Synthesis and Carbon-13 NMR Study of 2-Benzyl, 2-Methyl, 2-Aryloctahydropyrrolo[3,4-*c*]pyrroles and the 1,2,3,5-Tetrahydropyrrolo[3,4-*c*]pyrrole Ring System

Cyrus J. Ohnmacht, Jr.,* Clyde W. Draper and Robert F. Dedinas

Biomedical Research Department,

Philip Loftus* and J. J. Wong

Pharmaceutical Development Department, Stuart Pharmaceuticals, A Division of ICI Americas Inc., Wilmington, DE 19897

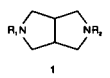
Received June 14, 1982

2-Benzyl, 2-phenyl, 2-(3-methoxyphenyl) and 2-(3-trifluoromethylphenyl)octahydropyrrolo[3,4-*c*]pyrrole (**9a**, **9b**, **9c**, and **9d**, respectively) were prepared in five steps from 1-benzylpyrrole-3,4-dicarboxylic acid (**2**). 2-Methyloctahydropyrrolo[3,4-*c*]pyrrole (**9'a**) was prepared analogously in six steps from 1-methylpyrrole-3,4-dicarboxylic acid (**3**). Diborane reduction of 1-benzyl-*N*-methyl-1*H*-pyrrole-3,4-dicarboximide (**7'a**) and 1,*N*-dibenzyl-1*H*-pyrrole-3,4-dicarboximide (**7a**) gave 5-benzyl-2-methyl and 2,5-dibenzyl-1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole (**19'** and **19**, respectively); the first reported members of the 1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole ring system. A detailed study of the carbon-13 nmr shifts permitted a complete assignment for all compounds. Mono and disubstituted products produce a systematic effect on the shifts for the bicyclic ring systems which can be readily interpreted in terms of substituent chemical shifts. The effect of protonation at nitrogen is also shown to produce a series of well defined chemical shifts for the octahydropyrrolo[3,4-*c*]pyrrole ring system.

J. Heterocyclic Chem., **20**, 321 (1983).

Within a program aimed at examining the pharmacological and physical properties of novel 5-5 fused ring systems we were interested in systematically probing the relatively unexplored octahydropyrrolo[3,4-*c*]pyrrole ring system (**1**). In particular, this series of compounds provided an opportunity to study the effects of steric strain and substituent and protonation effects on the carbon-13 chemical shifts of this unusual bicyclic ring system.

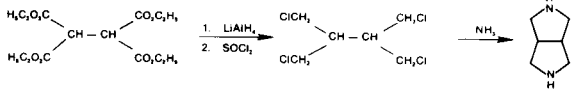
(Figure 1)



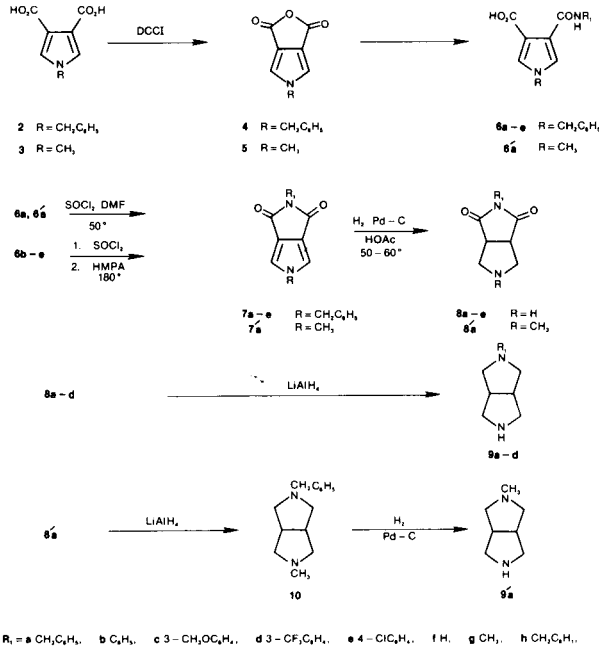
1

Although the parent ring system had been previously prepared by Weinges and Spänigs (1) (Scheme I), the overall yield was only 7%. An alternate synthesis was required particularly for **1** where $R_1 \neq R_2$ were desired.

Scheme I



Scheme II



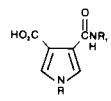
It was felt at the onset of this work that convenient syntheses of 2-benzyloctahydropyrrolo[3,4-*c*]pyrrole (**9a**), 2-methyloctahydropyrrolo[3,4-*c*]pyrrole (**9'a**) and 2-aryloctahydropyrrolo[3,4-*c*]pyrroles were required to allow fulfillment of our goal. Scheme II illustrates the synthetic sequence which satisfies the first two requirements and allows the synthesis of several 2-aryloctahydropyrrolo[3,4-*c*]pyrroles; a synthetic limitation being that the aryl moiety be stable to the catalytic hydrogenation conditions of 10% palladium on carbon in acetic acid at 50-60°.

The starting pyrrole-3,4-dicarboxylic acids **2** and **3** are most conveniently prepared by the method developed by Huisgen (2) (Scheme III). The reaction of the pyrrole-3,4-dicarboxylic acids with dicyclohexylcarbodiimide in tetrahydrofuran or acetonitrile gives good yields of the

Table I

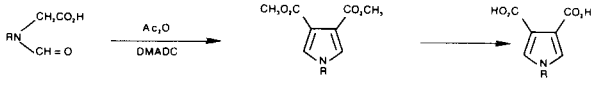
4-Carbamoyl and Substituted Carbamoyl-1*H*-Pyrrole-3-carboxylic Acids

(Figure 2)



