Synthesis and Antiinflammatory and Analgesic Activity of 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids. The 6-Substituted Compounds[1]

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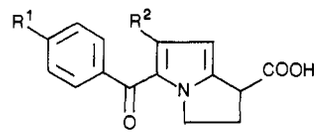
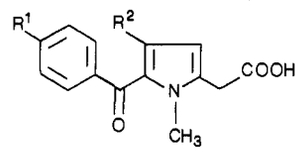
5-Aroyl-6-substituted-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids were synthesized and assayed for analgesic and antiinflammatory activity. Several of these compounds, notably the 5-(4-fluoro- and 4-chlorobenzoyl)-6-methyl derivatives **25** and **26** and the 5-(4-methyl-, 4-fluoro-, 4-chloro-, and 4-methoxybenzoyl)-6-chloro congeners **31–34** were of equal or greater potency than indomethacin as antiinflammatory and analgesic agents both in acute and chronic animal models.

The synthesis and pharmacological evaluation of a series of 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids as antiinflammatory and analgesic agents were recently described.[2] The parent member of this group of compounds I ($R^1 = R^2 = H$, ketorolac) is an analgesic in humans approximately equivalent to morphine sulfate for the relief of moderate to severe postoperative pain.[3] It was reported by Carson and Wong[4] that the introduction of a methyl group into the 4-position of certain 5-aroylpyrrole-2-acetic acids (II, $R^2 = CH_3$) resulted



I



II

in a twofold or greater increase in the antiinflammatory potency in animals, as measured by the rat paw kaolin edema assay, over the corresponding C-4 unsubstitued compounds. It was therefore of interest to determine the effect of a substitutent α to the aroyl group in the bicyclic series (I, $R^2 \neq H$), and this paper describes the synthesis and some of the pharmacology of such compounds.[5,6]

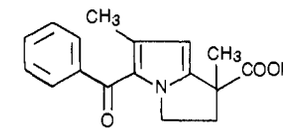
Chemistry

The carboxylic acids I were prepared by the potassium carbonate induced hydrolysis of the corresponding esters IV, which were obtained by acylation of the known[7] 6-substituted bicyclic carboxylic acid esters III (Scheme I, Tables I and II). The acylation of the esters III was accomplished with either the Vilsmeier–Haack reagent derived from an *N,N*-dimethylbenzamide and phosphorus oxychloride in boiling 1,2-dichloroethane[4] or an appropriate benzoyl chloride in xylene at reflux temperature in the absence of a catalyst[8] (methods A and B, see Experimental Section).

The 1-methyl derivative **46** of compound **23** was prepared by alkylation of the sodium salt of the ester **1** with methyl iodide followed by hydrolysis of the α-methylated ester **45** with potassium carbonate.

Discussion

The antiinflammatory and analgesic activities of the compounds listed in Table III were first determined by



45, R = *i*-Pr
46, R = H

using the carrageenan rat paw and mouse phenylquinone writhing assays.

The structure–activity studies in the 6-substituted-5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids described herein were guided by the observations made in the 6-unsubstituted series of compounds.[2] Thus it was previously shown that the most active compounds, as measured by the above two assays, were those in which the benzoyl group at C-5 was either unsubstituted or monosubstituted at the para position. Therefore the synthesis of ortho- or meta-substituted benzoyl congeners in the 6-substituted series was not examined.

The data in Table III show that high analgesic and antiinflammatory activity was found in most of the 6-substituted compounds except those bearing a 2-methoxyethyl or a 3-methoxypropyl moiety. Indeed, several of

