Articles

Aroyl(aminoacyl)pyrroles, a New Class of Anticonvulsant Agents

John R. Carson,*,† Richard J. Carmosin,† Philip M. Pitis,† Jeffry L. Vaught,†,‡ Harold R. Almond,† James P. Stables,§ Harold H. Wolf,|| Ewart A. Swinyard,|| and H. Steve White||

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477-0776, Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Federal Building, Room 114, Bethesda, Maryland 20892, and Anticonvulsant Screening Project, Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, Utah 84108

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2-Aroyl-4-(ω-aminoacyl)- (**4**) and 4-aroyl-2-(ω-aminoacyl)pyrroles (**9**) represent a new, structurally novel class of anticonvulsant agents. Compounds of type **4** were prepared by Friedel−Crafts acylation of a 2-aroylpyrrole with an ω-chloroacyl chloride followed by displacement of the chloro group by a primary or secondary amine. Compounds of type **9** were prepared by Friedel−Crafts aroylation of a 2-(ω-chloroacyl)pyrrole followed by displacement by an amine. These compounds were active in the mouse and rat maximal electroshock tests but not in the mouse metrazole test. The lead compound, RWJ-37868, 2-(4-chlorobenzoyl)-4-(1-piperidinylacetyl)-1,3,5-trimethylpyrrole (**4d**), showed potency and therapeutic index comparable to those of phenytoin and carbamazepine and greater than those of sodium valproate. This compound blocked bicuculline induced seizures, did not elevate seizure threshold following iv infusion of metrazole, and blocked influx of Ca^{2+} ions into cerebellar granule cells induced by K^+ or veratridine.

Introduction

The conditions grouped under the term epilepsy constitute an area of continuing medical need. It has been estimated that up to 20% of the patients with epilepsy using the first generation of antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, sodium valproate, and diazepam) were not able to obtain adequate control of seizures.[1] A group of new drugs including felbamate, gabapentin, lamotrigine, oxcarbamazepine, topiramate, vigabatrin, and zonisamide are entering clinical practice.[2] The impact of these newly marketed drugs has yet to be fully evaluated.

The classification of antiepileptic drugs by structure and mechanism is difficult to do precisely, but some generalizations can be formulated. Phenytoin, phenobarbital, and carbamazepine contain a urea function in proximity to phenyl rings. They prevent seizure spread and are thought to act as sodium channel modulators.[3,4] Sodium valproate is the lone example of a simple branched chain aliphatic carboxylate salt. It elevates seizure threshold as well as preventing seizure spread. The benzodiazepines (diazepam, clonazepam, nitrazepam, and clobazam) are GABA-A receptor modulators which elevate seizure threshold and are used to treat generalized absence seizures. Vigabatrin, gabapentin, and progabide, though they may not be mechanistically homogeneous, all share the GABA backbone. Topiramate[5] and zonisamide both have a sulfamyl group. Lamotrigine is a halophenyl amino-substituted polyaza aromatic.

New anticonvulsant agents continue to emerge.[6−12] The polyazaaromatics of Kelley and co-workers[9,10] and Moreau and co-workers[12] might be grouped with lamotrigine. The phenylacetyltriflamides of Wolfe and co-workers[8] may fall within the sulfamyl class. The enaminones described by Scott and co-workers[13] appear to be a novel class. Of all the structural classes of anticonvulsants, the only drug to show the pattern of two aromatic rings and a dialkylaminoalkyl chain, which is so prevalent among CNS drugs, is flunarizine.[14] Flunarizine appears to act by preventing calcium overload. The structures of some newer anticonvulsants have been summarized.[15]

No general theories have gained acceptance, which would explain why many epileptic patients are not adequately treated with current therapy. The strategy of seeking drugs that are structurally, mechanistically, and pharmacologically unique and testing them in these patients still seems to be an appropriate approach. We describe herein a series of anticonvulsant aroyl(aminoacyl)pyrroles that, we believe, fulfill these criteria.

Chemistry

The compounds showing anticonvulsant activity are of types **4** and **9**. The compounds of type **4** were prepared according to Scheme 1. Aroylpyrroles (**2**) where $R_1 = CH_3$, R_2 and $R_3 = H$ were prepared by refluxing the requisite aroyl chloride with *N*-methylpyrrole in toluene.[16] The aroylpyrroles where R_1, R_2, and $R_3 = CH_3$ or H were prepared as previously described.[17,18] Friedel−Crafts acylation of the aroylpyrroles with a ω-chloroalkanoyl chloride followed by displacement of chloride by the desired amine gave compounds of type **4**. Compounds of type **9** were prepared by Scheme 2 in which the order of attachment of the substituents was reversed. Compound **10** was

* Author to whom correspondence should be addressed.
† The R. W. Johnson Pharmaceutical Research Institute.
‡ Present address: Cephalon, Inc., West Chester, PA 19380.
§ National Institutes of Health.
|| University of Utah.
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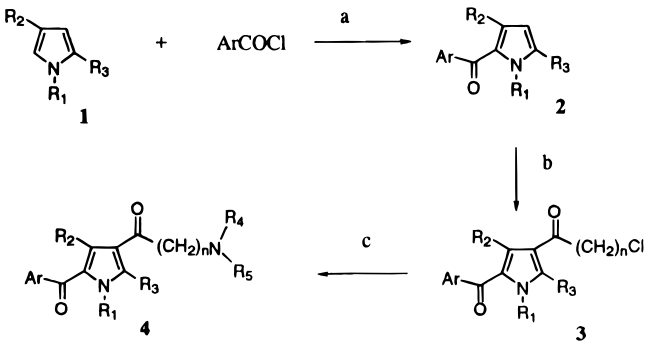
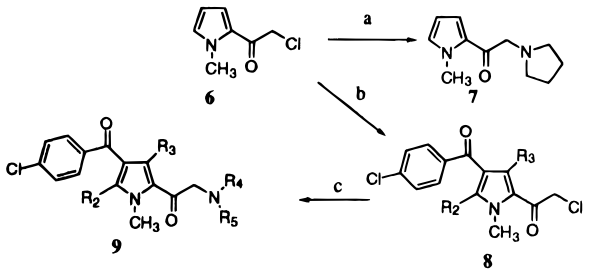
Scheme 1[a]



[a] Reagents and conditions: (a) 110−140 °C; (b) $Cl(CH_2)_nCOCl$, $AlCl_3$; (c) R_4NHR_5.

