	$C_7H_5N_2SF$	C, H, N, S, Cl
5d	$C(NH_2)=CHCN$	H	H	Cl	I	33	98.5-100	$C_7H_5N_2SCl$	C, H, N, S, Cl
6a	$COCH_2CN$	H	H	H	I	82	135-136[a]	C_7H_5NOS	C, H, N, S
6b	H	$COCH_2CN$	H	H	I	67	87-88	C_7H_5NOS	C, H, N, S
6c	$COCH_2CN$	H	H	F	I	75	93-95	C_7H_4NOSF	C, H, N, S, F
6d	$COCH_2CN$	H	H	Cl	I	71	117-118[b]	C_7H_4NOSCl	C, H, N, S, Cl
6e	$COCH_2CN$	H	H	Br	III	33	147-149	C_7H_4NOSBr	C, H, N, S, Br
6f	$COCH_2CN$	H	H	CH_3	III	34	108-109	C_8H_7NOS	C, H, N, S

[a] Lit.[17] mp 136-137 °C. [b] Lit.[17] mp 120 °C.

Other heteroaryl rings (e.g., pyridyl, furyl, and pyrrolyl) have been substituted for phenyl and thienyl but with no retention of antiinflammatory activity.

The modification of the cyanoacetyl side chain of benzoylacetonitrile and its effects upon the pharmacological profile were also investigated. Table IV lists some of those compounds which were prepared. Most of these compounds (7–14) are known in the literature. Benzoylfluoroacetonitrile (15) was obtained directly upon



workup by the reaction of perchloryl fluoride on the sodium salt of 17[18] as precedented in the literature.[19] Benzoyldifluoroacetonitrile (16) was synthesized by the action of perchloryl fluoride upon benzoylacetonitrile in the presence of 2 equiv of sodium ethoxide.[20]

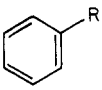
The facile acid hydrolysis of **1a** to **2a** and the similarity in biological profile of these two agents led us to speculate that the enamines, administered to rats by gavage, were quickly converted to their corresponding ketones upon contact with gastric fluid. Our attempt to substantiate this probability in a crude in vitro experiment was carried out by treatment of **1a** in aqueous hydrochloric acid (pH 1.2) at 37 °C. Reaction aliquots were quenched at 10, 30, 60, and 120 min, and the UV spectrum of each was determined. Comparison of these spectra to those of pure enamine and ketone suggested that the conversion of **1a** to **2a** was ca. 50% complete after 10 min and 95% complete after 30 min. We consider this strong evidence that a considerable amount of enamine **1a** could be absorbed as the ketone **2a** and may therefore be effective in that form. However, we recognize that other in vivo parameters not simulated in this experiment may considerably affect the hydrolysis and absorption process.

Metabolism. The possibility that the antiinflammatory effect of benzoylacetonitrile was due to an active metabolite was studied. A sample of benzoylacetonitrile-*carbonyl*-^{14}C was prepared as in eq 2 and dosed at 50 mg/kg in the rat. The percent total recovery of radioactivity over a 7-day period after dosing ranged from 93.3 to 99.7% in a group of four animals, with urinary excretion accounting for 81.7–90.4% of the dose in the first 24 h. Analysis of plasma and urine extracts by TLC and high-pressure liquid chromatography revealed that the drug was extensively metabolized. The major metabolites were purified by preparative TLC and identified by mass spectra analysis and TLC comparisons with authentic reference compounds known in the literature. Table V summarizes these results.

Evaluation of the four major metabolites for antiinflammatory activity proved them to be inactive in both the rat adjuvant arthritis and carrageenin edema assays.