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(1) Contribution No. 717 from the Syntex Institute of Organic Chemistry.
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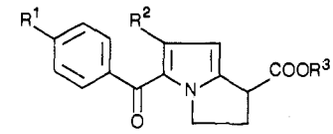
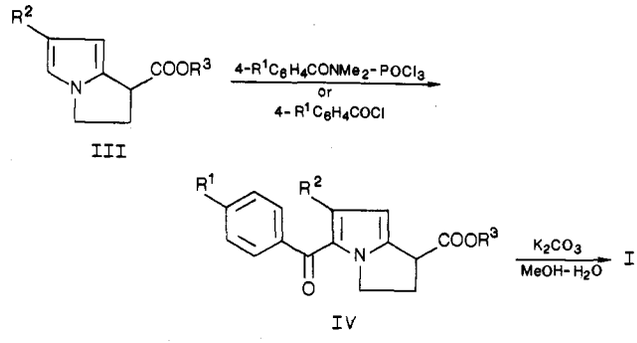
Table I. 5-Aroyl-6-substituted-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid Esters



no.	R^1	R^2	R^3	acylation method[a]	rctn time, h	% yield	mp, °C	recryst solvent[b]	emp formula	anal.[c]
1	H	CH_3	*i*-Pr	A	6	83	75	hex	$C_{19}H_{21}NO_3$	C, H
2	CH_3	CH_3	*i*-Pr	A	5	93	75	hex	$C_{20}H_{23}NO_3$	C, H
3	F	CH_3	*i*-Pr	A	15	69	oil	*d*	$C_{19}H_{20}FNO_3$	*e*
4	Cl	CH_3	*i*-Pr	A	10	99	88	hex	$C_{19}H_{20}ClNO_3$	C, H, Cl
5	CH_3O	CH_3	*i*-Pr	A	6	93	89	hex	$C_{20}H_{23}NO_4$	C, H
6	H	CH_3CH_2	*i*-Pr	A	20	52	oil	*f*	$C_{20}H_{23}NO_3$	*g*
7	F	CH_3CH_2	*i*-Pr	A	1.5	55	oil	*h*	$C_{20}H_{22}FNO_3$	*i*
8	H	Cl	CH_3	B	40	68	106	hex	$C_{16}H_{14}ClNO_3$	C, H, N
9	CH_3	Cl	CH_3	B	48	64	86	CH_2Cl_2–hex	$C_{17}H_{16}ClNO_3$	C, H, N
10	F	Cl	CH_3	B	28	32	117	CH_2Cl_2–hex	$C_{16}H_{13}ClFNO_3$	C, H, N
11	Cl	Cl	CH_3	B	18	71	85	hex	$C_{16}H_{13}Cl_2NO_3$	C, H, N
12	CH_3O	Cl	CH_3	B	48	71	111	MeOH	$C_{17}H_{16}ClNO_4$	C, H, N
13	CH_3S	Cl	CH_3	B	63	71	100	CH_2Cl_2–hex	$C_{17}H_{16}ClNO_3S$	C, H, N, S
14	CH_3SO_2	Cl	CH_3	*j*	0.7	60	155	acet–hex	$C_{17}H_{16}ClNO_5S$	C, H, N, S
15	H	Br	CH_3	B	48	81	93	CH_2Cl_2–hex	$C_{16}H_{14}BrNO_3$	C, H
16	F	Br	CH_3	B	24	87	131	CH_2Cl_2–hex	$C_{16}H_{13}BrFNO_3$	C, H, N
17	H	$CH_3O(CH_2)_2$	*i*-Pr	B	2	76	oil	*k*	$C_{21}H_{25}NO_4$	*l*
18	F	$CH_3O(CH_2)_2$	*i*-Pr	B	2	67	oil	*k*	$C_{21}H_{24}FNO_4$	*m*
19	Cl	$CH_3O(CH_2)_2$	*i*-Pr	B	2	72	oil	*f*	$C_{21}H_{24}ClNO_4$	C, H
20	H	$CH_3O(CH_2)_3$	*i*-Pr	B	0.6	83	oil	*k*	$C_{22}H_{27}NO_4$	C, H
21	F	$CH_3O(CH_2)_3$	*i*-Pr	B	0.6	69	oil	*k*	$C_{22}H_{26}FNO_4$	C, H
22	Cl	$CH_3O(CH_2)_3$	*i*-Pr	B	0.6	86	oil	*d*	$C_{22}H_{26}ClNO_4$	C, H

