Compounds in the Pyrrolo[3,4-*d*]pyrimidine Series. Derivatives with 6-Aryl Substituents (1a)

Philip L. Southwick, R. Madhav (1b) and James A. Fitzgerald (1c)

Department of Chemistry, Carnegie-Mellon University

Methods are described for the synthesis of 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines having an aryl substituent in the 6-position. 4-Hydroxy-, 4-amino, 2-amino-4-hydroxy and 2,4-diamino derivatives were obtained. The synthetic route involved the preparation of 1-aryl-4-cyano- or 4-carboalkoxy-3-pyrrolidinones and 1-aryl-4-cyano- or 4-carboalkoxy-3-amino-3-pyrrolines as key intermediates.

In recent publications from this laboratory, methods were described for the synthesis of a variety of compounds in the previously unknown pyrrolo[3,4-*d*]pyrimidine series (2,3). In the course of further work in this series efforts have been made to obtain compounds having aryl substituents at the 6-position. It was found that both in the reactions leading to the synthesis of pyrrolidine intermediates and in the final pyrimidine ring closures rather extensive modification was needed to adapt the previously used synthetic schemes to these additional new compounds. Most of the synthetic reactions examined would be useful in the synthesis of a number of other quite different types of compounds; hence, the results described here should find application beyond the confines of the pyrrolo[3,4-*d*] pyrimidine series. The reactions investigated are summarized in Chart I. (The same letter of the alphabet will indicate a given substituent R in all formulas; the list of substituents appears below formula I). Observations on each step will be discussed below under a separate heading. Yield data and other information regarding specific compounds will be presented in the Experimental Section and in the accompanying tables.

Reactions 1 and 2: Conjugate Additions of Primary Amines to Acrylate Esters or Acrylonitrile.

Observations on the scope of a number of published procedures for the addition of primary amines to methyl or ethyl acrylate or to acrylonitrile were made during the course of the study. The most highly basic of the amines used, compounds such as benzylamine and 3,4,5-*tri*-methoxybenzylamine, underwent these additions in ethanol solution at room temperature without the use of catalysts. The use of stannic chloride in benzene solution (4) was effective in promoting the addition of aniline to ethyl acrylate, but failed when applied to addition of *p*-chloroaniline or ethyl *p*-aminobenzoate to either methyl or ethyl acrylate. The addition of *p*-chloroaniline as well as *p*-aminobenzoic acid to methyl acrylate was achieved in a refluxing glacial acetic acid solution (5). Results in additions to acrylonitrile were parallel to the extent that benzylamine and 3,4,5-trimethoxybenzylamine reacted without solvent or in ethanol in the absence of added catalysts, and aniline and *p*-chloroaniline reacted in refluxing glacial acetic acid solutions. The cyanoethylation of *o*-aminobenzoic acid was achieved using a refluxing aqueous mixture containing triethylamine in addition to the reactants (6).

Reactions 3 and 4: Formation of the *N,N*-Disubstituted Glycine Esters (IV and V) by Alkylation of Amines (II and III) with Ethyl Bromoacetate.

In the case of compounds of types II and III in which the substituent R was an aryl group, relatively high conversions to the *N*-carbethoxymethyl derivatives (IV and V) were achieved by refluxing II or III for extended periods of time (24 to 48 hours) with two moles of ethyl bromoacetate in ethanol solution. (Sodium acetate has been used for removal of hydrogen bromide in some similar procedures, but it reacts directly with ethyl bromoacetate at an undesirably rapid rate and its use was unnecessary.) After basicification and destruction of excess ethyl bromoacetate with sodium hydroxide solution, IV or V were obtained in a relatively pure state (as shown by nuclear magnetic resonance (NMR) spectra) after use of a simple extraction procedure, and were suitable for use in the subsequent Dieckmann cyclizations without further purification. For the similar alkylation of the compounds of type II in which R was a benzyl or substituted benzyl group, neutralization of the liberated hydrogen bromide was necessary, and the reaction was carried out in 95% ethanol containing one mole of ethyl bromoacetate and one mole of suspended sodium bicarbo-