Compound	R	R_1	Yield %	Mp°C	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found			
6a	$CH_2C_6H_5$	$CH_2C_6H_5$	84	230-232 dec	ethanol	$C_{20}H_{18}N_2O_3$	C, 71.84;	H, 5.43;	N, 8.38	
							C, 72.00;	H, 5.50;	N, 8.47	
6b	$CH_2C_6H_5$	C_6H_5	93	247-249 dec	ethanol	$C_{19}H_{16}N_2O_3$	C, 71.24;	H, 5.03;	N, 8.74	
							C, 71.39;	H, 5.04;	N, 8.84	
6c	$CH_2C_6H_5$	$3CH_3OC_6H_4$	72	214-216 dec	acetic acid	$C_{20}H_{18}N_2O_4$	C, 68.56;	H, 5.18;	N, 8.00	
							C, 68.68;	H, 5.49;	N, 8.11	
6d	$CH_2C_6H_5$	$3CF_3C_6H_4$	76	245-248 dec		$C_{20}H_{15}F_3N_2O_3$	C, 61.86;	H, 3.89;	N, 7.21	
							C, 61.98;	H, 3.94;	N, 7.18	
6e	$CH_2C_6H_5$	$4\text{-}ClC_6H_4$	86	257.5-258.5 dec		$C_{19}H_{15}ClN_2O_3$	C, 64.32;	H, 4.26;	N, 7.90;	Cl, 9.99
							C, 64.50;	H, 4.47;	N, 7.95;	Cl, 10.09
6f	$CH_2C_6H_5$	H	97	239-240 dec		$C_{13}H_{12}N_2O_3$	C, 63.92;	H, 4.95;	N, 11.46	
							C, 63.94;	H, 5.08;	N, 11.45	
6g	$CH_2C_6H_5$	CH_3	78	201-205 dec	ethanol	$C_{14}H_{14}N_2O_3$	C, 65.11;	H, 5.46;	N, 10.85	
							C, 65.14;	H, 5.70;	N, 10.80	
6'a	CH_3	$CH_2C_6H_5$	98	237-240 dec	toluene	$C_{14}H_{14}N_2O_3$	C, 65.11;	H, 5.46;	N, 10.85	
							C, 65.08;	H, 5.28;	N, 10.81	
6'f	CH_3	H	87	251-257 dec						
13	C_6H_5	$CH_2C_6H_5$	70	216-220 dec	acetic acid	$C_{19}H_{16}N_2O_3$	C, 71.24;	H, 5.03;	N, 8.74	
							C, 70.98;	H, 5.25;	N, 8.43	

Scheme III



anhydrides **4** and **5**. Attempted anhydride formation with acetic anhydride, phosphorus pentoxide or thionyl chloride failed. Although these strained anhydrides can be isolated and purified, isolation was found to be unnecessary. The crude anhydride reaction mixture, after filtration to remove the dicyclohexylurea, was reacted with the appropriate amine or aniline to give high yields of the corresponding pyrrole acid-amides (Table I). These acid-amides decarboxylate readily upon melting precluding use of the usually efficient thermal method of cyclic imide formation (3). Conversion of the acid-amides **6a** and **6'a** to the cyclic imides **7a** and **7'a** was carried out with 1.25 to 2 equivalents of thionyl chloride in dimethylformamide at 50-60°. It is advantageous to use the benzyl amide-acid **6'a** in the synthesis of 2-methyloctahydropyrrolo[3,4-*c*]pyrrole (**9'a**) as the cyclization of the unsubstituted amide-acid **6'f** gives lower and inconsistent yields of cyclic imide **7'f**. An additional advantage of the selected route to **9'a** is the pyrrole diacid **3** is prepared more conveniently from a cheaper precursor (sarcoscine) than the diacid **2**.

Application of the thionyl chloride-dimethylformamide method to 1-benzyl-4-phenylcarbamyl-1*H*-pyrrole-3-carboxylic acid (**6b**) gives 55% of **7b** and a small amount of recovered **2**. The same procedure with **6c** (50°, 45 minutes) gives only recovered **6c**. When **6c** is treated with thionyl chloride-dimethylformamide overnight at 50° a 40% yield of **2** is obtained. Evidently the reaction of **6c** with thionyl chloride dimethylformamide to form the iminochloride **11** is more efficient than ring closure to the imide **7c**. Preparation of the acid chloride with thionyl

Equation I

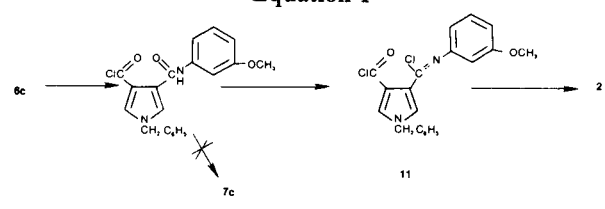
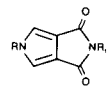


Table II

1*H*-Pyrrole-3,4-dicarboximides

(Figure 3)

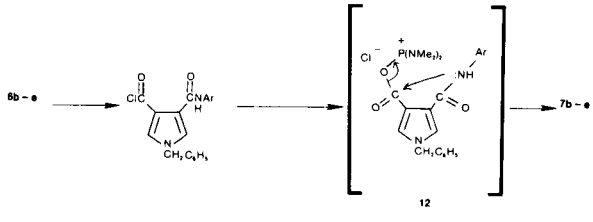


Compound	R	R_1	Yield %	Mp°C	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found			
7a	$CH_2C_6H_5$	$CH_2C_6H_5$	90	230-232	toluene	$C_{20}H_{16}N_2O_2$	C, 75.93;	H, 5.10;	N, 8.85	
							C, 75.88;	H, 5.24;	N, 8.72	
7b	$CH_2C_6H_5$	C_6H_5	63	191.5-193.5	ethanol	$C_{19}H_{14}N_2O_2$	C, 75.48;	H, 4.67;	N, 9.27	
							C, 75.56;	H, 4.73;	N, 9.26	
7c	$CH_2C_6H_5$	$3CH_3OC_6H_4$	75	154-156	toluene-hexane	$C_{20}H_{16}N_2O_3$	C, 72.28;	H, 4.85;	N, 8.43	
							C, 72.23;	H, 5.12;	N, 8.35	
7d	$CH_2C_6H_5$	$3CF_3C_6H_4$	83 (a)	107-109	toluene-hexane	$C_{20}H_{13}F_3N_2O_2$	C, 64.87;	H, 3.54;	N, 7.56	
							C, 65.05;	H, 3.70;	N, 7.42	
7e	$CH_2C_6H_5$	$4\text{-}ClC_6H_4$	71	202.5-203.5		$C_{19}H_{13}ClN_2O_2$	C, 67.76;	H, 3.89;	N, 8.32;	Cl, 10.53
							C, 67.71;	H, 3.66;	N, 8.31;	Cl, 10.37
7f	$CH_2C_6H_5$	H	60	237-239	dioxane (b)	$C_{13}H_{10}N_2O_3$	C, 69.02;	H, 4.66;	N, 12.38	
							C, 69.22;	H, 4.44;	N, 12.32	
7g	$CH_2C_6H_5$	CH_3	67	174-176	methanol	$C_{14}H_{12}N_2O_2$	C, 69.99;	H, 5.03;	N, 11.66	
							C, 70.30;	H, 5.31;	N, 11.68	
7'a	CH_3	$CH_2C_6H_5$	85	171-173	toluene	$C_{14}H_{12}N_2O_2$	C, 69.99;	H, 5.03;	N, 11.66	
							C, 70.13;	H, 5.00;	N, 11.48	
7'f	CH_3	H	51	>330	dimethyl-formamide					
14	C_6H_5	$CH_2C_6H_5$	83	198-200	ethanol	$C_{19}H_{14}N_2O_2$	C, 75.48;	H, 4.67;	N, 9.27	
							C, 75.34;	H, 4.82;	N, 9.31	