Scheme 2[a]



[a] Reagents and conditions: (a) pyrrolidine; (b) 4-ClPhCOCo, $AlCl_3$; (c) R_4NHR_5.

prepared by PPA isomerization of **4a**. Compounds **11** and **12** were obtained by reduction of **4a** with DIBAL. Compound **13** was prepared analogously to Scheme 1, starting with ethyl 1-methylpyrrole-2-carboxylate instead of a 2-aroylpyrrole. Reaction of **3a** with sodium formylformamide afforded the *N*,*N*-diformyl compound. Hydrolysis of the *N*,*N*-diformyl compound gave **4jj**. Compound **4ii** arose via nucleophilic aromatic substitution of chlorine by pyrrolidine. Compound **13** was prepared analogously to compounds of type **4** using ethyl 1-methylpyrrole-2-carboxylate as the starting material.

The physical properties of the intermediates and final products are summarized in Tables 1 and 2.

Results and Discussion

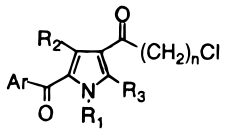
Biological Activity. The pharmacological evaluation of the compounds was carried out under the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch of the NINDS. The methods employed have been previously described.[4] The compounds were initially screened in the mouse maximal electroshock seizure (MES) test and the subcutaneous metrazole (scMET) test. Minimal motor impairment was measured by the rotorod (Tox) test. The compounds were classified into the following categories: active at <100 mg/kg (class 1), active at >100 mg/kg (class 2), inactive (class 3), and toxic or active but toxic (class 4). Compounds of class 1 and certain compounds of class 4 were then tested in the rat MES, scMET, and Tox tests. The rat classifications are as follows: 4/4 animals active, class 4; 3/4 animals active, class 3; 2/4 animals active, class 2; 1/4 animals active, class 1. The results of the classifications are shown in Table 1. The compounds that were active in mouse and rat were then evaluated quantitatively. The results of the quantitative studies are shown in Table 3.

The aroyl(aminoacyl)pyrroles, in general, were active in the MES test, indicative of their ability to prevent seizure spread. They were inactive in the scMET test, a test used to identify compounds that elevate seizure threshold. The aroyl(aminoacyl)pyrroles thus fall in a class with phenytoin and carbamazepine and are different in profile from the benzodiazepines, which are only active in the scMET test, and from sodium valproate, which is active in both the MES and scMET tests. The more potent compounds of the aroyl(aminoacyl)pyrrole series are comparable in potency to phenytoin and carbamazepine. Their protective indices in mice are slightly less than those of phenytoin and carbamazepine. The compounds of the aroyl(aminoacyl)pyrrole series, however, are substantially more potent than sodium valproate, and many have a substantially greater protective indices.

The compounds that were found to have acceptable potency and protective index in mouse and rat were evaluated in a series of secondary tests. These tests, the methods of which have been published elsewhere,[4] included the following: sc bicuculline, sc picrotoxin, and sc strychnine anticonvulsant tests, the kindled rat test and seizure threshold following iv infusion of metrazole. The biochemical tests performed included *in vitro* GABA receptor binding, adenosine uptake, and Ca^{2+} influx into cerebellar granule cells induced by elevated K^+ or by veratridine.

Compound **4d**, RWJ 37868, was chosen as the compound for more intensive scrutiny. Compound **4d** blocked seizures induced by bicuculline [ED_{50} (mg/kg,

Table 1. Physical Data for Chloro Ketones



no.	*n*	R_1	R_2	R_3	Ar	MP, °C	recryst[a] solv	formula	yield, %
3a	1	CH_3	H	H	*p*-ClPh	152−154	$CHCl_3$	$C_{14}H_{11}Cl_2NO_2$	83
3b	1	CH_3	CH_3	CH_3	*p*-ClPh	141−143	EtOAc/MCH	$C_{16}H_{15}Cl_2NO_2$	31
3c	1	CH_3	H	H	*o*-ClPh	121−124	EtOAc/MCH	$C_{14}H_{11}Cl_2NO_2$	91
3d	1	CH_3	H	H	*p*-CH_3OPh	157−159	EtOAc/MCH	$C_{15}H_{14}ClNO_2$	90
3e	1	CH_3	H	H	*p*-NO_2Ph	173−176	EtOAc/EtOH	$C_{14}H_{11}ClN_2O_4$	60
3f	1	CH_3	H	H	*m*-ClPh	116−119	toluene	$C_{14}H_{11}Cl_2NO_2$	67
3g	1	H	H	H	*p*-ClPh	196−197	*b*	$C_{13}H_9Cl_2NO_2$	91
3h	1	CH_3	CH_3	CH_3	2,4-ClPh	100−102	MCH	$C_{16}H_{14}Cl_3NO_2$	88
3i	3	CH_3	H	H	*p*-ClPh	95−97	MCH	$C_{16}H_{15}Cl_2NO_2$	39
3j	4	CH_3	CH_3	CH_3	*p*-ClPh	60−65	*c*	$C_{19}H_{21}Cl_2NO_2$	79

[a] MCH is methylcyclohexane. [b] Used without purification. [c] Purified by flash chromatography on silica gel with 5% acetone in hexane.