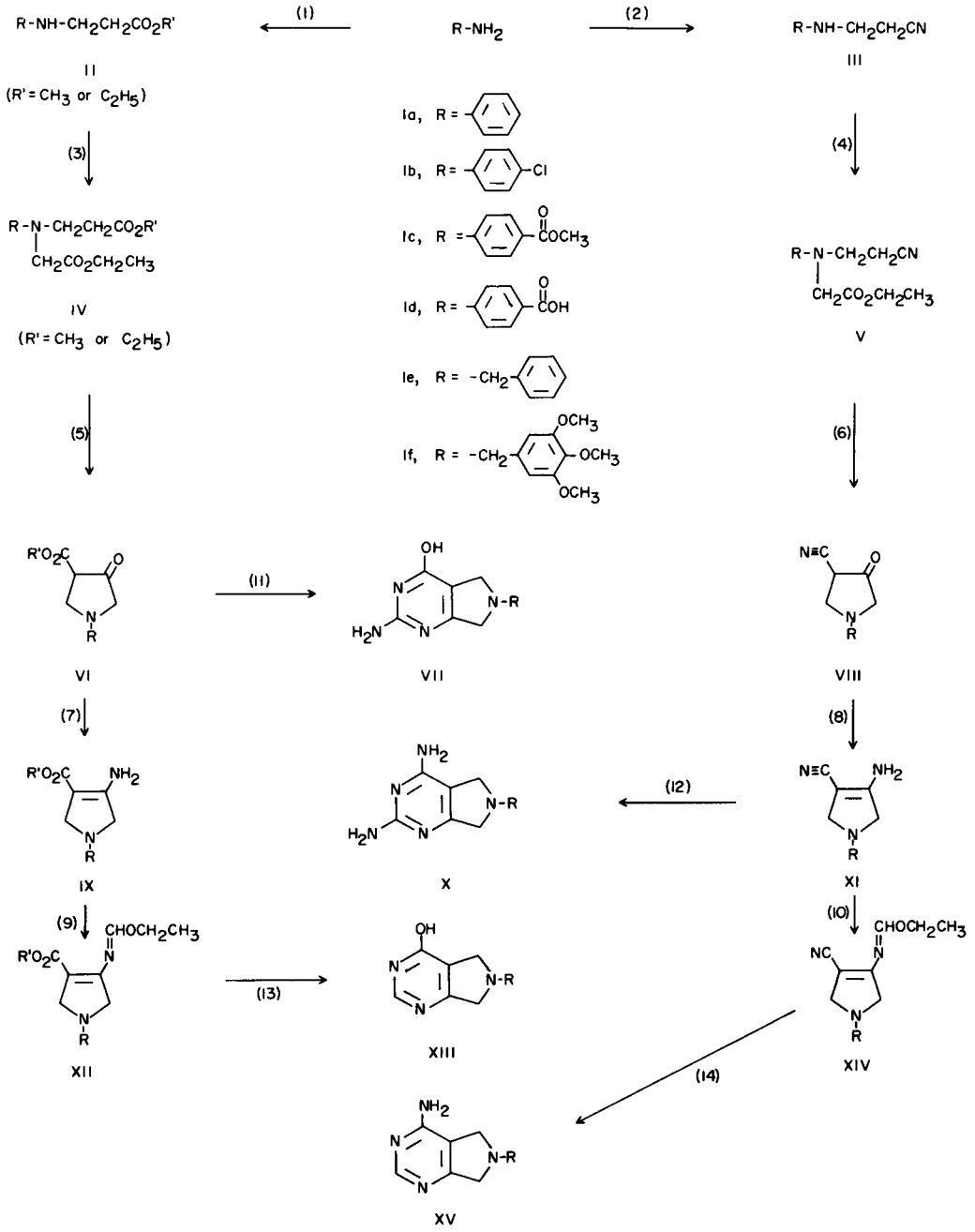
nate.

Reactions 5 and 6: Formation of 3-Pyrrolidinone Derivatives (VI and VIII) by Dieckmann Cyclizations of Diesters (IV) or Ester Nitriles (V).

The cyclizations of the Dieckmann type (2b, 2c) were carried out with sodium methoxide in methanol or sodium ethoxide in ethanol. The 4-cyano-3-pyrrolidinones (VIII) underwent decomposition when attempts were made to purify them by crystallization, and were fully characterized only in the form of the enamine derivatives (XI).

The rather low yields of VIII from the cyclization proce-

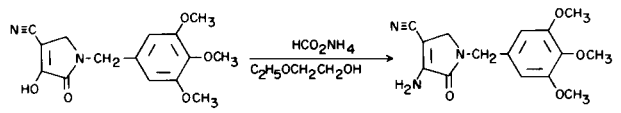
CHART I



dures must in part reflect the instability of these products. In the case of the diesters (IV) the possibility existed that Dieckmann cyclization might occur in an alternative manner to that shown and might yield 2-carbethoxy or carbomethoxy-3-pyrrolidinones (7). However, NMR spectra obtained from derived enamines (IX) effectively rule out the possibility that the major Dieckmann products have the ester function in the 2-position. Infrared spectra of the 4-carbethoxy or 4-carbomethoxy derivatives indicated that these compounds were completely enolized in the solid state (Nujol mull or potassium bromide pellet spectra), but the spectra of solutions in methylene chloride showed both enol and keto forms to be present. (Presence of the enol form was indicated by strong hydroxy absorption at *ca.* 3.05 μ and the keto form by ketonic carbonyl absorption at 5.65 μ which is absent from the enol form.) The 4-cyano compounds (VIII), on the other hand, appeared to be completely ketonic in the solid state or in chloroform solution.

Reactions 7 and 8: Formation of 4-Carboalkoxy- or 4-Cyano-3-amino-3-pyrrolines (IX or XI).

Conversion of the 3-pyrrolidinones (VI or VIII) to the 3-amino-3-pyrrolines (IX or XI) was carried out by treatment with ammonium formate. As in the examples described previously (2), reaction occurred in refluxing ethanol solutions in the case of 1-aryl derivatives. However, an attempt to apply these conditions to the 4-cyano-2,3-dioxopyrrolidine (XVI) (obtained by condensation of IIIf with diethyl oxalate in the presence of sodium ethoxide (8)) yielded merely the ammonium salt of the starting material, and conversion to the 3-amino-3-pyrroline (XVII) was achieved only by carrying out the reaction in refluxing 2-ethoxyethanol.