Pharmacology. The compounds listed in Tables I–V were screened in the previously described rat adjuvant arthritis assay.[27] Compounds which produced a statistically significant inhibition of the control grade were accepted as active. The activity was limited to parent compounds **1a** and **2a** and certain of their monofluor-

Table IV. Side-Chain Analogues of Benzoylacetonitrile



no.	R	mp or bp (mm), °C	lit. mp, °C	ref
7	$COCH_2CH_2CN$	72.5-74.5	76	21
8	$COCH_2C{\equiv}CH$	74-79	78-82	22
9	$COCH_2CONH_2$	108-110	114-116	23
10	$COCH_2CO_2H$	99-100[d]	99.5-100[d]	24
11	$SOCH_2CN$	62-64	66-67	25
12	SO_2CH_2CN	113-115		*a*
13	CONHCN	134-137	141-142	26
14	$COCHCH_3CN$	128-130 (3)		*a*
15	COCHFCN	65 (0.1)		*b*
16	$COCF_2CN$	60 (0.5)		*c*

[a] Commercially available. [b] Anal. (C_9H_6NOF) C, H, N; F: calcd, 11.65; found, 10.81. [c] Estimated purity ca. 95%. [d] Decomposition.

phenyl analogues (i.e., **1c,d** and **2b–d**), as well as the four unsubstituted thiophene analogues **5a,b** and **6a,b**. Dose–response data for a selected number of compounds from this group are presented in Table VI.

The compounds which showed activity against the adjuvant-induced arthritis model exhibited little or no activity against rat carrageenin-induced edema (with the exception of **1a**) or UV-induced erythema in guinea pigs and had little or no ulcerogenic potential in rats at total doses as high as 800 mg/kg daily. Additionally, the effect of benzoylacetonitrile on the net production of prostaglandin-like activity in a cell-free guinea pig lung preparation demonstrated that it had only about one-third the potency of aspirin as a prostaglandin synthetase inhibitor.

Conclusions

Benzoylacetonitriles and β-aminocinnamonitriles active in this series present a structurally novel class of antiinflammatory agents, highly effective in suppression of developing adjuvant arthritis in rats. In contrast to other nonsteroidal antiinflammatory agents, members of this series are, at best, only weak inhibitors of prostaglandin synthesis, as evidenced by both in vitro and in vivo experiments. It is concluded that these agents possess a profile of activity distinctly different from that of the nonsteroidal agents, such as aspirin, indomethacin, and phenylbutazone, and therefore have a unique potential in antiarthritic therapy. Initial studies suggest that stimulation of the reticuloendothelial system might represent one possible mechanism of action.[28]

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Proton NMR spectra were determined on a Varian HA-100 instrument, and signals were measured in parts per million from Me_4Si. IR spectra were determined on a Perkin-Elmer Model 21 as KBr pellets for solids or neat films for liquids.

***p*-Fluoro-β-aminocinnamonitrile (1d).** To a dry 250-mL three-neck flask was added 30 mL of hexane under argon, followed by 2.2 g (46 mmol) of 50% sodium hydride in oil. The mixture was stirred for 5 min and the hexane was siphoned off and replaced by 30 mL of ether. A solution of 5.0 g (41 mmol) of *p*-fluorobenzonitrile, 2.4 mL (46 mmol) of acetonitrile, and 0.4 mL (4 mmol) of *tert*-butyl alcohol diluted to 45 mL with ether was then added dropwise to the stirred sodium hydride mixture. When the addition was complete, the mixture was heated to reflux overnight. After 24 h, 40 mL of water was cautiously added, and the ether phase was separated. This solution was dried and evaporated to yield 6.4 g of off-white solid. This residue was dissolved in chloroform and filtered through a Magnesol pad, and

Table V. Metabolic Profiles of Benzoylacetonitrile in the Rat Following an Oral Dose of 50 mg of drug/kg of Body Weight

metabolite	structure[a]	% of total radioact. plasma	urine
benzoylaceto-nitrile	$Ph\overset{*}{C}OCH_2CN$	14	18
benzoylacetic acid	$Ph\overset{*}{C}OCH_2CO_2H$	33	41
3-phenylhydrac-rylonitrile	$Ph\overset{*}{C}H(OH)CH_2CN$	23	11
3-phenylglyceric acid[b]	$Ph\overset{*}{C}H(OH)CH(OH)CO_2H$	4	11
hippuric acid	$Ph\overset{*}{C}ONHCH_2CO_2H$		5

[a] An asterisk denotes ^{14}C-labeled site. [b] Characterized as the tris(Me_4Si) derivative.

the filtrate was concentrated on the steam bath and diluted with hexane. Upon cooling, 5.0 g (74%) of colorless product precipitated, mp 100–103 °C.