Table 2. Structure−Activity Data for Aroyl(aminoacyl)pyrroles

no.	*n*	R_1	R_2	R_3	R_4/R_5	R_5	Ar	mouse class[a]	rat[b] class	mp, °C	recryst solv	formula[c]
4a	1	CH_3	H	H	$-(CH_2)_4-$		*p*-ClPh	1	4	118−122	2-PrOH	$C_{18}H_{19}ClN_2O_2$
4b	1	CH_3	H	H	$-(CH_2)_5-$		*p*−ClPh	1	4	114−116	2-PrOH	$C_{19}H_21ClN_2O_2$
4c	1	CH_3	CH_3	CH_3	$-(CH_2)_2O(CH_2)_2-$		*p*-ClPh	1	3	96−98	2-PrOH	$C_{21}H_{23}ClN_2O_3$
4d	1	CH_3	CH_3	CH_3	−(CH2)5−		*p*-ClPh	1	4	102−104	2-PrOH	$C_{21}H_{25}ClN_2O_2$
4e	1	CH_3	H	H	$-CH_2CH_3$	CH_2CH_3	*p*-ClPh	1	4	182−185	CH_3CN	$C_{18}H_{21}ClN_2O_2\cdot HCl$
4f	1	CH_3	CH_3	CH_3	$-(CH_2)_4-$		*p*-ClPh	1	4	115−117	EtOH	$C_{20}H_{23}ClN_2O_2$
4g	1	CH_3	CH_3	CH_3	−CH−NCH−CH−		*p*-ClPh	3	3	195−197	EtOH	$C_{19}H_{18}ClN_3O_2$
4h	1	CH_3	CH_3	CH_3	$-CH_2CH_2$(3,4-CH_3OPh)	H	*p*-ClPh	1	3	210−213	EtOH	$C_{26}H_{29}ClN_2O_4\cdot HCl$
4i	1	CH_3	H	H	$-(CH_2)_2O(CH_2)_2-$		*p*-ClPh	2	4	131−135	CH_3CN	$C_{18}H_{19}ClN_2O_3$
4j	1	CH_3	CH_3	CH_3	Bn	CH_3	*p*-ClPh	1	4	155−156	EtOH	$C_{24}H_{25}ClN_2O_2\cdot C_2H_2O_2$
4k	1	CH_3	H	H	$-(CH_2)_6-$		*p*-ClPh	1	3	195−198	CH_3CN	$C_{20}H_{23}ClN_2O_2\cdot HCl\cdot 0.25H_20$
4l	1	CH_3	H	H	$-(CH_2)_4-$		*o*-ClPh	4	2	113−116	EtOH	$C_{18}H_{19}ClN_2O_2\cdot HCl$
4m	1	CH_3	H	H	$-CH_2CH(CH_3)OCH-(CH_3)CH_2-$		*p*-ClPh	1	1	258−260	MeOH	$C_{20}H_{23}ClN_2O_3\cdot HCl$
4n	1	CH_3	H	H	adamantane		*o*-ClPh	1	3	248(d)	MeOH	$C_{24}H_{27}N_2O_2\cdot HCl\cdot 0.25H_2O$
4o	1	CH_3	H	H	$-CH(CH_2OH)(CH_2)_3-$		*p*-ClPh	1	4	87−88	MeOH	$C_{19}H_{21}ClN_2O_3\cdot 0.8C_4H_4O_4\cdot 0.66H_2O$
4p	1	CH_3	H	H	adamantane		*p*-ClPh	3		273(d)	MeOH	$C_{24}H_{27}ClN_2O_2\cdot HCl$
4q	1	CH_3	H	H	$-(CH_2)_7-$		*p*-ClPh	2		211−213	CH_3CN	$C_{21}H_{25}ClN_2O_2\cdot HCl\cdot 0.25H_2O$
4r	1	CH_3	H	H	−CH=NCH=CH−		*p*-CH_3OPh	1	1	136−138	*d*	$C_{18}H_{17}N_3O_3$
4s	1	CH_3	H	H	$-(CH_2)_5-$		*p*-CH_3OPh	1	4	190−192	2-PrOH	$C_{20}H_{24}N_2O_3\cdot HCl$
4t	1	CH_3	H	H	$-CH_2CH_2C[(CH_2)_5]-CH_2CH_2-$		*o*-ClPh	3		268−271	EtOH	$C_{24}H_{29}ClN_2O_2\cdot HCl\cdot 0.3H_2O$
4u	1	CH_3	H	H	$-CH_2CH_2CH(Bn)-CH_2CH_2-$		*p*-ClPh	3		226−227	MeOH	$C_{26}H_{27}ClN_2O_2\cdot HCl$
4v	1	CH_3	H	H	$-CH_2CH_2CH(p$-FBz)$-CH_2CH_2-$		*p*-CH_3OPh	3		135−137	EtOH	$C_{27}H_{27}FN_2O_2$
4w	1	CH_3	H	H	$-(CH_2)_2O(CH_2)$ 2−		*p*-ClPh	1		125−127	CH_3CN	$C_{18}H_{19}ClN_2O_3$
4x	1	CH_3	H	H	cyclohexyl	CH_2CH_3	*p*-ClPh	4	4	171−176	EtOH	$C_{22}H_{27}ClN_2O_2\cdot C_4H_4O_4$
4y	1	CH_3	H	H	$-(CH_2)_2O(CH_2)_2-$		*p*-NO_2Ph			141−143	EtOH	$C_{18}H_{19}N_3O_5$
4z	1	CH_3	H	H	$-(CH_2)_5-$		*p*-NO_2Ph	1	4	225−227	EtOH	$C_{19}H_{21}N_3O_4\cdot HCl$
4aa	1	CH_3	H	H	$-CH_2C(CH_3)_2(CH_2)_3-$		*p*-ClPh	2		105−107	CH_3CN	$C_{21}H_{25}ClN_2O_2$
4bb	1	CH_3	H	H	$-(CH_2)_5-$		*m*-ClPh	1	2	190−193	CH_3CN	$C_{19}H_{21}ClN_2O_2\cdot HCl$
4cc	1	CH_3	H	H	$-(CH_2)_4-$		*m*-ClPh	1	0	243−245	CH_3CN	$C_{18}H_{19}ClN_2O_2\cdot HClO_4$
4dd	1	CH_3	H	H	$-(CH_2)_2O(CH_2)_2-$		*m*-ClPh	1	2	198−200	CH_3CN	$C_{18}H_{19}ClN_2O_3\cdot HCl$
4ee	1	H	H	H	$-(CH_2)_4-$		*p*-ClPh	1	4	243−245(d)	CH_3CN	$C_{17}H_{17}ClN_2O_2\cdot HClO_4$
4ff	1	H	H	H	$-(CH_2)_2O(CH_2)_2-$		*p*-ClPh	1	3	173−176	CH_3CN	$C_{17}H_{17}ClN_2O_3$
4gg	1	CH_3	H	H	H	CH_2CH_3	*p*-ClPh	1	4	259−262	MeOH	$C_{16}H_{17}ClN_2O_2\cdot HCl\cdot 0.25H_2O$
4hh	1	CH_3	H	H	$-CH_2CH_3$	CH_2CH_3	*p*-CH_3OPh	1	4	165−168	2-PrOH	$C_{19}H_{24}N_2O_3\cdot HCl$
4ii	3	CH_3	H	H	$-(CH_2)_4-$		*p*-pyrrol-Ph	1		203−206	CH_3CN	$C_{24}H_{31}N_3O_2\cdot HCl\cdot O.4CH_3CN$
4jj	1	CH_3	H	H	H	H	*p*-ClPh	1	4	290(d)	MeOH	$C_{14}H_{13}ClN_2O_2\cdot HCl$
4kk	1	CH_3	CH_3	CH_3	$-CH_2CH_3$	CH_2CH_3	*p*-ClPh	1	4	176−178	EtOH	$C_{20}H_{25}ClN_2O_2\cdot 1.5C_4H_4O_4\cdot 0.1$EtOH
4ll	1	CH_3	CH_3	CH_3	$-(CH_2)_4-$		2,4-diClPh	4	4	177−179	2-PrOH	$C_{20}H_{22}Cl_2N_2O_2\cdot HCl\cdot 0.4H_2O\cdot 0.4$(2-PrOH)
4mm	1	CH_3	CH_3	CH_3	$-CH_2CH_3$	CH_2CH_3	2,4-diClPh	4	3	165−168	EtOH	$C_{20}H_{24}Cl_2N_2O_2\cdot C_4H_4O_4$
4nn	1	CH_3	CH_3	CH_3	$-CH_3$	CH_3	2,4-diClPh	4	4	119	EtOH	$C_{18}H_20Cl_2N_2O_2\cdot HCl\cdot 0.75H_2O$
4oo	1	CH_3	H	H	$-C(CH_3)$=NCH=CH−		*p*-ClPh	1	3	218−219	*d*	$C_{18}H_{16}ClN_3O_2$
4pp	4	CH_3	CH_3	CH_3	$-CH_2CH_3$	CH_2CH_3	*p*-ClPh	1	2	71−73	MeOH	$C_{23}H_{31}ClN_2O_2$
4qq	1	CH_3	CH_3	CH_3	$-(CH_2)_5-$		*p*-ClPh	1	0	177−178	MeOH	$C_{24}H_{31}ClN_2O_2\cdot C_4H_4O_4$
4rr	1	CH_3	H	H	$-(CH_2)_5-$		*o*-ClPh	1	1	169−171	EtOH	$C_{19}H_{21}ClN_2O_2\cdot C_4H_4O_4$
7								3	1	126−129	2-PrOH	$C_{11}H_{16}N_2O\cdot C_4H_4O_4$
9a	1	CH_3	H	H	$-(CH_2)_5-$		*p*-ClPh	1	2	129−130	2-PrOH	$C_{19}H_{21}ClN_2O_2$
9b	1	CH_3	H	H	$-(CH_2)_4-$		*p*-ClPh	4	3	265−267	EtOH	$C_{18}H_{19}ClN_2O_2\cdot HCl$
9c	1	CH_3	H	H	$-(CH_2)_2O(CH_2)_2-$		*p*-ClPh	1	2	264−267	MeOH	$C_{18}H_{19}ClN_2O_3\cdot HCl$
10								3		105−108	CH_3CN	$C_{18}H_{19}ClN_2O_2$
11								3		122−124	CH_3CN	$C_{18}H_{23}ClN_2O_2$
12								3		131−134	CH_3CN	$C_{18}H_{21}ClN_2O_2$
13								3		198−201		$C_{14}H_{20}N_3O_3\cdot HCl$