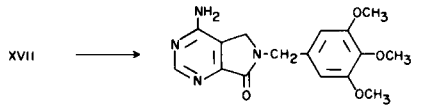


XVI XVII

The NMR spectra of the enamines (IX) in deuteriochloroform were fully consistent with the assigned structure. Thus, the 1-phenyl and 1-*p*-chlorophenyl-4-carbomethoxy compounds showed, in addition to the expected aromatic pattern, and a broad two-proton signal for the amine group, a three-proton singlet at *ca.* 6.3 τ (methyl ester resonance) and a rather broad but unresolved four-proton signal at *ca.* 5.9 τ representing the protons at the 2 and 5 positions of the pyrroline ring. It is not surprising that the chemical shift of the protons in these two locations in structure IX should be very similar since both are located on carbon atoms which are attached to the same nitrogen atom and to doubly bonded carbon atoms holding substituents which should have similar influences on chemical shifts. The NMR spectrum of the 1-phenyl-4-carbethoxy derivative differed slightly from the 4-carbomethoxy compound in that the signals at *ca.* 5.9 τ were split into multiplets (partially obscured by the quartet from the methylene portion of the *O*-ethyl group) apprently reflecting small coupling constants (2-4 Hz) such as might result from coupling of protons at position 2 with those at position 5 (9).

Reactions 9, 13, 10 and 14: Ring Closures to 4-Hydroxy- or 4-Amino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine Derivatives (XIII or XV).

In the previous application of ring closures of this type which were performed on 1-acyl derivatives, the first operation was treatment of the 4-carbethoxy or 4-cyano-3-amino-3-pyrroline with ethyl orthoformate and acetic anhydride (2). However, in the case of the 1-aryl derivatives (IX) employed in this investigation, the result of the same procedure was simply acetylation of the 3-amino group, not the desired formation of the ethoxymethylene intermediates (XII). This difficulty was circumvented by omitting the acetic anhydride and treating the compounds of type IX with ethyl orthoformate containing a small amount of formic acid. The *N*-ethoxymethylene intermediates (XII) obtained after distillation to remove other components of the reaction mixtures were not fully purified, but were treated in the crude state with ethanolic ammonia solution to effect conversion to the 4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (XIII). The same procedure was successfully applied to 4-cyano-3-amino-3-pyrrolines (XI) for the preparation of the 4-amino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (XV), and also to the 4-cyano-3-amino-3-pyrrolin-2-one (XVII), which yielded 4-amino-6-(3,4,5-trimethoxybenzyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)one (XVIII)



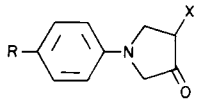
XVIII

Reaction 12: Ring Closure to 2,4-Diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (X).

The 1-aryl-3-amino-4-cyano-3-pyrrolines (XI) were converted to 6-aryl-2,4-diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (X) by treatment with guanidine carbonate in refluxing 2-ethoxyethanol (3c). The 3-amino-4-cyano-3-pyrrolin-2-one (XVII) was also converted into a diaminopyrrolo[3,4-*d*]pyrimidine derivative in the same refluxing solvent, but in this instance, guanidine itself (obtained by treatment of guanidine hydrochloride with

TABLE I

4-Carboalkoxy- and 4-Cyano-1-aryl-3-pyrrolidinones (VI and VIII)

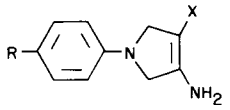


R-	X-	M.P.	Procedure	Alkylation Step Time (hours)	Alkylation Step Yield, % (a)	Cyclization Step Time (hours)	Cyclization Step Yield, %	Formula	Analysis of Pyrrolidinones Calcd. % C	H	N	Found % C	H	N
H-	$-CO_2Et$	70-71° (b)	B	5	90	0.33	76							
H-	$-CO_2Me$	106-107°	A	24	70	1	72	$C_{12}H_{13}NO_3$	65.74	5.98	6.39	65.48	5.95	6.19
Cl-	$-CO_2Me$	83-83.5°	A	48	87	2	70	$C_{12}H_{12}ClNO_3$	56.81	4.77	5.52	56.85	4.73	5.48
$CH_3O-\overset{O}{\overset{\|}{C}}-$	$-CO_2Me$	149-151°	C	48	51	1.5	77	$C_{14}H_{15}NO_5$	60.64	5.45	5.05	60.75	5.27	4.89
H-	-CN	128-130°	D	24	72 (c)	1	37				(d)			
Cl-	-CN	135-138°	D	48	75	1	34				(d)			

(a) The yields of the alkylated products quoted were based on amounts of material showing NMR spectra corresponding to the expected structure. (b) Lit. m.p. 69-70°, see A. T. De Mouilpied, *J. Chem. Soc.*, 435 (1905). (c) Based on the quantity of aniline used. (d) Suitable analytical sample not obtained because of the difficulty in purification.

TABLE II

4-Carboalkoxy- and 4-Cyano-1-aryl-3-amino-3-pyrrolines (IX and XI)

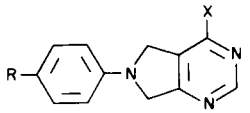


R-	X-	M.P.	Moles Ammonium Formate Per mole substrate	Solvent Volume (ml.) Per 0.1 mole Cpd.	Reflux Time (hours)	Yield %	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
H-	$-CO_2Et$	141-143°	4	300	14	92	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.08	6.80	12.05
Cl-	$-CO_2Me$	195-196°	4	400	12	80	$C_{12}H_{13}ClN_2O_2$	57.03	5.18	11.09	57.15	5.21	11.15
$CH_3-O-\overset{O}{\overset{\|}{C}}-$	$-CO_2Me$	223-226°	2.2	2000 (a)	10	95	$C_{14}H_{16}N_2O_4$	60.86	5.84	10.14	60.81	5.81	9.96
H-	-CN	217-219°	4	600	10	68	$C_{11}H_{11}N_3$	71.33	5.99	22.69	71.22	6.11	22.42
Cl-	-CN	213-214°	4	600	3	51	$C_{11}H_{10}ClN_3$	60.14	4.59	19.13	59.88	4.50	18.98

(a) The solvent was 1:3 - benzene:absolute ethanol.