(a) Plus a 9% yield of 1-benzyl-3-dimethylcarbamoyl-4-(3-trifluoromethylphenyl)carbamoyl-1*H*-pyrrole, mp 160-165°. *Anal.* Calcd. for $C_{22}H_{20}F_3N_3O$: C, 63.61; H, 4.85; N, 10.12. Found: C, 63.62; H, 4.89; N, 10.09. (b) Recrystallization from ethanol (trace H_3O+) yields ethyl 1-benzyl-3-carbamoyl-1*H*-pyrrole-3-carboxylic acid, mp 181.5-183.5°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.18; H, 6.26; N, 10.01.

chloride followed by heating in hexamethylphosphoramide gives the arylimides **7b-e** in good yields (Table II). As hexamethylphosphoramide is reported to react with acid chlorides at room temperature (4) **12** is suggested as an intermediate in this reaction.

Equation II



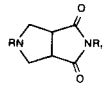
The pyrrole-3,4-dicarboximides **7a-d** and **7'a** were catalytically reduced to the tetrahydropyrrole-3,4-dicarboximides **8a-d** and **8'a** in good yields (Table III). The 4-chlorophenyl substituted imide, **7e**, however gave a mixture of **8b** and **8e** which was not carried further. Selective hydrogenolysis of what was initially the pyrrole benzyl moiety proved an advantage of the method. The use of 5% rhodium on alumina (5) in the hydrogenation of **7'a** gave overreduction of the benzyl moiety to the cyclohexylmethyl derivative **8'h**.

Reduction of the tetrahydropyrrole-3,4-dicaboximide **8a-d** with lithium aluminum hydride gives good yields of the targets **9a-d** (**9a** in 50% overall yield from **2**). Similarly reduction of **8'a** with lithium aluminum hydride followed by catalytic debenzylation gives the target 2-methyloctahydropyrrolo[3,4-*c*]pyrrole **9'a** (54% from **3**). While as previously stated, **9'a** can be prepared from **2** as well as **3**, there is apparently not a similar choice of routes to the aryloctahydropyrrolo[3,4-*c*]pyrroles. Unexpectedly, under the usual hydrogenation conditions, *N*-phenyl-*N'*-benzyl-

Table III

Tetrahydro-1*H*-pyrrole-3,4-dicarboximides

(Figure 4)

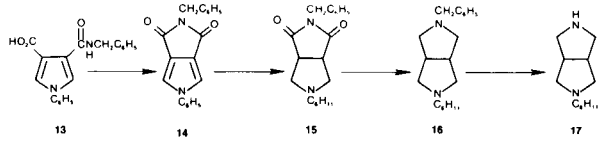


Compound	R	R_1	Yield %	Mp°C	Salt	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found			
8a	H	$CH_2C_6H_5$	78 (a) 100	242-245 dec	HCl	ethanol	$C_{13}H_{15}ClN_2O_2$	C, 58.54; C, 58.58;	H, 5.67; H, 5.75;	N, 10.50; N, 10.42;	Cl, 13.29 Cl, 13.30
8b	H	C_6H_5	75 (b) 91	245-249 dec	HCl	ethanol	$C_{12}H_{13}ClN_2O_2$	C, 57.04; C, 57.01;	H, 5.18; H, 5.34;	N, 11.08; N, 11.01;	Cl, 14.03 Cl, 13.92
8c	H	$3CH_3OC_6H_4$	60	234-238 dec	HCl	ethanol	$C_{13}H_{15}ClN_2O_3$	C, 55.23; C, 55.10;	H, 5.35; H, 5.30;	N, 9.91; N, 10.15;	Cl, 12.54 Cl, 12.34
8d	H	$3CF_3C_6H_4$	57	268-280 dec	HCl	methanol-ether	$C_{13}H_{12}ClF_3N_2O_2$	C, 48.69; C, 48.35;	H, 3.77; H, 3.75;	N, 8.73; N, 8.86;	Cl, 11.05 Cl, 11.31
8'a	CH_3	$CH_2C_6H_5$	91	96-97.5		toluene	$C_{14}H_{16}N_2O_2$	C, 68.83; C, 68.98;	H, 6.60; H, 6.69;	N, 11.47 N, 11.22	
8'f	CH_3	H	73	283-285 dec	HCl	methanol	$C_7H_{11}ClN_2O_2$	C, 44.11; C, 44.12;	H, 5.82; H, 5.98;	N, 14.69; N, 14.82;	Cl, 18.60 Cl, 18.69
8'h	CH_3	$CH_2C_6H_{11}$	84	256-258 dec	HCl	ethanol	$C_{14}H_{23}ClN_2O_2$	C, 58.63; C, 58.83;	H, 8.08; H, 8.23;	N, 9.77; N, 10.25;	Cl, 12.36 Cl, 12.60
15	C_6H_{11}	$CH_2C_6H_5$	86	270-272 dec	HCl	methanol	$C_{19}H_{25}ClN_2O_2$	C, 65.41; C, 65.24;	H, 7.22; H, 7.27;	N, 8.03; N, 8.09;	Cl, 10.16 Cl, 9.95

(a) Acetate salt, mp, 132-135°. (b) Acetate salt, mp, 142-146°.

pyrrole-3,4-dicarboximide (**14**) yields only *N*-cyclohexyl-*N'*-benzyltetrahydropyrrole-3,4-dicarboximide (**15**) in 86% yield (Scheme IV).

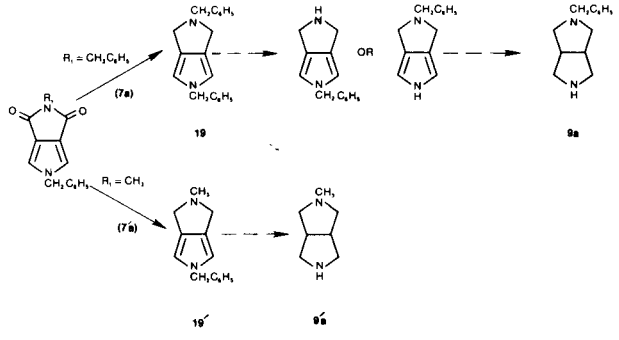
Scheme IV



An alternate sequence of reduction in which the pyrrole-3,4-dicarboximide carbonyls are reduced first was also examined (Scheme V). While borane reduction of **7a** and **7'a** gave low yields of **19** and **19'**, the attempted reduction of the unsubstituted dicarboximides **7f** or **7'f** was unsuccessful. Attempted reduction of **7a** or **7'a** with lithium aluminum hydride or diisobutylaluminum hydride also failed. The synthesis of **19** and **19'** is believed to be the first reported synthesis of the 1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole ring system.