***p*-Fluorobenzoylacetonitrile (2d).** A two-phase mixture of 5.0 g (0.029 mol) of *p*-fluoro-β-aminocinnamonitrile (**1d**), 50 mL of chloroform, and 30 mL of 3 N aqueous hydrochloric acid was stirred overnight at 25 °C. After 15 h, the layers were separated, and the chloroform phase was dried over sodium sulfate and filtered through a pad of Magnesol. The product was crystallized directly from the filtrate to provide 4.3 g (86%) of colorless solid, mp 84–86 °C.

3,4-Difluoroacetophenone (3, X = 3,4-F_2). Dry aluminum chloride (26 g, 0.19 mol) was added to a 250-mL three-neck flask under argon, and the flask was cooled in ice. Acetyl chloride (14 mL, 0.19 mol) was then added dropwise, followed by 20 g (0.18 mol) of *o*-difluorobenzene. The ice bath was removed, and the reaction was slowly warmed and eventually held at 100 °C for 3.5 h. The hot reaction solution was then poured onto ice and extracted with ether. The organic extracts were washed with aqueous sodium bicarbonate and evaporated. The dark residue (23 g) was distilled at 39 °C (0.1 mm), providing 20 g (73%) of colorless 3,4-difluoroacetophenone, mp ca. 20 °C.

3,4-Difluorophenacyl Bromide (4, X = 3,4-F_2). To a solution of 10.1 g (0.065 mol) of 3,4-difluoroacetophenone in 100 mL of glacial acetic acid was added dropwise 3.4 mL (0.065 mol) of bromine. When the addition was complete, the solution was stirred for 0.5 h and then stripped to dryness under reduced pressure. The residue was dissolved in chloroform and washed with aqueous sodium bicarbonate. Evaporation of the organic phase provided 14.8 g (97%) of colorless liquid product.

3,4-Difluorobenzoylacetonitrile (2r). A solution of 13.2 g (0.056 mol) of 3,4-difluorophenacyl bromide was dissolved in 100 mL of ethanol and cooled to 5 °C in ice. A solution of 7.6 g (0.16 mol) of sodium cyanide in 40 mL of water was added dropwise over 0.5 h and the reaction was stirred for an additional 1 h. At that time, the mixture was diluted with 100 mL of water and filtered through Celite. Acidification of the filtrate gave a cloudy mixture, which was extracted with methylene chloride. The organic phase was dried, filtered through Magnesol, and evaporated. Recrystallization of the residue from carbon tetrachloride provided 5.3 g (52%) of colorless solid: mp 74–75 °C; IR (KBr) 2370 (CN), 1701 (C=O), 1517, 1437 cm^{-1}. Anal. ($C_9H_5NOF_2$) C, H, N.

Benzoylfluoroacetonitrile (15). A solution of sodium methoxide was prepared by dissolving 0.6 g (0.025 mol) of sodium in 100 mL of absolute ethanol. The solution was cooled to 0–5 °C under nitrogen and 4.8 g (0.026 mol) of **17** dissolved in 30 mL of ethanol was introduced. After 10 min, a stream of perchloryl fluoride was bubbled in. After 1 h, the gas flow was stopped and the reaction was allowed to warm to room temperature for 1 h. It was then degassed with argon and allowed to stand overnight. The reaction was diluted with water and the product extracted with ether whereby 3.8 g of a crude oil was obtained. Distillation at 110 °C (0.2 mm) provided a colorless liquid: NMR ($CDCl_3$) δ 6.23 (d, 1, J = 46 Hz, CHF), 7.52–8.01 (m, 5). Anal. (C_9H_6NOF) C, H, N.

Table VI. Effect of Antiinflammatory Agents on Developing Adjuvant Arthritis in Rats (Pooled Data)[a]

compd	oral dose, mg/kg	mean wt gain, g day 14	day 21	% inhibn of swelling (primary lesion) day 14	day 21
normal rats		77	112		
adjuvant controls		36	31	0	0
indomethacin (historical data)	2	68	68	51	24
	1	63	65	46	19
	0.5	53	51	40	20
1a	100	49	64	65	54
	50	39*	50	58	52
	25	50	44	39	25
1d	100	78	67	53	29
	50	66	57	43	25
	25	53	50	26	14*
2a	100	49	65	63	48
	50	53	59	51	42
	25	54	56	54	33
2b	100	65	53	35	14*
	50	69	61	52	40
	25	56	54	29	16*
2d	100	63	71	46	32
	50	61	58	56	37
	25	55	48*	33	17
5a	100	45*	51*	49	27
	50	54	59	44	23
	25	65	58	35	10*
5b	100	50*	51	58	33
	50	52	56	48	27
	25	37*	59	37	20*
6a	200	34*	54*	72	29
	100	52*	69	58	42
	50	56	48*	46	18
6b	100	68	75	46	29
	50	62*	59	55	40
	25	70	89	52	31