TABLE III

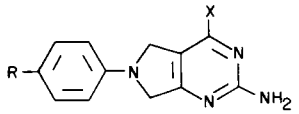
4-Amino- and 4-Hydroxy-6-aryl-6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidines (XV and XIII)



R-	X-	M.P.	Ethyl Orthoformate, ml., Per gram of substrate	Reflux Time (hours)	Ammonia Soln., ml., Per gram of substrate	Time (hours)	Yield %	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
H-	-OH	293-316°	20	2	50	2	57	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.44	5.30	19.71
H-	-OH	335-341°	20	2	50	2	60	$C_{12}H_{10}ClN_3O$	58.19	4.07	16.97	57.94	4.26	16.77
$CH_3O\text{-}\overset{O}{\overset{\|}{C}}\text{-}$	-OH	323-340°	50	3	200	2	79	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49	62.18	4.81	15.33
H-	$-NH_2$	285-295°	25	5	50	2.5	90	$C_{12}H_{12}N_4$	67.90	5.70	26.40	67.64	5.74	26.45
Cl-	$-NH_2$	290-305°	25	6	38	3	95	$C_{12}H_{11}ClN_4$	58.42	4.50	22.71	58.62	4.63	22.53

TABLE IV

2-Amino-4-hydroxy- and 2,4-Diamino-6-aryl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (VII and X)

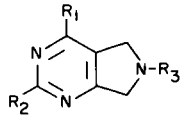


R-	X-	M.P.	Procedure	Solvent Volume (ml.)	Yield %	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
H-	-OH	310-322°	A	50	50	$C_{12}H_{12}N_4O$	63.14	5.30	24.55	63.18	5.45	24.37
Cl-	-OH	325-340° (a)	A	50	58	$C_{12}H_{11}ClN_4O\cdot\frac{1}{2}H_2O$	53.04	4.45	20.62	53.34	4.94	20.44
H-	$-NH_2$	265-270°	B	25	70	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.14	5.95	30.96
Cl-	$-NH_2$	263-267°	B	30	86	$C_{12}H_{12}ClN_5$	55.07	4.62	26.76	55.01	4.83	26.60

(a) Crystallized from a dimethylformamide-water mixture. Analysis suggests that the compound is a hemi-hydrate.

TABLE V

Nuclear Magnetic Resonance Spectra (a)
6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines



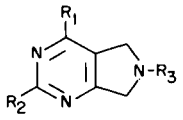
R_1-	R_2-	R_3-	5- and 7-CH_2	τ 2-CH	R_3-
HO-	H-	C_6H_5-	4.41, 4.56	0.93	2.18-2.40
HO-	H-	*p*-Cl-C_6H_4-	4.48, 4.61	0.95	2.18-2.40
HO-	H_2N-	C_6H_5-	4.58, 4.78	–	2.38
H_2N-	H-	C_6H_5-	4.35, 4.45	0.92	2.28
H_2N-	H-	*p*-Cl-C_6H_4-	4.49, 4.58	1.05	2.20-2.60
H_2N-	H_2N-	C_6H_5-	4.59	–	2.27
H_2N-	H_2N-	*p*-Cl-C_6H_4-	(b)	–	2.37

(a) All NMR spectra were determined in trifluoroacetic acid solution, with tetramethylsilane as an internal reference. (b) The 5- and 7-methylene protons could not be separately assigned. Signals at 4.68 (4H), 6.60 (2H), and 6.71 (2H) were observed, and in addition, a peak at 1.55 (1H) was evident.

TABLE VI

Ultraviolet Spectra

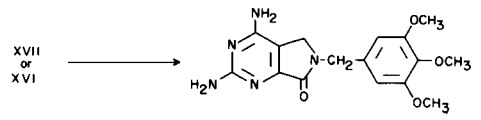
6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines



R_1-	R_2-	R_3-	Solvent	λ max, mμ (log ε)
HO-	H-	C_6H_5-	10% NaOH	238 (4.29) 298 (3.32) sh
HO-	H-	*p*-Cl-C_6H_4	10% NaOH	257 (4.28) 205 (3.32) sh
HO-	H-	*p*-MeO_2C-C_6H_4-	10% NaOH	291 (4.29) 295 (4.29) sh
HO-	H_2N-	C_6H_5-	10% NaOH	242 (4.35) 270 (4.08) sh 305 (3.38) sh
HO-	N_2N-	*p*-Cl-C_6H_4-	10% NaOH	255 (4.27) 310 (3.26) sh
H_2N-	H-	C_6H_5-	10% HCl	247 (4.26) 300 (3.28) sh
H_2N-	H-	*p*-Cl-C_6H_4-	10% HCl	252 (4.30) 299 (3.45)
H_2N-	H_2N-	C_6H_5-	10% HCl	230 (a) sh 272 (a)
H_2N-	H_2N-	*p*-Cl-C_6H_4-	10% HCl	247 (a) 285 (a) sh

(a) The extinction coefficients were not determined because not all of the compound dissolved.

sodium ethoxide in ethanol) was used rather than guanidine carbonate. The product, 2,4-diamino-6-(3,4,5-trimethoxybenzyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-one (XIX) was also obtained from the 4-cyano-2,3-dioxopyrrolidine (XVI) by the action of guanidine carbonate in refluxing 2-ethoxyethanol, but the procedure utilizing XVII as the intermediate appears to be the more reliable of the two.



XIX

Reaction 11: Cyclization to 2-Hydroxy-4-amino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (VII).