[a] Mouse classifications: ip active at <100 mg/kg (class 1), active at >100 mg/kg (class 2), inactive (class 3), and toxic or active but toxic (class 4). [b] The rat classifications are as follows: po 4/4 animals active, class 4; 3/4 animals active, class 3; 2/4 animals active, class 2; 1/4 animals active, class 1. [d] Purified by flash chromotography on silical gel 10:1 CH_2Cl_2/MeOH.

ip) 25.2 (8.84−61.1)]. Phenytoin and carbamazepine are inactive in this test while sodium valproate is active. Compound **4d** did not block seizures induced by picrotoxin or strychnine and was inactive in the kindled rat procedure. Compound **4d** showed no significant effect on seizure threshold following iv infusion in mice. In this test, phenytoin lowers seizure threshold, carbamazepine has no effect, and sodium valproate raises minimal seizure threshold. These findings suggest that, in contrast to phenytoin, compound **4d** lacks proconvulsant activity. Compound **4d** had potent, long-lasting local anesthetic activity when injected into the mouse hind limb. Compound **4d**, at a concentration of 100 mM, blocked influx of Ca^{2+} into cerebellar granule cells induced by elevated K^+ or by veratridine. Unpublished results from the ADD laboratories have demonstrated that flunarizine shows activity in this test. Compound **4d** was not active in inhibiting *in vitro* GABA receptor binding or adenosine uptake.