[a] Acylation methods: A, Vilsmeier–Haack reaction; B, acid chloride and ester in boiling xylene; see Experimental Section. [b] hex = hexene; acet = acetone; eth = ether. [c] Elements shown analyzed to within ±0.4% of the calculated values. [d] Purified by column chromatography on silica gel; hex–EtOAc (9:1). [e] MS M^+ 329. [f] Purified by TLC; hex–EtOAc (85:15). [g] MS M^+ 325. [h] Purified by TLC; hex–EtOAc (95:5). [i] MS M^+ 343. [j] Peracid oxidation of **13**. [k] Purified by TLC; hex–EtOAc (4:1). [l] MS M^+ 355. [m] MS M^+ 373.

Scheme I



the compounds (**23–26, 30, 37**) were of comparable activity to ketorolac (I, R^1, R^2 = H; 350 × aspirin) in the mouse writhing assay and seven (**25–27, 32, 33, 35, 36**) were, as expected from the observations of Carson and Wong[4] (see above), two- to threefold more potent in the rat paw assay (ketorolac = 36 × phenylbutazone). The high activity found in this class of compounds implies that the region of the cyclooxygenase[9] receptor site[10,11] occupied by the 6-substituent can tolerate some though not an excessive degree of steric bulk. This could account for the low activity observed for the compounds with a 2-methoxyethyl or a 3-methoxypropyl group at this position (**39–44**), although other explanations such as inappropriatly high lipophilicity, adverse hydrogen-bonding effects, or rapid metabolic inactivation are also possible.

One of the expected effects of substitution at C-6 is to twist the phenyl group out of the CO–pyrrolyl plane, a conformation found to exist in ketorolac in the solid state[13] and one that is probably of significance at the receptor level.[10,12] The NMR spectral data provide strong support for the predominance in solution of such a conformation, at least for the 6-methyl compounds. The absorption for the 6-methyl group in the bicyclic ester III (R^2 = CH_3, R^3 = *i*-Pr) is found at δ 2.03 whereas in the corresponding 5-benzoylated esters (**1–5**) it is observed at δ 1.85 ± 0.03 (1.86 ± 0.04 for the acids **23–27**). This upfield shift is opposite to that predicted on the basis of substituent effects, but is consistent with the methyl group occupying the positive shielding region above the plane of the phenyl ring.[14]

The introduction of a methyl group α to the carboxylic acid moiety, as in **46**, resulted in considerable diminution in both the analgesic and antiinflammatory activity as compared to the α-unsubstituted analogue **23**. This result is analogous to that observed previously in the 6-unsubstituted series and is doubtless associated with the minimal tolerance for steric bulk in this region of the receptor.[2,10]

A number of the compounds that showed high activity in the acute screens were chosen for study in chronic models of inflammation, which included the cotton pellet granuloma and adjuvant-induced arthritis assays. All of

(9) Several of the more active compounds were shown to be potent cyclooxygenase inhibitors. For example, compounds **25** and **26** were 2.3- and 3.8-fold more potent than indomethacin (IC_{50} = (1.44 ± 0.45) × 10^{-6} M) for the inhibition of human platelet microsomal prostaglandin synthetase (Hammerström, S.; Falardeau, P. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3691. Flower, R. J.; Cheung, H. S.; Cushman, D. W. *Prostaglandins* **1973**, *4*, 325).

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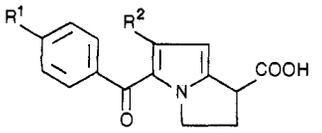
Table II. 5-Aroyl-6-substituted-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids



no.	R^1	R^2	rctn time, h	% yield	mp, °C	recryst solvent [a]	emp formula	anal.[b]
23	H	CH_3	5	89	169	CH_2Cl_2–hex	$C_{16}H_{15}NO_3$	C, H, N
24	CH_3	CH_3	6	88	187	MeOH	$C_{17}H_{17}NO_3$	C, H, N
25	F	CH_3	3	75	204	MeOH–H_2O	$C_{16}H_{14}FNO_3$	C, H, F
26	Cl	CH_3	6	92	204	EtOAc	$C_{16}H_{14}ClNO_3$	C, H, Cl
27	CH_3O	CH_3	6	92	182	MeOH	$C_{17}H_{17}NO_4$	C, H, N
28	H	CH_3CH_2	1.5	82	177	EtOH–eth	$C_{17}H_{17}NO_3$	C, H
29	F	CH_3CH_2	1.5	78	196	EtOH–H_2O	$C_{17}H_{16}FNO_3$	C, H
30	H	Cl	3	90	190	MeOH–H_2O	$C_{15}H_{12}ClNO_3$	C, H, Cl, N
31	CH_3	Cl	3	94	198	MeOH	$C_{16}H_{14}ClNO_3$	C, H, Cl, N
32	F	Cl	3	91	206	MeOH–H_2O	$C_{15}H_{11}ClFNO_3$	C, H, Cl, N
33	Cl	Cl[c]	2	95	200	MeOH	$C_{15}H_{11}Cl_2NO_3$	C, H, Cl, N
34	CH_3O	Cl	1	93	182	MeOH	$C_{16}H_{14}ClNO_4$	C, H, Cl, N
35	CH_3S	Cl	1.5	87	197	MeOH–H_2O	$C_{16}H_{14}ClNO_3S$	C, H, Cl, N, S
36	CH_3SO_2	Cl	1	63	169–170	MeOH–H_2O	$C_{16}H_{14}ClNO_5S$	C, H, Cl, N, S
37	H	Br	1.5	90	199	EtOAc–hex	$C_{15}H_{12}BrNO_3$	C, H
38	F	Br	1.5	80	217	EtOAc	$C_{15}H_{11}BrFNO_3$	C, H, N
39	H	$(CH_2)_2OCH_3$	2	67	140	CH_2Cl_2–eth–hex	$C_{18}H_{19}NO_4$	C, H
40	F	$(CH_2)_2OCH_3$	2	83	148–149	CH_2Cl_2–eth	$C_{18}H_{18}FNO_4$	C, H
41	Cl	$(CH_2)_2OCH_3$	2	85	160	acet–hex	$C_{18}H_{18}ClNO_4$	C, H
42	H	$(CH_2)_8OCH_3$	12	85	110–111	eth–hex	$C_{19}H_{21}NO_4$	C, H, N
43	F	$(CH_2)_3OCH_3$	12	94	135–136	eth–hex	$C_{19}H_{20}FNO_4$	C, H, N
44	Cl	$(CH_2)_3OCH_3$	12	70	161–162	eth–hex	$C_{19}H_{20}ClNO_4$	C, H, N

[a] See Table I for key to abbreviations. [b] Elements shown analyzed to within ±0.4% of the calculated values. [c] For an alternative synthesis of this compound, see ref 6.

Table III. Antiinflammatory and Analgesic Activities of 5-Aroyl-6-substituted-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids

no.	rat paw assay, phenylbutazone = 1[a]	mouse writhing assay, aspirin = 1[b]
23	43 (23–88)[c]	250[d] (24)[e]
24	43 (28–67)	250[d] (24)
25	103 (58–179)	302 (166–574)[c]
26	122 (65–228)	167 (108–274)
27	73 (39–167)	130[d] (24)
28	26 (11–59)	108 (82–143)
29	46 (17–114)	121 (75–209)
30	10 (2–47)	246 (43–1563)
31	32 (11–324)	158 (68–417)
32	139 (74–277)	151 (114–198)
33	88 (36–409)	167 (93–323)
34	55 (31–112)	201 (150–278)
35	68 (23–161)	100[d] (24)
36	<1[d] (12)[f]	≤0.8[d] (16)
37	7.4 (4.3–13)	314 (166–622)
38	96 (54–209)	120[d] (24)
39	≤0.3[d] (12)	7.6 (4.1–13)
40	≤0.3[d] (12)	1.1 (0.6–5.2)
41	<0.3[d] (12)	5 (2.5–12)
42	<10[d] (12)	≤3[d] (16)
43	<3[d] (12)	~1[d] (32)
44	1.2 (0–7.4)	≥1.5[d] (16)
46[h]	<7[d] (18)	40[d] (30)