Conversion of the 4-carbethoxy or 4-carbomethoxy-3-pyrrolidinones (VI) to pyrrolo[3,4-*d*]pyrimidine derivatives of type VII was performed efficiently by refluxing the starting materials in ethanol solutions of guanidine carbonate (10).

EXPERIMENTAL (11)

Preparation of Methyl and Ethyl *N*-Substituted-β-aminopropionates and *N*-Substituted-β-aminopropionitriles (II and III).

Instances of the use of the different procedures for the addition of amines to acrylate esters or acrylonitrile are exemplified by the experiments described below.

Procedure A.

Methyl *N*-*p*-Chlorophenyl-β-aminopropionate (IIb).

A mixture of 127.5 g. (1.0 mole) of *p*-chloroaniline, 344 g. (4 moles) of methyl acrylate and 100 ml. of acetic acid was heated under reflux for 10 hours. The reaction mixture was evaporated almost to dryness, poured into water and made basic with 40% sodium hydroxide solution. The solid that separated was collected by filtration and recrystallized from an ethanol-water mixture. The yield was 107 g. (50%) of product, m.p. 58-60°. Recrystallization from a mixture of Skellysolve B and methylene chloride raised the m.p. to 61.5-62°.

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.54. Found: C, 56.06; H, 5.77; N, 6.41.

Methyl *N*-*p*-Carboxyphenyl-β-aminopropionate (IId).

A mixture of 137 g. (1.0 mole) of *p*-aminobenzoic acid, 344 g. (4 moles) of methyl acrylate and 344 ml. of acetic acid was refluxed for 9 hours. The reaction mixture was cooled and the crystalline product which separated was collected by filtration, then washed with ether until all traces of acetic acid and methyl acrylate were removed. A 140 g. (63%) yield of product of m.p. 188-190° was obtained. (Lit. (5), m.p. 186-187°.)

Procedure B.

Ethyl *N*-3,4,5-trimethoxybenzyl-β-aminopropionate (IIf).

A solution of 7.5 g. (0.038 mole) of 3,4,5-trimethoxybenzylamine and 3.8 g. (0.038 mole) of ethyl acrylate in 20 ml. of absolute ethanol was allowed to stand overnight at room temperature, and the solvent was evaporated under reduced pressure to yield an amount of yellow oil corresponding to a quantitative yield (11.3 g.). This product was used in subsequent steps without purification since the NMR spectrum did not indicate the presence of significant amounts of other materials.

Procedure C.

N-*p*-chlorophenyl-β-aminopropionitrile (IIIb).

A solution of 127.5 g. (1.0 mole) of *p*-chloroaniline and 100 ml. of acetic acid in 266 ml. (4.0 mole) of acrylonitrile was refluxed for 24 hours. The solvent was removed under reduced pressure, and the residual oil was poured into 500 ml. of water, made strongly basic with sodium hydroxide solution, and cooled. The product was separated by filtration and recrystallized from an ethanol-water mixture. The yield was 67 g. (37%) of a product melting at 72-75° (Lit. (12), m.p. 74-75°).

Procedure D.

N-*p*-Carboxyphenyl-β-aminopropionitrile (IIId).

A solution of 100 g. (0.73 mole) of *p*-aminobenzoic acid, 72.5 ml. (1.18 mole) acrylonitrile, and 69 ml. (0.50 mole) of triethylamine in 750 ml. of water was refluxed for 48 hours. The reaction mixture was cooled and acidified with 70 ml. of concentrated hydrochloric acid. The product was collected by filtration and recrystallized from a dimethylformamide-methanol mixture to give 55% yield of product, m.p. 219°. (Lit. (13), m.p. 220-221.5°).

Procedure E.

N-3,4,5-Trimethoxybenzyl-β-aminopropionitrile (IIIf).

A solution of 19.0 g. (0.0965 mole) of 3,4,5-trimethoxybenzylamine (14) and 5.3 g. (0.10 mole) of acrylonitrile in 20 ml. of absolute ethanol was allowed to stand at room temperature for 8 hours. The solvent was evaporated to yield a viscous yellow liquid which was used in subsequent reactions without purification since the NMR spectrum indicated a satisfactory state of purity.

Preparation of Methyl *N*-*p*-Carbomethoxyphenyl-β-aminopropionate (IIc).

To a suspension of 100 g. (0.45 mole) of methyl *N*-*p*-carboxyphenyl-β-aminopropionate (IId) in 475 ml. of methanol was cautiously added 90 ml. of concentrated sulfuric acid. The resulting solution was refluxed for 20 hours and then poured into 2.5 l. of ice water. The product was collected by filtration and recrystallized from 95% ethanol to yield 78 g. (73%) of the methyl ester as white needles, m.p. 116-117°. (Lit. (5), m.p. 116-117°.)

Preparation of *N*-*p*-Carbomethoxy-β-aminopropionitrile (IIIc).

To an excess of diazomethane (*ca.* 6 g. from 20.6 g. (0.20 mole) of *N*-methyl-*N*-nitrosourea (15)) in 300 ml. of ether at 0° was added 20 g. (0.105 mole) of *N*-*p*-carboxyphenyl-β-aminopropionitrile in small portions with stirring. The mixture was allowed to come to room temperature and stirred for two hours. Acetic acid (2 ml.) was added to destroy the excess diazomethane, and the product was collected by filtration to give 19.45 g. of white powder, m.p. 116-118°. Recrystallization from ethanol gave white needles, m.p. 120-121°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.66; H, 6.03; N, 13.54.

Preparation of 4-Carboalkoxy- and 4-Cyano-1-aryl-3-pyrrolidinones (VI and VIII).

The procedures are described below and results are compiled

in Table I.