SAR. Starting with the basic structure **4**, modifications were carried out to try to define the nature of the pharmacophore. Both acyl functions seem to be necessary for activity. Compound **7**, which lacks an aroyl group was inactive. Compounds **11** and **12** where one or both of the carbonyl groups were reduced were also inactive. Compound **13** where the aroyl group was replaced by a carboxylic ester was inactive. Activity was found in isomers **4** and **9** which, depending on the rotational preferences of the carbonyl groups, can be

Table 3. Quantitative Studies

no.	mouse MES[a,e] ED_{50}	mouse tox[b,e]	mouse TI[c]	rat MES ED_{50}[a,e]	rat tox[d,e]
4a	49.1 (36.9−70)	240.40 (197.62−271.36)	4.89	17.9 (13.7−24.4)	>500[f]
4b	24.4 (20.1−30.1)	74.2 (52.8−94.4)	3.05	8.40 (5.64−12.1)	341.7 (274−401)
4c	87.6 (47.3−161)	233.4 (147.6−372.8)	2.66		
4d	23.9 (17.3−30.7)	113 (75.3−146)	4.73	28.1 (16.7−41.3)	>500[f]
4e	14.4 (13.0−16.8)	40.5 (32.8−47.1)	2.81	19.3 (31.0−41.8)	>500[f]
4f	15.2 (11.2−20.7)	54.8 (32.9−81.4)	3.60	16.2 (10.3−23.2)	202.7 (131−270)
4k	27.5 (22.1−35.1)	46.1 (39.3−55.3)	1.67	22.0 (11.8−38.3)	>500[f]
4n	159. (119−236)	>250	>1.57		
4cc	16.5 (14.4−18.6)	55.6 (38.3−74.6)	3.38		
4dd	37.4 (35.4−40.1)	110 (96.3−124)	2.96	72.0 (53.1−98.5)	>500[f]
4ff	86.2 (70.8−105)	84.1 (76.6−89.5)	0.98	41.0 (31.6−58.9)	88.0 (70−110)
4hh	33.0 (28.0−38.0)	45.1 (39.4−51.7)	1.37		
4kk	10.3 (8.6−12.4)	37.7 (35.2−41.5)	3.65	15.5 (10.7−20.85)	>250[f]
4ll	10.3 (8.5−12.5)	23.79 (16.94−30.08)	2.30	19.0 (15.8−233.94)	>200[f]
4mm	14.9 (11.6−17.8)	50.6 (45.9−56.3)	3.38	19.4 (13.3−27.6)	>500[f]
9a	59.71 (54.21−67.72)	141.00 (117.8−161.1)	2.36		
phenytoin[h]	6.48 (5.7−7.2)	42.8 (36.4−47.5)	6.6	23.2 (21.4−25.4)	>500[f]
carbamazepine[g]	9.9 (8.8−10.7)	47.8 (39.2−59.2)	4.93	36 (24.1−47.2)	
Na valproate[g]	287 (237−359)	483 (412−571)	1.7	395 (332−441)	859 (714−1148)

[a] Maximal electroshock seizures ED_{50}0 (mg/kg) ip. [b] TD_{50} (mg/kg) ip as measured by rotating rod test. [c] TD_{50}/ED_{50}. [d] TD_{50} (mg/kg) ip as measured by overt evidence of ataxia. [e] 95% confidence limits in parentheses. [f] Not toxic in a single two animal determination up to the indicated dose. [g] Values of the reference compounds were measured as part of the current study.

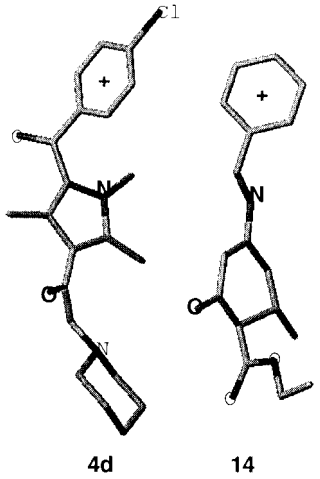


Figure 1. Structural comparison of **4d** and **14**; carbonyl O, amine N, and ring centers in superposition orientation.

isosteric. Isomer **10**, which is not isosteric with **4** and **9**, showed only toxicity.

Some substituent effects at the amino group could be seen. Primary (**4jj**), secondary (**4gg**), and tertiary amines are all active. Compounds with very bulky groups on nitrogen (e.g. **4t**, **4u**, and **4v**) were inactive. The *N*-cyclohexyl compound **4x** showed toxicity. The *N*-adamantyl compounds (**4n** and **4p**) were weakly active or inactive. Optimal activity seemed to reside in the compounds with moderate sized groups on nitrogen. *N*,*N*-Diethylamino, pyrrolidino, and piperidino groups all showed good activity and were somewhat more active than the morpholino compounds (**4c** vs **4d**). Chain lengths of one, three, and four carbon atoms between the carbonyl group and the amino group were tolerated without losing activity (**4ii**, **4pp**).

Substituent effects on the aromatic rings are more difficult to assess. The pyrroles bearing the 1,2,4-trimethyl substitution pattern, in general, showed good activity. In certain instances they were more potent than the analogous 1-methyl compound (**4f** vs **4a**). Compounds lacking methyl substitution on nitrogen were active. Only minor changes in activity resulted from varying the substitution pattern on the aroylphenyl group. The 4-chloro compound **4e** was more potent

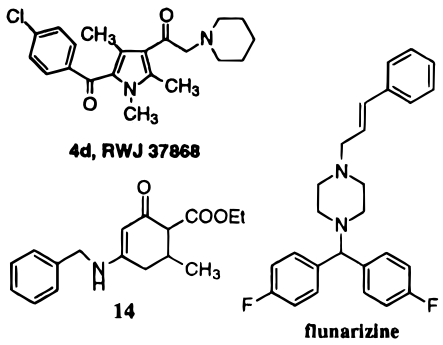


Figure 2.

than the corresponding 4-methoxy compound **4hh**. Compounds with an *o*-chloro group (**4rr**, **4ll**, and **4mm**) had good potency.