A subset of these compounds (as given in Table V) were chosen for investigation by carbon-13 nmr. The spectrum of **9'a** consists of four sharp lines. The methyl and methine signals can be directly assigned on the basis of their off

Scheme V



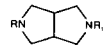
resonance decoupled multiplicities leaving only the two methylene carbons at δ 48.8 and 57.7. The β effect of the methyl group is expected to produce a 10 ppm shift to low field (6) so that the signal at δ 48.8 can readily be assigned to C_1.

Compounds **17** and **18** can be assigned similarly, taking account of the chemical shifts of the appropriately substituted cyclohexanes. The identity of the exocyclic *N*-methylene in **18** was determined by selective decoupling of the corresponding sharp singlet in the proton spectrum at δ 3.48. Compound **19'** was assigned in a similar manner.

Table IV

Octahydropyrrolo[3,4-*c*]pyrroles

(Figure 5)



Compound	R	R_1	Yield %	Mp°C or Bp (mm)	Salt	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found			
9a	H	$CH_2C_6H_5$	78	126-128(0.5)			$C_{13}H_{18}N_2$	C, 77.18; C, 77.34;	H, 8.97; H, 8.99;	N, 13.85 N, 13.82	
9b	H	C_6H_5	60	146-148(0.6)(a) 160-163 dec	succinate	methanol	$C_{16}H_{22}N_2O_4$	C, 62.73; C, 62.60;	H, 7.24; H, 7.37;	N, 9.14 N, 9.00	
9c	H	$3CH_3OC_6H_4$	45	149-150(0.15)(b) 81-83		sublimed 80° (0.2)	$C_{13}H_{18}N_2O$	C, 71.53; C, 71.39;	H, 8.31; H, 8.29;	N, 12.83 N, 12.77	
9d	H	$3CF_3C_6H_4$	35	120(0.05)(b) 126-129 dec	succinate	acetonitrile	$C_{17}H_{21}F_3N_2O_4$	C, 54.54; C, 54.55;	H, 5.65; H, 5.41;	N, 7.48 N, 7.64	
9'a	H	CH_3	90	80-81 (20)			$C_7H_{14}N_2$	C, 66.62; C, 66.38;	H, 11.18; H, 11.25;	N, 22.20 N, 22.16	
10	$CH_2C_6H_5$	CH_3	91	108-111(0.07) 135-137	disuccinate	methanol-ether	$C_{22}H_{32}N_2O_8$	C, 58.40; C, 58.30;	H, 7.13; H, 7.18;	N, 6.19 N, 6.15	
16	C_6H_{11}	$CH_2C_6H_5$	81	258-261	2 HCl		$C_{19}H_{30}Cl_2N_2$	C, 63.85; C, 63.28;	H, 8.46; H, 8.38;	N, 7.84; N, 7.81;	Cl, 19.84 Cl, 19.59
17	C_6H_{11}	H	98	77-78.5		sublimed	$C_{12}H_{22}N_2$	C, 74.17; C, 74.28;	H, 11.41; H, 11.42;	N, 14.42 N, 14.60	
18	CH_3	$CH_2C_6H_{11}$	86	267-269 dec	2 HCl	methanol-ether	$C_{14}H_{28}Cl_2N_2$	C, 56.94; C, 57.02;	H, 9.56; H, 9.53;	N, 9.49; N, 9.56;	Cl, 24.01 Cl, 24.22

(a) Readily forms a carbonate salt on exposure to air. (b) Kugelrohr; bulb temperature.

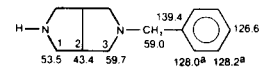
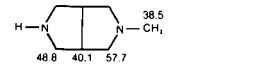
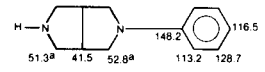
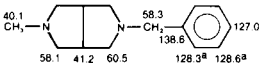
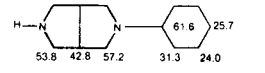
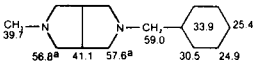
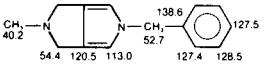
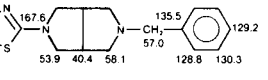
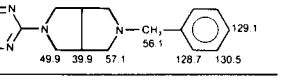
The signals corresponding to the quarternary carbons in the benzene and pyrimidine rings of **21** were not observed but, otherwise, the assignment of this and the remaining compounds were straightforward.

The substituent effects on the octahydropyrrolo-[3,4-*c*]pyrrole ring system can be considered in terms of aliphatic and aromatic substitution at nitrogen and protonation of one or both ring nitrogen atoms. In the case of aliphatic substitution at nitrogen, the presence of a methyl group would be expected to produce a downfield shift of about 10 ppm at C3 (6) and a corresponding upfield shift of around 2.5 ppm at C2 (7). The difference in shift between C3 and C1 in **9'a** is 8.9 ppm, in good agreement with this hypothesis, but the substituent effects α and β to amine fuctions are highly sensitive to the nature of the alkyl substituent (8) and the values for alkyl substitution obtained from **17** and **9a** (cyclohexyl and benzyl substituents) are 3.4 and 6.2 ppm indicating that, although the presence of such a shift can be used diagnostically, the value obtained can often be much smaller than might initially be expected.

The β substituent effects for alkyl replacement are difficult to unravel in this system since they are both small in magnitude (2.5 ppm upfield shift as noted above) and complicated by the effects of ring protonation which are discussed below. In the case of the diprotonated compounds, the addition of a second alkyl substituent to **9'a** *cf.* **18** and **10** produces a downfield shift of 1.0 and 1.4 ppm respectively but this is not sufficient data to say whether or not such behaviour is typical in these systems.