Procedure A.

1-Aryl-4-carbomethoxy-3-pyrrolidinones (VI).

A solution of 0.11 mole of the methyl *N*-aryl-β-aminopropionate (II) and 0.2 mole of ethyl bromoacetate in 40 ml. of 95% ethanol was refluxed for 24 to 48 hours. The reaction mixture was cooled, poured into *ca.* 200 ml. of ice water, and made strongly basic with 40% sodium hydroxide solution. The mixture was stirred at 0° until the odor of ethyl bromoacetate was no longer evident and then was extracted with ether. The combined ether extracts were washed with water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure.

The viscous residual oil was weighed and dissolved in 50 to 100 ml. of anhydrous methanol. A solution prepared from sodium (1.5 g. atoms per mole of the crude product) dissolved in 50 to 100 ml. of anhydrous methanol was added, and the resulting solution was refluxed for two hours. Water (100 to 150 ml.) was added to partially dissolve the precipitated sodium enolate, and the stirred suspension was acidified with acetic acid. The keto ester was collected by filtration and recrystallized. The *p*-carboxyphenyl derivative was recrystallized from a dimethylformamide-ethanol solution; all of the other products were recrystallized from aqueous ethanol.

Procedure B.

4-Carbethoxy-1-phenyl-3-pyrrolidinone (VIa).

A solution of 53.5 g. (0.277 mole) of ethyl *N*-phenyl-β-aminopropionate (IIa), 46.3 g. (0.277 mole) of ethyl bromoacetate, and 37.7 g. (0.277 mole) of sodium acetate trihydrate in 50 ml. of 95% ethanol was refluxed for 5 hours. The reaction mixture was poured into *ca.* 200 ml. of ice water, made basic with 40% sodium hydroxide solution, and extracted with ether. The combined ether extracts were washed with water and saturated sodium chloride solution, the solvent was evaporated under reduced pressure, and the product was distilled under reduced pressure. The fraction distilling at 165° (2 mm.) was collected, yielding 70 g. (90%) of a colorless viscous oil.

A solution of the liquid in 50 ml. of anhydrous ethanol was treated with a solution prepared from 2.4 g. (0.105 mole) of sodium in 105 ml. of anhydrous ethanol. After refluxing the resulting solution for 20 minutes, water (100 ml.) was added, and the keto ester was isolated as in Procedure A.

Procedure C.

4-Carbomethoxy-1-*p*-carbomethoxyphenyl-3-pyrrolidinone (VIc).

A solution of 23.7 g. (0.1 mole) of methyl *N*-*p*-carbomethoxyphenyl-β-aminopropionate (IIc), 33 ml. (0.3 mole) of ethyl bromoacetate, 40 ml. of 95% ethanol, and 13.6 g. (0.1 mole) of sodium acetate trihydrate was refluxed for 48 hours. The product (IVc) was isolated and cyclized as in Procedure A.

Procedure D.

1-Aryl-4-cyano-3-pyrrolidones (VIII).

The *N*-aryl-β-aminopropionitrile (III) (0.1 mole) was refluxed in 10 ml. of 95% ethanol with 22 ml. (0.2 mole) of ethyl bromoacetate for 24 to 60 hours. The reaction mixture was poured into 200 ml. of ice-water, made strongly basic with 40% sodium hydroxide solution, and stirred at 0° until the odor of ethyl bromoacetate was no longer present. The mixture was then extracted with ether; the combined ether extracts were washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield viscous orange to red oils. The crude yields were calculated from the weights of these crude oils.

The products of the alkylations were dissolved in *ca.* 100 ml. of absolute ethanol and to this solution was added a solution of 1.5 equivalents of sodium dissolved in 50 to 100 ml. of absolute ethanol. The mixture was refluxed from one to four hours, and the precipitated sodium enolate was collected by filtration and washed with ethanol and ether. The salt was suspended in water (*ca.* 200 ml.), acidified with acetic or dilute hydrochloric acid, and the cyanopyrrolidinone was collected by filtration. In all cases these compounds were found to be unstable in warm solutions and hence could not readily be purified by recrystallization.

Preparation of 4-Carboalkoxy- and 4-Cyano-3-amino-1-aryl-3-pyrrolines (IX and XI).

Solutions of 1-aryl-4-carboalkoxy-3-pyrrolidinones (VI), or 1-aryl-4-cyano-3-pyrrolidinones (VIII) and an excess of ammonium formate were refluxed in 95% ethanol for 3 to 14 hours. The solution was cooled to 0° and filtered to collect the product. In most cases, the products were pure enough to use in subsequent reactions. Analytical samples were usually prepared by recrystallizations from ethanol. The details and results of the individual experiments are tabulated in Table II.

Preparation of 4-Amino- and 4-Hydroxy-6-aryl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (XV and XIII).

The 4-carboalkoxy- and 4-cyano-1-aryl-3-amino-3-pyrrolines (IX and XI) were refluxed in ethyl orthoformate containing 1 ml. of formic acid for two to six hours. The solvent was then removed by distillation under reduced pressure, and the resulting oily semisolids were suspended in ethanol saturated with anhydrous ammonia and stirred at room temperature for two to seven hours. The amino pyrimidines were collected by filtration. To isolate the hydroxy pyrimidines it was necessary to distill off about half of the solvent under reduced pressure and to add an equal volume of ether, before the product was collected by filtration. All products were recrystallized from dimethylformamide. Individual details and results are listed in Table III.

Preparation of 2-Amino-4-hydroxy- and 2,4-Diamino-6-aryl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (VII and X).

The individual details and results are listed in Table IV.