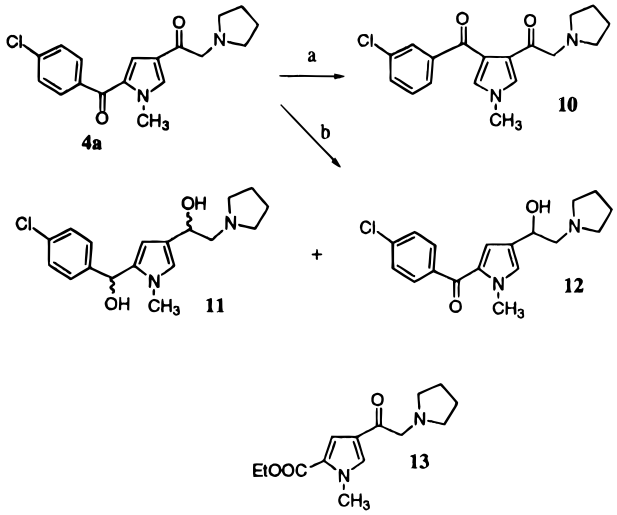
Among substances reported in the literature to possess anticonvulsant activity, a class that could have structural similarity to the aroyl(aminoacyl)pyrroles is the series of *N*-aryl and *N*-benzyl enaminones described by Scott and co-workers, typified by **14**.[13] Extensive charge delocalization involving the nitrogen atom and the carbonyl oxygen occurs in both acyl pyrroles[19] and enaminones.[20] To evaluate these charge effects well, structures **4d** and **14** were modeled and minimized with the SPARTAN program[21] using the AM1 model with geometry optimization. Superposition of the phenyl ring centers, the nitrogen atoms, and the carbonyl groups shows a congruent spatial relationship of like features (Figure 1).

The aroyl(aminoacyl)pyrroles and flunarizine are both anticonvulsants which possess a basic tail, and both are able to block calcium reuptake.

Conclusions

In summary, the 2-aroyl-4-(ω-aminoacyl)- (**4**) and 4-aroyl-2-(ω-aminoacyl)pyrroles (**9**) represent a new, structurally novel class of anticonvulsant agents. Since they are active in the in the MES but not the sc MET assay, they would seem to fall within the phenytoin−carbamazepine class. The prototype compound, **4d**, lacked proconvulsant activity and showed activity in the veratridine induced calcium entry assay.

Scheme 3[a]



[a] Reagents: (a) PPA; (b) DIBAL.

Structure−activity requirements were examined. Isomers of types **4** and **9** were active, but the isomer of type **10** was not. Both the aroyl function and the aminoacyl function were required for activity. Diverse substituents were tolerated on the aryl ring of the aroyl function and the pyrrole ring. Compact substituents were preferred on the amino group.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AC-300 (300 MHz), AM-360WB (MHz), or AM-400 (400 MHz) spectrometer with $(CH_3)_4Si$ as the internal standard. Chemical ionization mass spectra (CI-MS) were determined on a Finnegan 3300-6100 system with methane as the reagent gas. Elemental analyses were carried out by the Analytical Services group in Raritan, NJ. Where elemental analyses are reported by the symbols of the elements, the results are within 0.4% of the calculated values. The compounds of this paper have been described in preliminary form in a patent.[22] Representative procedures are presented here to illustrate each of the transformations shown in in Schemes 1−3.

Biology. The maximal electroshock tests in mouse were carried out by administration of a suspension of the test compound at doses of 30, 100, and 300 mg/kg ip to one to four mice. Separate tests were carried out, one with a 30 min observation time and one with a 4 h observation time. The maximal electroshock tests in rat were carried out by administration of a suspension of the test compound at doses 50 mg/kg po to a group of four animals. Separate tests were carried out with 0.25, 0.5, 1, 2, and 4 h observation times.

Molecular Modeling. Structures **4d** and **14** were modeled with the Spartan programs[21] using the AM1 model with geometry optimization. These conformations were transferred to the SYBYL[23] program where they were superimposed. The phenyl ring centers, carbonyl oxygens, and nitrogens (pyrrole to benzyl-N) were fit for minimum distances. The orientations are shown, side by side, in Figure 1: RMS deviation = 0.38 Å; volume **4d** = 320 Å^3; volume **14** = 254 Å^3; common volume = 168 Å^3.

(4-Methoxyphenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (2) (Ar = 4-Methoxyphenyl, R_1 = CH_3, R_2, R_3 = H). A solution of 5 g (0.060 mol) of *N*-methylpyrrole and 13.3 g (0.078 mol) of 4-methoxybenzoyl chloride in 50 mL of dry toluene was heated under reflux overnight with an argon stream bubbling through the reaction mixture. After cooling, 40 mL of 20% 3-(dimethylamino)propylamine in H_2O was added and the mixture stirred for 45 min. Et_2O added, the organic solution was washed with 1 N HCl, $NaHCO_3$, water, and brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue recrystallized from EtOH to give 3.68 g (26.5%) of product: mp 66−68 °C; mass spectrum CI-MS *m*/*z* 216 ($M^+ + H$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H), 6.9−7.1 (d, s, 3H), 6.7 (d, 1H), 6.15 (d, 1H), 4.1 (s, 3H), 3.9 (s, 3H). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

2-Chloro-1-[5-(4-chlorobenzoyl)-1,2,4-trimethyl-1*H*-pyrrol-3-yl]ethanone (3b). A 60 g (0.24 mol) sample of 2-(4-chlorobenzoyl)-1,3,5-trimethyl-1*H*-pyrrole in 460 mL of 1,2-dichloroethane was cooled in an ice bath. A sample of 79 g (0.60 mol) of $AlCl_3$ was added in portions. After the addition was complete, stirring was continued for 30 min. A sample of 47.5 mL (0.60 mol) of chloroacetyl chloride was added dropwise. The reaction was stirred at room temperature for 72 h and then poured into 3 N HCl and ice. The organic layer was washed with water, 1 N NaOH, water, and brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give a solid. Recrystallization from EtOAc/methylcyclohexane gave 60.5 g (77%) of **3b**: mp 141−143 °C; ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3H), 2.6 (s, 3H), 3.7 (s, 3H), 4.4 (s, 2H), 7.25 (s, 1H), 7.5 (d, 2H), 7.8 (d, 2H); CI-MS *m*/*z* 324 ($M^+ + H$). Anal. ($C_{16}H_{15}Cl_2NO_2$) C, H, N.