Aromatic substitution at nitrogen is interesting in that it seems to produce very little effect on the corresponding α-carbon shifts, giving values of δ 53.9, 49.9 and 52.8 for compounds **20**, **21** and **9b** respectively. Since the nitrogen atom being considered in these compounds is non-protonated in each case, they should be compared with the corresponding value of δ 57.2 in compound **17**. Even ignoring the possible effects of ring protonation, the mean value for a ring methylene α to an alkyl substituted nitrogen is δ 58.1 while the corresponding value for aryl substitution is only δ 52.2. This effect is often observed for aryl substitution. For example, the methylene and methyl shifts in *N,N*

TABLE V

Structure No.	Salt Form	Carbon - 13 Chemical Shifts (δ)
9a	–	
9'a	2 HCl	
9b	CH_3-COOH / CH_2-COOH	
10	2 CH_3-COOH / CH_2-COOH	
17	–	
18	2 HCl	
19'	HCl	
20	maleate	
21	HCl	

a denotes interchangeable assignments.

diethylaniline are 44.2 and 12.5 ppm respectively (9) while the corresponding values for triethylamine are 46.9 and 12.6 (10).

Viewed as the effect of nitrogen substitution onto an aromatic ring, the normal aryl substituent shifts are observed, the values for C_1, C_2, C_3 and C_4 of the benzene ring in compound **9b** of δ 148.2, 113.2, 128.7 and 116.5 closely paralleling those for *N,N*-diethylaniline itself of δ 147.8, 112.0, 129.1 and 115.5, respectively, showing that there is virtually the same degree of delocalization of the nitrogen lone pair into the aromatic ring. A similar effect is observed for the *meta* and *para* positions in the pyrimidine ring of compound **21** which give values of 157.5 and 110.0 ppm respectively. Compared to the equivalent values for the parent compound of 157.5 and 122.1 ppm (11) these show the classic marked upfield shift for the *para* carbon with virtually no effect at the *meta* position. In the case of the thiazole ring in compound **20**, there is only one effective conjugation pathway producing shifts of 139.6 and 108.1 ppm for the methine carbons adjacent to nitrogen and sulfur respectively compared to the corresponding values in the parent compound of 142.5 and 118.5 ppm (12). This clearly shows the marked upfield shift observed for the methine adjacent to the sulfur atom in these systems.

The expected effect of protonation in these systems is to produce an upfield shift of 2.3 ppm at the α-carbon and 3.8 ppm at the β carbon (13). The values for an unsubstituted nitrogen in the non-protonated state in compounds **17** and **9a** are 53.8, and 53.5 for the α-carbon and 42.8 and 43.4 ppm for the β-carbon. These β-carbon values are the two lowest field values, in the series indicating that, in all cases, protonation leads to an upfield shift at the β-position. The corresponding protonation values for compounds **9'a** and **9b** are 48.8 and 51.3 for the α-carbon and 40.1 and 41.5 ppm for the β-carbon. Consequently, both the α and β carbons exhibit the expected upfield shift although the magnitude of the shift for the β-carbon appears to be only about half that which might have been expected. Interestingly, there appears to be virtually no effect on the α-carbon for protonation at an alkyl substituted nitrogen, a fairly constant shift value of *ca.* 58.1 ppm being observed in all cases. It can also be seen that diprotonation shows little additional effect at the β-position, the values for mono and diprotonated species being essentially the same.

Compound **19'** contains the tetrahydropyrrolo[3,4-*c*]pyrrole ring system. This might by expected to produce a noticeable increase in the overall molecular strain but it is interesting to note that the C_1 shift of δ 54.4 is highly consistent with that of the fully saturated ring system. The increased strain within the pyrrole ring itself does, however, produce a marked effect on the observed shifts of 120.5 and 113.0 ppm compared to the expected values of 1,3,4-trimethylpyrrole (derived from 1-methylpyrrole (14)) of 118.2 and 112.6 ppm respectively. The same approach can be used to predict the basic shift values for the octahydropyrrolo[3,4-*c*]pyrrole ring system itself starting from the values for pyrrolidine (δ 47.1 and 25.7 for C_1 and C_2 (15)) and gives values of δ 54.0 and δ 44.4 which are in reasonably close agreement with the values observed.

Consequently, despite the degree of steric strain inherent in the octahydropyrrolo[3,4-*c*]pyrrole ring system, its spectral properties can be understood in terms of conventional substituent chemical shift and protonation effects with the exception of the bridgehead carbons which generally lack sensitivity to β-substitution and, while showing a clear but reduced sensitivity to mono-protonation of the ring system, show little or no additional effect on diprotonation. The two nitrogen atoms exhibit normal electron donor behaviour forming well delocalized ring systems with aromatic substituents.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B spectrophotometer. Proton nuclear magnetic resonance spectra were taken on a Varian EM360A instrument and chemical shifts are reported as δ units with tetramethylsilane as an internal standard. Carbon-13 spectra were recorded at 62.9 MHz on a Bruker WM-250 instrument at a probe temperature of *ca.* 35°. Samples (25 mg)

were dissolved in 2 ml of dimethylsulfoxide-d_6 which was also used as an internal standard with an assigned value of δ 39.6 Elemental analyses were performed by Dr. F. Cheng of ICIA.

1-Benzyl-1*H*-pyrrole-3,4-dicarboxylic acid (**2**) (16) and 1-methyl-1*H*-pyrrole-3,4-dicarboxylic acid (**3**) (17) were prepared from the corresponding dimethyl esters which were in turn prepared essentially by a method described by Huisgen (2) in the preparation of dimethyl-1-phenyl-1H-pyrrole-3,4-dicarboxylic acid. The following preparation of (**2**) is illustrative.

N-Benzyl-*N*-formylglycine.

N-Benzylglycine hydrochloride (18) [prepared in 82% yield by four hours reflux of concentrated hydrochloric acid and *N*-benzylglycine ethyl ester (Aldrich Chemical Co., 200 ml/mole)] was converted to the free aminoacid (19) in 86% yield by the method of Blomquest, *et al.* (20). Formylation by the procedure described by Sheehan and Yang (21), after crystallization from benzene, yielded 94% of *N*-benzyl-*N*-formylglycine, mp, 117-122°. Recrystallization from benzene gave analytical material, mp 119-121°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.33; H, 5.79; N, 7.18.

1-Benzyl-1*H*-pyrrole-3,4-dicarboxylic Acid (**2**).