[a] All values in the treated group, other than those marked with an asterisk, are significantly different from the adjuvant arthritic controls; $p < 0.05$ by Student's t test.

Benzoyldifluoroacetonitrile (16). Benzoylacetonitrile (5.0 g, 0.034 mol) was dissolved in a solution of 3.8 g (0.070 mol) of sodium methoxide in 150 mL of ethanol. The solution was cooled to 0 °C and purged with nitrogen. Perchloryl fluoride was bubbled into the reaction solution at such a rate as to maintain the reaction temperature below 15 °C. When the exothermic reaction ceased, the cooling bath was removed and the reaction stirred for another 0.5 h. The system was again purged with nitrogen and then diluted with water. Extraction of the product with methylene chloride, evaporation of the solvent, and distillation of the residue provided 1.7 g of a colorless oil: bp 60 °C (0.5 mm); IR ($CHCl_3$) 1709 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$, signals downfield from Me_4Si) 106.1 (t, J = 260 Hz, CF_2), 110.22 (t, J = 42 Hz, CN), 129.42 (s), 130.31 (s), 136.18 (s), 180.98 ppm (t, J = 180 Hz, C=O); ^{19}F NMR ($CDCl_3$, signal upfield of Freon 11) 92.56 ppm (s). Anal. Calcd for $C_9H_5NOF_2$: C, 59.67; H, 2.79; N, 7.74; F, 20.98. Found: C, 58.50; H, 3.26; N, 7.41; F, 18.98.

Hydrolysis of β-Aminocinnamonitrile (1a) to Benzoylacetonitrile (2a) with Simulated Gastric Fluid. Methanolic solutions of pure β-aminocinnamonitrile (**1a**) and benzoylacetonitrile (**2a**), as well as mixtures of these compounds, were prepared and their UV spectra were determined: **1a**, λ_{max} 290 nm; **2a**, λ_{max} 243 nm. The ratios of absorbances at 243/290 nm for each of the solutions above were plotted against the percent of **2a**.

A sample of 0.50 g of β-aminocinnamonitrile (**1a**) was finely

ground and added all at once to 50 mL of a vigorously stirred 37 °C stock solution prepared by dissolving 7 mL of concentrated HCl and 2 g of NaCl in 1 L of water. Vigorous stirring was maintained and aliquots were withdrawn at 10-, 30-, 60-, and 120-min time intervals. Samples were neutralized with aqueous $NaHCO_3$ to pH 7 and extracted three times with CH_2Cl_2. The solvent was evaporated and the UV spectra were determined in methanol. Comparison of ratios of absorbances at 243/290 nm for each sample to those for standard solutions was made. By this method, the hydrolysis appeared ca. 50% complete in the first 10 min and ca. 95% complete after 30 min. Samples taken at 60 and 120 min also indicated ca. 95% completion.

Benzoyl-*carbonyl*-^{14}*C*-acetonitrile. A mixture of 6.8 g (0.05 mL) of methyl benzoate-*carbonyl*-^{14}C (104 mCi; New England Nuclear), 5.0 g (0.05 mL) of potassium *tert*-butoxide, and 3.3 mL (0.063 mol) of acetonitrile was stirred and heated in an oil bath at 70–90 °C. After 1.5 h, 25 mL of water was added to the mixture, and this solution was extracted with CH_2Cl_2. The aqueous phase was acidified with concentrated HCl and extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with 10% aqueous $NaHCO_3$, dried over magnesium sulfate, filtered through a Magnesol pad, and then evaporated. The residue was recrystallized from CH_2Cl_2–hexanes to provide 4.1 g (57%) of product: mp 80–80.5 °C; specific activity 14.3 mCi/g.

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