[a] ED_{30} = 15 mg/kg. [b] ED_{50} = 70 mg/kg. [c] 95% confidence limits. [d] Graphical estimate only. [e] Number of mice. [f] Number of rats. [h] Tested as dicyclohexylammonium salt.

the compounds showed substantial activity with the dichloro compound **33** being several times more potent than indomethacin (see Table IV). These compounds were also evaluated for gastrointestinal erosive activity in a 7-day assay in rats. The minimum dose effective in causing erosion (MED) was then used to calculate a therapeutic ratio for the compounds (MED divided by the ED_{30} for the carrageenan rat paw assay). The dichloro compound, which displayed the highest activity in the chronic models of inflammation, was also the most erosive. Several of the other compounds did, however, show better therapeutic ratios, two of which, **25** and **31**, were not greatly different from zomepirac.

Experimental Section

The animal assays referred to above were carried out as described below.

(1) Inhibition of Carrageenan-Induced Edema. This assay was conducted as described in recent publications from these laboratories.[15]

(2) Inhibition of Cotton Pellet Granuloma. This assay was carried out by a modification[16] of a procedure first described by Meier et al.[17]

(3) Inhibition of Adjuvant-Induced Arthritis. This assay was performed by using a modification[16] of a procedure of Pearson.[18]

(4) Inhibition of Phenylquinone-Induced Writhing. This assay was conducted as described by Rooks et al.[16]

(5) Chronic Gastrointestinal Erosive Activity. This assay was carried out as described in the previous publication in this series of compounds.[2]

Physical Constants. The melting points were determined in a Mel-Temp melting point apparatus and are corrected. The IR spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrophotometer as solutions in chloroform. The UV spectra were recorded in methanol solution with a Perkin-Elmer Model 402 ultraviolet–visible spectrometer. The NMR spectra were measured with a Varian T-60 or a Varian HA-100 NMR spectrometer in $CDCl_3$ solutions. The chemical shifts are ex-

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Table IV. Antiinflammatory Profile of Selected 5-Aroyl-6-substituted-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids

no.	rat paw, phenylbutazone = 1[a]	mouse writhing, aspirin = 1[a]	cotton pellet, indomethacin = 1[b]	adjuvant arthritis, naproxen = 1[c]	GI erosion, MED,[d] mg/kg per day	therapeutic ratio[e]
23	43	250	1 (63)[f]	1 (60)[f]	~1.7 (15)[f]	~5
24	43	250	0.7 (72)	3 (36)	2.5 (15)	7
25	103	302	~1 (106)	~3 (118)	1.2–1.7 (60)	8–12
26	122	167	~2 (92)	3.5 (120)	~0.6 (45)	~5
30	10	246	0.6 (36)	≤8 (47)	~1.7 (47)	~1
31	32	158	0.2 (36)	11 (96)	5 (96)	11
32	139	151	1 (36)	13 (60)	~0.3 (60)	~3
33	88	167	3 (36)	40 (107)	~0.2 (107)	~1
34	55	201	0.7 (36)	4 (95)	~1.3 (95)	~5
zomepirac[g]	26 (13–62)[h]	36 (29–44)[h]			10	17
naproxen	11 (7–17)	7 (4–12)	0.2	1	30	22
indomethacin	16 (8–31)	~60 (100)[i]	1	7		

[a] Data for compounds **23–26** and **30–34** taken from Table III. ED_{30} of phenylbutazone = 15 mg/kg (rat paw). ED_{50} of aspirin = 70 mg/kg (mouse writhing). [b] ED_{50} = 3 mg/kg (2.0–4.6). [c] ED_{50} = 1.7 mg/kg (0.9–2.8). [d] Gastrointestinal erosion, 7-day chronic assay; minimum effective dose; see Experimental Section. [e] MED GI erosion/ED_{30} rat paw. [f] Number of rats. [g] Data for zomepirac taken from ref 2; data for naproxen and indomethacin taken from ref 19. [h] 95% confidence limits. [i] Number of mice.

pressed in parts per million (δ) from internal Me_4Si. The low-resolution mass spectra were obtained with Atlas CH-4, Varian MAT CH-7, and AEI MS-9 spectrometers. The high-resolution mass spectra were recorded on a Varian MAT 311A mass spectrometer.