Procedure A.

6-Aryl-2-amino-4-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (VII).

Suspensions of 0.02 moles of 1-aryl-4-carbomethoxy-3-pyrrolidinones (VI) and 3.60 g. (0.02 mole) of guanidine carbonate in 50 ml. of absolute ethanol were refluxed with stirring for 18 hours. The mixtures were cooled, poured into 150 ml. of water, and acidified with acetic acid. The products were collected by filtration and washed with water, ethanol, and ether (16).

Procedure B.

6-Aryl-2,4-diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines (X).

The 1-aryl-3-amino-4-cyano-3-pyrroline (XI) (0.01 mole) and guanidine carbonate (0.01 mole) were refluxed with stirring in 2-ethoxyethanol for *ca.* four hours. The reaction mixtures were cooled, and water (75 to 100 ml.) was added. The products were collected by filtration and washed with water, ethanol, and ether.

All products were recrystallized from dimethylformamide to

obtain analytical samples.

Preparation of 4-Cyano-2,3-dioxo-1-(3,4,5-trimethoxybenzyl)-pyrrolidine (XVI).

A solution of 24.1 g. (0.965 mole) of *N*-cyanoethyl-3,4,5-trimethoxybenzylamine and 14.1 g. (0.965 mole) of diethyl oxalate in 20 ml. of absolute ethanol was added to a cold solution of 2.3 g. (0.1 mole) of sodium metal dissolved in 60 ml. of absolute ethanol. This mixture was kept at 0° for 30 minutes and then allowed to stir overnight at room temperature. The precipitate that formed was dissolved in 800 ml. of water and the resulting solution was acidified with 20% hydrochloric acid. The white granular solid that precipitated was collected by filtration and washed with 75% aqueous ethanol, yielding 22.2 g. (76%) of product, m.p. 188-190° dec. Recrystallization from a benzene-ethanol solution raised the melting point to 190-191°.

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.21. Found: C, 59.25; H, 5.26; N, 9.10.

Preparation of 3-Amino-4-cyano-1-(3,4,5-trimethoxybenzyl)-2-oxo-3-pyrroline (XVII).

A mixture of 3.04 g. (0.01 mole) of 4-cyano-2,3-dioxo-1-(3,4,5-trimethoxybenzyl)pyrrolidine (XVI), 1.26 g. (0.01 mole) of ammonium formate, and 10 ml. of 2-ethoxyethanol was refluxed for 4 hours. The brown-colored reaction mixture was cooled to 0°, and diluted with petroleum ether (b.p. 30-60°). The precipitated solid was collected by filtration, washed with petroleum ether and crystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30-60°) with decolorization by Norite. The product (2.1 g., 70% yield) was obtained as small colorless needles, m.p. 164-166°.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.20; H, 5.79; N, 12.33, 12.93 (17).

Preparation of 4-Amino-6-(3,4,5-trimethoxybenzyl)-5*H*-pyrrolo-[3,4-*d*]pyrimidin-7(6*H*)-one (XVIII).

A mixture of 0.75 g. (2.5 mmoles) of compound XVII, 10 ml. of ethyl orthoformate and 2.5 ml. of formic acid was refluxed for 2 hours. The volatile components were removed by distillation under reduced pressure, and the residue was treated with an excess of ammonia in absolute ethanol. After the mixture had been allowed to stand overnight the product which had separated was collected by filtration. Crystallization from ethyl acetate with Norite decolorization, followed by recrystallization from a mixture of ethyl acetate and petroleum ether (b.p. 30-60°) afforded white needles, m.p. 246-248°; yield 0.17 g. (21%).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; N, 5.49; N, 16.96. Found: C, 57.77; H, 5.39; N, 16.80.

Preparation of 2,4-Diamino-6-(3,4,5-trimethoxybenzyl)-5*H*-pyrrolo-[3,4-*d*]pyrimidine-7(6*H*)-one (XIX).

A solution of 0.6 g. (10 mmoles) of guanidine was prepared by treating 0.96 g. (10 mmoles) of guanidine hydrochloride with an equivalent quantity of sodium ethoxide solution in absolute ethanol, adding 25 ml. of 2-ethoxyethanol and removing ethanol by distillation. Compound XVII (1.5 g., 5 mmoles) was added and the mixture was refluxed for 20 hours. The precipitated products were collected by filtration, washed with cold water to remove sodium chloride, and crystallized from glacial acetic acid to yield 1.15 g. (67%) of compound XIX as a powdery white solid, m.p. 306-309°, UV λ max (10% hydrochloric acid) 220 (log ε 4.51), 252 (log ε, 3.90, shoulder), 295 mμ (log ε, 3.72, shoulder).

Anal. Calcd. for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55; N, 20.28. Found: C, 55.59; H, 5.50; N, 20.32.

REFERENCES

(1a) This investigation was supported by a research grant (GM-04371) from the National Institutes of Health, U. S. Public Health Service. (b) Postdoctoral Research Associate. (c) This paper is based principally upon a thesis submitted by James A. Fitzgerald in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie-Mellon University, 1967.

(2a) P. L. Southwick and G. H. Hoffman, *J. Org. Chem.*, 28, 1332 (1963). (b) T. Sheradsky and P. L. Southwick, *ibid.*, 30, 194 (1965). (c) T. Sheradsky and P. L. Southwick, *J. Heterocyclic Chem.*, 4, 1 (1967).