To a stirred slurry of 692.7 g (3.59 moles) of *N*-benzyl-*N*-formylglycine and 1600 ml of acetic anhydride was added over 15 minutes, 562.3 g (3.96 moles) of dimethyl acetylenedicarboxylate. The mixture was heated to 100° where a mild exothermic reaction occurred. The mixture was cooled to 100°, the cooling bath removed and the mixture maintained at 100° with out external heating for one-half hour. The solution was then heated at 120-130° for 3 hours, cooled and treated with 200 ml of water over a 20 minute period. The temperature slowly rose to 40° over a 3.5 hour period. An additional 200 ml of water was then added over a 10 minute period; the temperature rose to a peak of 65° after 1 hour. After standing overnight the acetic acid was removed *in vacuo* and the residual red oil treated with a solution of 477.8 g (8.53 moles) of potassium hydroxide in 1200 ml of water. Ethanol (1100 ml) as added and the dark red solution refluxed for 5 hours. The alcohols were removed *in vacuo*, the residue diluted with 10 ℓ of water and acidified with 800 ml of concentrated hydrochloric acid. The resulting tan solid was filtered off, washed with 50% solution of ethanol in ether and then with ether. The dried **2** weighed 649.1 g with mp 206-210° dec [lit (16) mp 216-218° dec]. Concentration of the wash liquors yielded a second crop of 103.6 g of **2**, mp, 202-207 dec. Total yield was 86% of theory.

1-Benzyl-1*H*-pyrrole-3,4-dicarboxylic Anhydride (**4**).

N,N'-Dicyclohexylcarbodiimide (33 g, 0.16 mole) in 150 ml of tetrahydrofuran was added in one portion to a stirred slurry of 37.7 g (0.154 mole) of **2** and 400 ml of tetrahydrofuran. The mixture was stirred at reflux overnight, cooled, filtered and the insoluble *N,N'*-dicyclohexylurea was washed well with tetrahydrofuran. The filtrate was evaporated to yield a gummy solid which was triturated with a solution of 10% benzene in low boiling petroleum ether. The yellow crystals were filtered off, washed with benzene, then petroleum ether and oven dried to yield 30.8 g (88%) of solid, mp 146-149°. A pale yellow analytical sample recrystallized several times from benzene had mp 146-149°; ir (potassium bromide): 1850, 1820 and 1770 cm^{-1} (anhydride C=O).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.68; H, 3.93; N, 6.16.

1-Methyl-1*H*-pyrrole-3,4-dicarboxylic Anhydride (**5**).

This compound was isolated in 86% yield analogously to **4** with the exceptions that acetonitrile was the reaction solvent (**5** is only slightly soluble in cold tetrahydrofuran) and benzene was used as trituration solvent. A white analytical sample was obtained from dioxane, mp 255-260°, ir (potassium bromide): 1850, 1825 and 1765 cm^{-1} (anhydride C=O).

Anal. Calcd. for $C_7H_5NO_3$: C, 55.64; H, 3.34; N, 9.27. Found: C, 55.38; H, 3.61; N, 9.15.

The isolation of the crude anhydrides **4** and **5** is not necessary in the synthesis of the amide-acids described in Table I. A shorter reflux period can be used without decrease in the yield of anhydride (see synthesis of **6a** below).

1-Benzyl-4-benzylcarbamoyl-1*H*-pyrrole-3-carboxylic Acid (**6a**).

N,N'-Dicyclohexylcarbodimide (181.6 g, 0.88 mole) in 500 ml of tetrahydrofuran was added in one portion to a stirred slurry of 200 g (0.816 mole) of **2** and 1ℓ of tetrahydrofuran. The mixture was refluxed for 2 hours, cooled, filtered and the insoluble *N,N*-dicyclohexylurea washed well with tetrahydrofuran. The stirred solution of **4** was then treated with 94.3 g (0.88 mole) (22) of benzylamine over a 15 minute period and the mixture heated at 60° overnight. The precipitate was filtered off, washed well with tetrahydrofuran, followed by ether. The yield of oven dried **6a** was 217 g (80%) mp 224-229° dec. Addition of excess benzylamine to the tetrahydrofuran liquors gave a precipitate of the benzylamine salt of **6a** which on work-up through aqueous base and acidification yielded a second crop of 10.5 g (4%) of **6a**, mp 226-231° dec. The **6a** thus obtained was used in the subsequent reaction without further purification. An analytical sample was obtained from ethanol, mp 230-232° dec (Table I).

The acid-amides in Table I were prepared by similar procedures; specific modifications are noted below.

Compounds **6f, 6g** and **6'f** were prepared by bubbling the appropriate gas (ammonia or methylamine) through a stirred solution of the appropriate anhydride in tetrahydrofuran or acetonitrile. Removal of the solvent *in vacuo*, addition of water, filtration and acidification with concentrated hydrochloric acid gave the acid-amides in good yields.

Compounds **6b** and **6e**, precipitated from reaction of the appropriate aniline with an acetonitrile solution of **4**. Compound **6b** was initially purified through base.

The amide-acid **6d** was obtained by evaporation of the tetrahydrofuran reaction mixture and trituration with ether; followed by recrystallization from ethanol.

1-Benzyl-*N*-methyl-1*H*-pyrrole-3,4-dicarboximide (**7g**).

A mixture of 5.5 g (0.021 mole) of **6g** and 11 ml of thionyl chloride was stirred at room temperature for 3 hours. The excess thionyl chloride was exaporated *in vacuo* and the residue heated at 185° (still under water aspirator vacuum) for 10 minutes. Toluene (10 ml) was added and the mixture refluxed for 0.5 hours, cooled and treated with 25 ml of high petroleum ether. The tan crystals were filtered off and oven dried, 5.2 g (100%) mp 156-166°. Recrystallization from methanol returned 3.4 g (67%) of **7g**, mp 174-176°.

1-Benzyl-1*H*-pyrrole-3,4-dicarboximide (**7f**).

A mixture of 15.0 g (0.061 mole) of **6f** and 15 ml of thionyl chloride was heated at reflux for 0.5 hours, cooled and treated with ether containing a little benzene. The precipitate was filtered off, washed with ethanol and air dried, 8.3 g (60%), mp 236-238° dec. Recrystallization of a sample from dioxane gave analytical material, mp 237-239° dec.

1-Methyl-1*H*-pyrrole-3,4-dicarboximide (**7'f**).

To a stirred slurry of 5.0 g (0.03 mole) of **6'f** and 35 ml of dimethylacetamide was added dropwise 3.8 g (0.031 mole) of thionyl chloride. The temperature was maintained at 45-55° for 2 minutes and the mixture treated with cold water. The precipitate was filtered off, washed with ethanol, then ether and air dried to yield 2.3 g (51%) of an off white solid, mp >330°.

N,1-Dibenzyl-1*H*-pyrrole-3,4-dicarboximide (**7a**).