Acylation of the Bicyclic Esters III. Method A. Vilsmeier–Haack Reaction. A solution of the appropriate known *N,N*-dimethylbenzamide (10 mmol) and phosphorus oxychloride (10 mmol) in anhydrous 1,2-dichloroethane (50 mL) was heated at reflux temperature in a nitrogen atmosphere for 1 h. A solution of the bicyclic ester III (R^2 = CH_3, CH_3CH_2; R^3 = *i*-Pr; 5 mmol) in the same solvent (10 mL) was added and heating at reflux temperature was maintained for the time indicated in Table I. The solution was cooled to room temperature, a solution of sodium acetate (50 mmol) in water (60 mL) was added cautiously, and the mixture was heated under reflux for 8–24 h. The organic phase was separated, washed with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified by the method indicated in Table I. If the ester was an oil, it was usually characterized only by its spectroscopic properties; e.g., compound **6** had UV 210, 246, 314 nm (ϵ 9770, 7940, 14 800); IR 1730 cm^{-1}; NMR δ 0.97 (t, 3 H, $J \simeq 6.5$ Hz), 1.27 (d, 6 H, $J = 6$ Hz), 2.20 (q, 2 H, $J \simeq 6.5$ Hz), 2.77 (m, 2 H), 3.92 (m, 1 H), 4.23 (m, 2 H), 5.00 (m, 1 H), 5.92 (s, 1 H), 7.38 (m, 5 H).

Crystalline esters were characterized by elemental analysis and by the full range of spectroscopic properties.

Method B. Noncatalyzed Acylation of Bicylic Esters III with Acid Chlorides in Boiling Xylene. A solution of the bicyclic ester (10 mmol) in dry xylene (20–90 mL) containing the acid chloride (1–3 equiv) was heated at reflux temperature for the period of time indicated in Table I. The solvent was removed in vacuo and the residue was purified either by column chromatography on silica gel using hexane–ethyl acetate (9:1) for compounds **8–13**, **15**, **16**, and **22** or by the technique given in Table I.

Methyl 5-[4-(Methylsulfonyl)benzoyl]-6-chloro-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (14). A solution of 80–85% *m*-chloroperbenzoic acid (1.94 g) in dry dichloromethane (20 mL) was added to a stirred and cooled (0 °C) solution of compound **13** (1.13 g, 3.23 mmol) in the same solvent (100 mL). After completion of the addition, stirring at 0 °C was continued for 40 min at which time it was shaken with a saturated aqueous solution of sodium bicarbonate (30 mL). The organic phase was separated, washed well with saturated salt solution, dried over sodium sulfate, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (110 g), first eluting with hexane–ethyl acetate (7:3) and then 1:1 hexane–ethyl acetate. The solid product (0.84 g) was then further purified by crystallization (see Table I).

1,6-Dimethyl-5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (46). A solution of the ester **1** (0.311 g, 1 mmol) in anhydrous dimethoxyethane (10 mL) was added dropwise to a stirred suspension of sodium hydride (50% in mineral oil, 0.53 g, 1.1 mmol) in the same solvent (10 mL) maintained in an atmosphere of nitrogen. After 0.5 h a solution of methyl iodide (0.31 mL, 0.71 g, 5 mmol) in dimethoxyethane (5 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and the product was extracted into ether. The extract was dried and evaporated in vacuo and the residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (9:1) as the eluting solvent. The ester **45** was obtained as an oil (0.252 g, 77% yield): UV 247, 315 nm (ϵ 6920, 16 600); MS, *m/e* 325 (M^+).