(3) Recent publications on this series of compounds by other investigators include the following: (a) J. F. Cavalla, *Tetrahedron Letters*, 2807 (1964); (b) J. F. Cavalla, N. E. Webb and J. A. D. Willis, *J. Chem. Soc.*, C, 698 (1967); (c) J. F. Cavalla and J. A. D. Willis, *ibid.*, 963 (1967); (d) K. Thomae, British Patent 1,037,640 (Aug. 3, 1966); *Chem. Abstr.*, 65, 20146a (1966); (e) N. E. Britikova, K. A. Chkhikvadze and O. Yu. Magidson, (To All-Union Scientific-Research Chemical-Pharmaceutical Institute) U.S.S.R. Patent 179,321, (Feb. 8, 1966); (f) N. E. Britikova, E. I. Metel'Kova, E. I. Chkhikvadze and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.*, 1089 (1967); *Chem. Abstr.*, 69, 52092a (1968); (g) G. Ohnacker, (To Boehringer Indelheim G.m.b.H.). U.S. Patent 3,342,819 (Sept. 19, 1967); (h) K. Okumura and M. Ikezaki, (To Tanabe Feiyaku Co., Ltd.) Japanese Patents 1873 (1967) and 1874 (1967) (Jan. 27, 1967); *Chem. Abstr.*, 66, 95077e and 95078f (1967).

(4) W. S. Johnson, E. L. Worsch and B. G. Buell, *J. Am. Chem. Soc.* 71, 1901 (1949).

(5) M. Lipp, F. Dallacker and H.-G. Rey, *Chem. Ber.*, 91, 2239 (1958).

(6) P. Buckus, G. Dienys and R. Stonyte, *Lietuvos TSR Aukstuju Mokyklu Mokslu Darbai*, Chem. in Chem. Tech., 3, 65 (1963); *Chem. Abstr.*, 59, 12702h (1963).

(7) It has been demonstrated that under equilibrating conditions (use of sodium ethoxide in ethanol) ethyl *N*-ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)glycinate cyclizes to yield 1,4-dicarbethoxyl-3-pyrrolidinone rather than 1,2-dicarbethoxy-3-pyrrolidinone. See J. Blake, C. D. Willson and H. Rapoport, *J. Am. Chem. Soc.*, 86, 5293 (1964).

(8) The condensation with ethyl oxalate was conducted in the manner described in the doctoral thesis of J. A. Vida, Carnegie Institute of Technology, 1960, p. 147; cf. R. Adams, S. Miyano and M. D. Nair, *J. Am. Chem. Soc.*, 83, 3323 (1961).

(9) Long range proton-proton couplings of similar magnitude have been observed in other heterocyclic systems. Cf. A. Hofmann, W. V. Philipsborn and C. H. Eugster, *Helv. Chim. Acta.*, 48, 1332 (1965) and J. E. Anderson, *J. Chem. Soc.*, B, 712 (1967).

(10) B. R. Baker, *J. Am. Chem. Soc.*, 81, 3108 (1959).

(11) All melting points are corrected. Microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, Galbraith Laboratories, Knoxville, Tennessee and M-H-W Laboratories, Garden City, Michigan. All infrared data were obtained from Nujol mulls, unless otherwise noted, on Perkin-Elmer Model 21 and Infracord spectrophotometers. Ultraviolet determinations were made on the Cary Model 11 spectrophotometer. All NMR spectral determinations were made at 60 MHz with a Varian A-60 spectrometer, and, unless otherwise noted, were obtained from deuteriochloroform solutions at ambient temperature, using tetramethylsilane as an internal reference.

(12) A. F. Bekhli, *Dokl. Akad. Nauk S.S.S.R.*, 113, 588 (1957); *Chem. Abstr.*, 51, 14577d (1957).

(13) R. B. Zhurin and V. N. Ivina, *Zh. Obshch. Khim.*, **33**, 3045 (1963); *Chem. Abstr.*, 60, 1729a (1964).

(14) 3,4,5-Trimethoxybenzylamine was obtained in yields of *ca.* 80% by reduction of either 3,4,5-trimethoxybenzamide or 3,4,5-trimethoxybenzonitrile with lithium aluminum hydride using 4 moles of hydride to 1 of substrate in tetrahydrofuran solution. The reductions were carried out at reflux temperature, with a reaction period of 3 hours for the nitrile, 20 hours for the amide.

(15) F. Arndt in "Organic Synthesis," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(16) Compound VIIa, the phenyl derivative, which crystallized form dimethylformamide in the form of large plates and showed prominent infrared bands at 2.89, 2.99, 5.93, 6.24-6.31, and 6.40 μ (Nujol mull), could be dissolved in 20% aqueous sodium hydroxide and precipitated by acidification with acetic acid to yield a substance having a different infrared spectrum (Nujol mull) closely resembling that of the corresponding 6-*p*-chlorophenyl derivative (VIIb). (Both had prominent bands at *ca.* 2.94, 3.19, 5.94, 6.08 and 6.24 μ). The latter compound gave analytical data corresponding to a hemihydrate. The acid-precipitated form of VIIa reverted to the original form when crystallized again from dimethylformamide.

(17) The reason for the variable and somewhat low values from the Dumas nitrogen determinations on this compound was not established, but the problem is reminiscent of similar difficulties with other heterocyclic nitriles. That the nitrogen determination was at fault was demonstrated by examination of the high-precision mass spectrum of the compound, which showed the molecular ion at an m/e value of 303.1231 as compared with the calculated value of 303.1219 for $C_{15}H_{17}N_3O_4$. Impurities, if any, were not evident in the mass spectrum. (Determination by J. R. Boal with an AEI-MS-9 mass spectrometer.)

Received April 28, 1969 Pittsburgh, Pennsylvania 15213