1-[5-(4-Chlorobenzoyl)-1,2,4-trimethyl-1*H*-pyrrol-3-yl]-2-(1-piperidinyl)ethanone (4d). A 40 g (0.12 mol) sample of **3b** in 160 mL of ethanol was brought to reflux. A 42 mL (0.36 mol) sample of piperidine was added, and refluxing was continued for 45 min. The solvent was evaporated *in vacuo*, and the residue was taken up in Et_2O/THF mixture, washed twice with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and recrystallization twice from 2-PrOH gave 37.07 g (83%) of **4d**: mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 2H), 1.6 (m, 4H), 2.0 (s, 3H), 2.4 (m, 4H), 2.5 (s, 3H), 3.45 (s, 2H), 3.7 (s, 3H), 7.4 (d, 2H), 7.75 (d, 2H); CI-MS *m*/*z* 373 ($M^+ + H$). Anal. ($C_{21}H_{25}ClN_2O_2$) C, H, N.

1-[5-(4-Pyrrolidin-1-ylbenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-4-(pyrrolidin-1-yl)butanone (4ii). A 10 g (0.03 mol) sample of 1-[5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-4-chlorobutanone was added to 18 mL (0.216 mol) of pyrrolidine and refluxed for 4 h. The pyrrolidine solution was evaporated *in vacuo* and the residue triturated with Et_2O. The mixture was filtered and the filtrate treated with ethereal HCl to give the salt. Recrystallization from CH_3CN gave 1.18 g (9% yield) of a yellow solid: mp 203−206 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.85−2.05 (m, 10H), 2.87−3.05 (m, 4H), 3.1−3.15 (m, 2H), 3.3−3.4 (m, 4H), 3.45−3.55 (br s, 2H), 3.9 (s, 3H), 6.62 (d, 2H), 6.96 (s, 1H), 7.72 (d, 2H), 7.92 (s, 1H). Anal. ($C_{24}H_{31}N_3O_2$·HCl·0.4CH_3CN) C, H, N.

1-[4-(4-Chlorobenzoyl)-1-methyl-1*H*-pyrrol-2-yl]-2-aminoethanone (4jj). A 10 g (0.034 mol) sample of 1-[5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-2-chloroethanone, 3.8 g (0.041 mol) of sodium diformylamide, and 80 mL of CH_3CN were refluxed overnight under argon. Sodium diformylamide (2.0 g) was added, and reflux was continued for 1.5 h. After evaporation of the solvent *in vacuo*, the residue was passed through a flash column (silica gel, 3:1 hexane/acetone then 2:1 hexane/acetone) to give 6.18 g of solid 2-[bis(formyl)amino]-1-[5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]ethanone: mp 279−282 °C; CI-MS *m*/*z* 333 ($M^+ + H$). This sample (0.0186 mol) was stirred 3 days in 5% HCl/EtOH. Concentrated HCl (0.5 mL) was added, and the reaction mixture was stirred for an additional 2 days. The solid was collected. Et_2O was added and a second crop taken. It was washed with hot MeOH: mp 290 °C dec; CI-MS *m*/*z* 277 ($M^+ + H$). ^{1}HNMR (Me_2SO-d_6) δ 8.2 (br s, 4H), 7.85 (d, 2H), 7.6 (d, 2H), 7.2 (s, 1H), 4.3 (s, 2H), 4.0 (s, 3H). Anal. ($C_{14}H_{13}ClN_2O_2$) C, H, N.

2-[5-(4-Chlorobenzoyl)-1,2,4-trimethyl-1*H*-pyrrol-3-yl]-1-(*N*,*N*-diethylamino)ethanone (4kk). 1-[5-(4-Chlorobenzoyl)-1,2,4-trimethyl-1*H*-pyrrol-3-yl]-2-chloroethanone (5 g, 0.015 mol), 4.64 mL (0.045 mol) of diethylamine, and 50 mL of toluene were heated for 5 h. After cooling, the organics were washed with water and then extracted twice with 1 N HCl. The acidic aqueous layer was washed with Et_2O and then made basic with $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the organics were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue converted to the fumarate salt in 2-PrOH. The

resulting salt was recrystallized from 2-PrOH/EtOH to give the product: mp 176−178 °C; CI-MS *m/z* 361 ($M^+ + H$); ^{1}H NMR (Me_2SO-d_6) δ 7.7 (d, 2H), 7.6 (d, 2H), 6.6 (s, 1H), 3.8 (s, 2H), 3.4 (s, 3H), 2.7 (q, 4H), 2.5 (s, 3H), 1.95 (s, 3H), 1.0 (t, 6H). Anal. ($C_{20}H_{25}ClN_2O_2 \cdot 0.66C_4H_4O_4$) C, H, N.

2-Chloro-1-[4-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-2-yl]ethanone (8). A 60 g sample of $AlCl_3$ (0.45 mol) was added in portions to an ice-cooled solution of 30 g (0.19 mol) of (1-methyl-1*H*-pyrrol-2-yl)-2-chloroethanone[24] in 180 mL of 1,2-dichloroethane (DCE) under Ar. After 10 min of stirring, a solution of 24 mL (0.19 mol) of *p*-chlorobenzoyl chloride in 110 mL of DCE was added dropwise. The mixture was stirred at 25 °C for 16 h. The reaction was poured into 1 N HCl/ice, and the aqueous layer was extracted with CH_2Cl_2. The organics were combined, washed with water, 1 N NaOH, water, and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave a solid which was recrystallized from EtOAc/methylcyclohexane to give 27.67 g (49.4%) of a solid: mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (m, 2H), 7.6−7.4 (m, 4H), 4.5 (s, 2H), 4.0 (s, 3H). Anal. ($C_{14}H_{11}Cl_2NO_2$) C, H, N.

1-[4-(4-Chlorobenzoyl)-1-methyl-1*H*-pyrrol-2-yl]-2-(1-piperidinyl)ethanone (9a). 2-Chloro-1-[4-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-2-yl]ethanone (4 g, 0.013 mol), 4.08 mL (0.039 mol) of piperidine, and 60 mL of 2-PrOH were refluxed for 1 h. The solvent was evaporated *in vacuo*, and the residue was taken up in Et_2O/THF, washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a tan solid which was recrystallized from 2-PrOH to give 3.65 g (81.6%) of product: mp 129−130 °C; CI-MS *m/z* 345 ($M^+ + H$); ^{1}H NMR ($CDCl_3$) δ 7.8 (m, 2H), 7.6 (s, 1H), 7.45 (d, 2H), 7.35 (s, 1H), 4.0 (s, 3H), 3.6 (s, 2H), 2.5 (br s, 4H), 1.6 (m, 4H), 1.4 (m, 2H). Anal. ($C_{19}H_{21}Cl_2N_2O_2$) C, H, N.