To a stirred cooled (initial temperature 18°, ice bath) slurry of 213.8 g (0.64 mole) of **6a** and 500 ml of dimethylformamide was added dropwise over 15 minutes 96 g (0.8 mole) of thionyl chloride. During the addition a pale yellow color had developed. Toward the end of the addition an exothermic reaction occurred as precipitate formed formed and the temperature rose to 45°. After the reaction mixture cooled to 25°, the ice bath was removed and the reaction stirred at room temperature for 45

minutes. The solid was filtered off, washed with a little dimethylformamide followed by several water washes. The dried off-white **7a** weighed 181.6 g (90%), mp 227-230°. An analytical sample recrystallized from toluene (1 g/60 ml) had mp 230-232°.

Compounds **7b** and **7'a** were prepared by a procedure analogous to that used to prepare **7a** [thionyl chloride/DMF, 50-60°; **7b**, 1 hour, **7'a**, 0.5 hours]. Both **7b** and **7'a** were initially isolated by pouring the cooled reaction mixture onto ice water, filtering off the resulting precipitate and washing with ethanol. Compound **7b** was further purified by recrystallization from DMF-water (analytical sample from ethanol) while **7'a** was recrystallized from toluene.

Compound **13** [thionyl chloride/DMF, 50°, 1 hour] gave 72% of white **14** mp 198-200°, on filtration of the reaction mixture and a second crop [11%, mp 198-200°, after recrystallization (ethanol, Darco)] from the DMF-water filtrate wash.

1-Benzyl-*N*-(3-methoxyphenyl)-1*H*-pyrrole-3,4-dicarboximide (**7c**).

To a stirred slurry of 40.0 g (0.114 mole) of **6c** and 200 ml of benzene was added dropwise 14.9 g (0.125 mole) of thionyl chloride and the mixture refluxed for 1.5 hours. The mixture was cooled and the benzene removed *in vacuo*. To the resulting reddish yellow solid was added 75 ml of hexamethylphosphoramide and the mixture (a solution resulted on warming) rapidly heated to 180° by means of a heating mantle; the heating mantle removed and the mixture allowed to cool. The solution was poured onto 500 ml of water and the resulting tan solid filtered off and air dried. The crude material was dissolved in 400 ml of refluxing toluene (Darco), filtered and treated hot with 400 ml of hexane. The resulting light yellow solid weighed 28.6 g (75%), mp 154-156°.

Compounds **7d** and **7e** were obtained by a procedure analogous to that used for **7c**. Crude **7d** was initially purified by column chromatography (alumina-ether eluent).

N-Benzyltetrahydro-1*H*-pyrrole-3,4-dicarboximide Acetate (**8a** Acetate).

A slurry of 75.0 g (0.24 mole) of **7a**, 10 g of 10% Pd-C and 225 ml of glacial acetic acid was hydrogenated on a Parr apparatus at 50 lb/in² and 55° for 18 hours. The catalyst was filtered off by suction through a "Super Cel" pad and the filtrate evaporated *in vacuo* to an oil. Trituration with 100 ml of absolute ethanol gave a white solid which was filtered off and washed well with ether. Vacuum drying at room temperature gave 71 g (quantitative yield) of acetate salt, mp 132-135°.

A solution of **8a** free base (light yellow viscous oil, bp 182-189°/0.3 mm) in ethanol was treated with hydrogen chloride in ethanol to yield the hydrochloride salt of **8a**, mp 242-245° dec.

With the exception of **8a** and **8b** which yield relatively pure acetate salts (**8b**, trituration with ethanol-ether) and **8'a** which was purified as the free base, the tetrahydro-1*H*-pyrrole-3,4-dicarboximides in Table III were initially purified by addition of hydrogen chloride gas to an alcoholic solution of the crude acetate salts.

The catalyst used in the preparation of **8'f** and **8'h** was 5% rhodium-alumina (20 and 15 weight %, respectively).

In some Pd-C reductions when little hydrogen was taken up after two or three hours the following procedure proved successful: after filtration of the mixture to remove the catalyst fresh Pd-C was added, the mixture heated to 50° on a steam bath and replaced on the Parr apparatus.

2-Benzyloctahydropyrrolo[3,4-*c*]pyrrole (**9a**).

A solution of 24.4 g (0.44 mole) of potassium hydroxide in 250 ml of methanol was added to a solution of 107.6 g (0.37 mole) of **8a** acetate in 750 ml of methanol. The methanol was removed *in vacuo* and the residue extracted with four 200 ml portions of tetrahydrofuran. The tetrahydrofuran solution was concentrated to 400 ml and added dropwise over a one hour period to a stirred slurry of 42.2 g (1.11 moles) of lithium aluminum hydride and 2 ℓ of ether under a nitrogen atmosphere. After addition was complete the mixture was stirred at reflux under nitrogen for an additional 16 hours. The mixture was cooled and cautiously treated dropwise with consecutive portions of 42 ml of water, 42 ml of 15% sodium hydroxide solution and 126 ml of water. After stirring at room temperature for 0.5 hour the white salts were filtered off and washed well with ether. The combined organic filtrates were concentrated *in vacuo* to yield 64.0 g of yellow oil. Distillation through a three-inch Vigreaux column returned 58.9 g (78%) of colorless oil, bp 103-121° (0.1 mm).

The octahydropyrrolo[3,4-*c*]pyrroles in Table IV except **9'a** (prepared by catalytic debenzylation of **10**; 10% Pd-C, ethanol, 60°) were prepared analogously.

5-Benzyl-2-methyl-1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole Hydrochloride (**19'**).

A solution of 8.8 g (0.037 mole) of **7g** in 125 ml of tetrahydrofuran was added dropwise to a stirred, cooled (-5°) solution of 200 ml of 1*M* borane in tetrahydrofuran under a nitrogen atmosphere. The mixture was refluxed under nitrogen for 6.5 hours then stirred at room temperature overnight. The mixture was cautiously treated dropwise with 30 ml of 6*N* hydrochloric acid and the tetrahydrofuran distilled off. The aqueous phase was extracted with benzene (discarded), made strongly basic with potassium hydroxide pellets and extracted with methylene chloride. The methylene chloride solution was extracted with two 100 ml portions of 15*N* hydrochloric acid. Basification of the aqueous phase and extraction with ether yielded 3.6 g of crude **19'** which was further purified by sublimation at 80-90°/0.1 mm to yield 2.7 g (35%) of **19'**, mp 62-72°. The methylene chloride phase was evaporated and residue chromatographed (alumina-benzene; then ether eluent) to yield an additional 1.1. g (14%) of **19'**, mp 63-71°. The combined solid was converted to the hydrochloride salt, 3.4 g, mp 170-172° dec. Recrystallization from ethanol-ether gave 3.0 g (33%) of analytically pure, white, **19'** hydrochloride, mp 175-177° dec; nmr (DMSO-d_6): δ 2.90 (s, 3H, CH_3), 4.29 (s, 4H, CH_2), 5.12 (s, 2H, benzyl CH_2), 6.80 (s, 2H, pyrrole H), 7.35 (s, 5H, phenyl H), 11.6-12.6 (broad, 1H, NH).