The crude ester was then hydrolyzed in the manner described below and the carboxylic acid **46**, obtained as an oil, was dissolved in dichloromethane and an equal weight of dicyclohexylamine was added thereto. After 18 h the solvent was removed in vacuo and benzene was added to the residue. The crystalline solid (57% yield based on the ester) was collected by filtration and then washed successively with benzene and hexane. After drying in vacuo it had mp 134–135 °C. Anal. ($C_{29}H_{40}N_2O_3$) C, H, N.

Hydrolysis of the Esters with Potassium Carbonate in Aqueous Methanol. A solution of the ester (10 mmol) in methanol (60–180 mL) containing water (10–100 mL) and potassium carbonate (10–40 mmol) was heated at reflux temperature in a nitrogen atmosphere for the time specified in Table II. The methanol was removed in vacuo, the residue was diluted with water, and the solution obtained thereby was extracted with ethyl acetate. The aqueous alkaline phase was cooled to 0 °C and made acidic with 2 N hydrochloric acid. The product was extracted into ethyl acetate, and the extract was dried and then evaporated in vacuo. The residue was crystallized from the solvent system indicated in Table II.

Registry No. **1**, 107115-61-7; **2**, 107115-62-8; **3**, 66635-94-7; **4**, 107115-63-9; **5**, 107115-64-0; **6**, 107115-65-1; **7**, 107115-66-2; **8**, 81564-90-1; **9**, 81564-96-7; **10**, 81564-94-5; **11**, 81564-95-6; **12**, 81564-97-8; **13**, 81564-98-9; **14**, 81565-06-2; **15**, 81564-91-2; **16**, 81564-99-0; **17**, 107115-67-3; **18**, 107115-68-4; **19**, 107115-69-5; **20**, 107115-70-8; **21**, 107115-71-9; **22**, 107115-72-0; **23**, 107115-73-1; **24**, 66635-95-8; **25**, 107115-74-2; **26**, 83073-36-3; **27**, 83073-35-2; **28**, 107115-75-3; **29**, 83073-37-4; **30**, 81564-92-3; **31**, 81565-01-7; **32**, 81565-00-6; **33**, 80965-12-4; **34**, 81565-02-8; **35**, 81565-03-9; **36**, 81565-10-8; **37**, 81564-93-4; **38**, 81565-04-0; **39**, 107115-76-4; **40**, 107115-77-5; **41**, 107115-78-6; **42**, 107115-79-7; **43**, 107115-80-0; **44**, 107115-81-1; **45**, 107115-82-2; **46**, 107115-83-3; **46**·dicyclohexylamine, 107115-84-4; **III** (R_2 = CH_3, R_3 = $CH(CH_3)_2$), 68204-67-1; **III** (R_2 = Et, R_3 = $CH(CH_3)_2$), 83820-76-2; **III** (R_2 = Cl, R_3 = CH_3), 81564-88-7; **III** (R_2 = Br, R_3 = CH_3), 81564-89-8; **III** (R_2 = $H_3CO(CH_2)_2$, R_3 = $CH(CH_3)_2$), 83820-77-3; **III** (R_2 = $H_3CO(CH_2)_3$, R_3 = $CH(CH_3)_2$), 83820-79-5; $C_6H_5CON(CH_3)_2$, 611-74-5; 4-$H_3CC_6H_4CON(CH_3)_2$, 14062-78-3; 4-$FC_6H_4CON(CH_3)_2$, 24167-56-4; 4-$ClC_6H_4CON(CH_3)_2$, 14062-80-7; 4-$H_3COC_6H_4N(CH_3)_2$, 7291-00-1; C_6H_5COCl, 98-88-4; 4-$H_3CC_6H_8COCl$, 874-60-2; 4-FC_6H_4COCl, 403-43-0; 4-ClC_6H_4COCl, 122-01-0; 4-$H_3COC_6H_4COCl$, 100-07-2; 4-$H_3CSC_6H_4COCl$, 1442-06-4.