1-[4-(4-Chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-2-(1-pyrrolidinyl)ethanone (10). 1-[5-(4-Chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-2-(1-pyrrolidinyl)ethanone (10 g, 0.03 mol) was added to PPA (100 mL) and heated for 6 h at 95−97 °C under argon. The reaction was basified to pH 8 with ice cold 3 N KOH and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated to a solid. Recrystallized from CH_3CN to give 5.5 g (55%) of a tan solid: mp 105−108 °C; CI-MS *m/z* 331 ($M^+ + H$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H), 7.42−7.3 (m, 3H), 6.8 (s, 1H), 3.7 (s, 3H), 3.47 (s, 2H), 2.35 (m, 4H), 1.5 (m, 4H). Anal. ($C_{18}H_{19}ClN_2O_2$) C, H, N.

α-(4-Chlorophenyl)-1-methyl-α′-(1-pyrrolidinylmethyl)-1*H*-pyrrole-2,4-dimethanol (11). To a solution of (10 g, 0.03 mol) 1-[5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-2-(1-pyrrolidinyl)ethanone in CH_2Cl_2 (1 L) was added 40 mL of 1.5 M DIBAL at −65 °C under argon and stirred for 2.5 h. Then an additional 20 mL of 1.5 M DIBAL at −65 °C was added and stirred an additional 1.25 h. MeOH was added, and the organic layer was washed with 3 N NaOH. The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated *in vacuo* to a solid which was recrystallized from CH_3CN to give 2.38 g (24%) of a tan solid: mp 122.5−124.5 °C; CI-MS *m/z* 335 ($M^+ + H$;. ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 4H), 6.62 (d, 2H), 5.8 (d, 2H), 4.6 (q, 1H), 3.55 (s, 3H), 2.88 (t, 1H), 2.78−2.68 (m, 2H), 2.55−2.32 (m, 4H), 2.2 (s, 1H), 1.7 (m, 4H). Anal. ($C_{18}H_{23}ClN_2O_2$) C, H, N.

(4-Chlorophenyl)[4-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-1-methyl-1*H*-pyrrol-2-yl]methanone (12). To a solution of 10 g (0.03 mol) of 1-[5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrol-3-yl]-2-(1-pyrrolidinyl)ethanone in CH_2Cl_2 (1 L) was added 20 mL of 1.5 M DIBAL at −75 °C. The mixture stirred under argon for 1.5 h. Another 20 mL of 1.5 M DIBAL was added and the mixture stirred at −75 °C for 2.5 h. A 500 mL portion of of 3 N NaOH was added, and the mixture was allowed to warm to 0 °C. MeOH was added and the CH_2Cl_2 solution separated, dried ($MgSO_4$), and evaporated *in vacuo* to an oil. Chromatography on the Waters Prep 500 (95:5 CH_2Cl_2/MeOH) gave 1.9 g of a solid. The solid was washed with Et_2O, dissolved in 0.05 N HCl, and filtered through Celite. The acidic solution was made basic with K_2CO_3, extracted with THF/Et_2O, dried ($MgSO_4$), and evaporated *in vacuo* to a solid. It was recrystallized from CH_3CN to give 450 mg (4.3%) of a white solid: mp 131−134 °C; CI-MS *m/z* 333 ($M^+ + H$); ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.42 (d, 2H), 6.88 (d, 1H), 6.64 (d, 1H), 4.65 (q, 1H), 4.00 (s, 3H), 2.9−2.68 (m, 3H), 2.58−2.48 (m, 3H), 1.8 (m, 4H). Anal. ($C_{18}H_{21}ClN_2O_2$) C, H, N.

Ethyl 1-Methyl-4-(1-pyrrolidylacetyl)pyrrole-2-carboxylate Hydrochloride (13). A 30.6 g (0.2 mol) sample of ethyl 1-methylpyrrole-2-carboxylate in 100 mL of 1,2-dichloroethane was stirred while cooling in an ice bath. A suspension of 80.0 g (0.6 mol) of $AlCl_3$ and 68.0 g (0.6 mol) of chloroacetyl chloride in 250 mL of 1,2-dichloroethane was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into 3 N HCl/ice and extracted twice with $CHCl_3$. The organics were washed twice with 10% NaOH and brine and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave 44.8 g of a solid. Recrystallization from EtOAc−hexane and then EtOAc gave 39.6 g of ethyl 4-(chloroacetyl)-1-methyl-1*H*-pyrrole-2-carboxylate: mp 114−117 °C; CI-MS *m/z* 344 ($M^+ + H$); ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 1H), 7.34 (m, 1H), 4.43 (s, 2H), 4.32 (q, 2H), 3.97 (s, 3H), 1.37 (t, 3H). A 29.7 g (0.13 mol) sample of ethyl 4-(chloroacetyl)-1-methyl-1*H*-pyrrole-2-carboxylate was dissolved in 250 mL of benzene. A 18.4 g (0.26 mol) sample of pyrrolidine was added, and the mixture was stirred for 15 min. The reaction mixture was poured into 10% NaOH and ice and extracted three times with 100 mL of benzene. The organics were combined, washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave a brown oil which, upon crystallization, was recrystallized twice from Et_2O. Treatment with ethereal HCl gave 8.3 g (15.7%) of ethyl 1-methyl-4-(1-pyrrolidylacetyl)pyrrole-2-carboxylate hydrochloride as a white solid: mp 198−201 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.0 (s,1H), 7.35 (s, 1H), 4.8 (s, 1H), 4.25 (q, 2H), 3.95 (s, 3H), 2.5 (m, 4H), 1.95 (m, 4H), 1.3 (t, 3H). Anal. ($C_{14}H_{20}N_2O_3 \cdot HCl$) C, H, N.

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