Anal. Calcd. for $C_{14}H_{17}ClN_2$: C, 67.60; H, 6.89; Cl, 14.25; N, 11.26. Found: C, 67.35; H, 6.93; Cl, 14.36; N, 11.42.

2,5-Dibenzyl-1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole (**19**).

A 185 ml solution of 1*M* borane in tetrahydrofuran was added to 13.4 g (0.042 mole) of **7a** under a nitrogen atmosphere over a 20 minute period. The mixture was stirred at room temperature for 30 minutes and then at reflux for 2 hours. The mixture was cooled, cautiously treated with 50 ml of 3*N* hydrochloric acid and allowed to stir at room temperature overnight. The tetrahydrofuran was distilled off and the residue made strongly basic with potassium hydroxide solution. The milky solution was stirred in an ice-bath for 1.5 hours and the resulting crystals filtered off; 2.2 g, mp 82-87°. The filtrate was evaporated to dryness *in vacuo* and extracted with methylene chloride. The methylene chloride evaporated and the gummy residue purified by extraction with hot (steam bath) concentrated hydrochloric acid, clarification by filtration through "Super Cel", basification and filtration of the resulting solid, 3.2 g, mp 79-86°. Recrystallization of the total crude from toluene-hexane returned 3.7 g (30%) of pale yellow **19**, mp 91-93.5°. An analytical sample (hexane) had mp 94.5-96°; nmr (deuteriochloroform): 3.65 (s, 4H, CH_2), 3.85 (s, 2H, benzyl CH_2), 4.88 (s, 2H, benzyl CH_2), 6.29 (s, 2H, pyrrole H), 6.94-7.43 (m, 10H, Ar-H).

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.41; H, 7.10; N, 9.66.

Octahydro-2-benzyl-5-(2-thiazolyl)pyrrolo[3,4-*c*]pyrrole (**20**).

A mixture of 4.1 g (0.02 mole) of **9a**, 3.3 g (0.02 mole) of 2-bromothiazole, 2.8 g (0.02 mole) of potassium carbonate and 60 ml of dimethylformamide was stirred at reflux for 18 hours. The residue, after evaporation of the dimethylformamide *in vacuo*, was treated with 40 ml of 10% sodium hydroxide solution and extracted with ether. The ether extracts were dried (magnesium sulfate), filtered and evaporated to an orange oil which was distilled (Kugelrohr) at 155-160° (bath temperature) (0.03 mm). The yield of yellow oil was 4.8 g (84%). The free base was converted to the maleate salt (recrystallized twice from 2-propanol), 4.8 g (60%) mp 159-162° dec.

Anal. Calcd. for $C_{20}H_{23}N_3O_4S$: C, 59.83; H, 5.77; N, 10.47; S, 7.99. Found: C, 59.95; H, 5.86; N, 10.55; S, 8.01.

Octahydro-2-benzyl-5-(2-pyrimidinyl)pyrrolo[3,4-*c*]pyrrole (**21**).

This compound was prepared similarly to **20** except toluene was used as reaction solvent. The yield of free base (yellow oil which solidified upon standing) was 4.5 g (80%) bp 160-170° (bath temperature, Kugelrohr) (0.03 mm). Conversion to the hydrochloride salt gave a white solid (methanol-ether), mp 242-247° dec.

Anal. Calcd. for $C_{17}H_{21}ClN_4$: C, 64.45; H, 6.68; N, 17.68; Cl^-, 11.19. Found: C, 64.53; H, 6.81; N, 17.86; Cl^-, 11.50.

Acknowledgement.

The authors wish to thank Dr. T. P. Mori for the large scale synthesis of several intermediates used in this work and Dr. F. C. Cheng for the elemental analysis.

REFERENCES AND NOTES

(1) K. Weinges and R. Spänig, *Chem Ber.*, **101**, 3010 (1968).

(2) R. K. Huisgen US 3,285,931 (Nov. 15, 1966) to Union Carbide Corporation; *Chem. Abstr.*, **66**, p553805 (1967).

(3) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry", John Wiley and Sons, New York, NY, 1953, p 567.

(4) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(5) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., p 370.

(6) F. W. Wehrli and T. Wirhiln, "Interpretation of Carbon-13 NMR Spectra", Heyden, 1980.

(7) R. J. Abraham and P. Loftus, "Proton and Carbon-13 NMR Spectroscopy", Heyden, 1979.

(8) M. Shamma and D. M. Hinderlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum, 1979.

(9) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", John Wiley and Sons, 1972.

(10) H. Eggert and C. Djerassi, *J. Am. Chem. Soc.*, **95**, 3710 (1973).

(11) R. J. Pugmire and D. M. Grant, *ibid.*, **90**, 697 (1968).

(12) R. Garnier, R. Fause, A. Babadjamian and E. J. Vincent, *Bull. Soc. Chim. France.*, 1040 (1972).

(13) W. J. Horsley, H. Sternlicht and J. S. Cohen, *J. Am. Chem. Soc.*, **92**, 680 (1970).

(14) E. Lippmaa, M. Mägi, S. S. Novikov, L. I. Khmelnitski and A. S. Prihodko, *Org. Magn. Reson.*, **4**, 153 (1972).

(15) E. Breitmaier, G. Haas and W. Volker, "Carbon-13 NMR Data", Heyden, 1979.

(16) L. Mandell and W. A. Blanchard, *J. Am. Chem. Soc.*, **79**, 6198 (1957).

(17) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(18) Ch. Granächer, G. Wolf and A. Weidinger, *Helv. Chim. Acta*, **11**, 1228 (1928).

(19) A. T. Mason and G. R. Winder, *J. Am. Chem. Soc.*, **65**, 188 (1894).

(20) A. T. Blomquist, B. P. Hiscock and D. N. Harpp, *Synth. Commun.*, **3**, 343 (1973).

(21) J. C. Sheehan and D. D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1154 (1957).

(22) Usually two equivalents of amine were required with those amines basic enough to form a salt with the resulting acid-amide (*i.e.*, **6f**, **6g**, **6'a**, **6'f** and **13**). In these cases, the workup through aqueous sodium hydroxide solution (often large volumes) is less convenient than that described for **6a**. A stoichiometric amount (or 10% excess) of the appropriate aniline was used in the preparation of **6b-e**.