2-Amino-4-aryl-6-(ω-carboxyalkyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)ones. Preparation *via* a One-Pot Synthesis of 1-(ω-Carboxyalkyl)-4-carbethoxy-2,3-dioxopyrrolidines

R. Madhav, Carroll A. Snyder and Philip L. Southwick

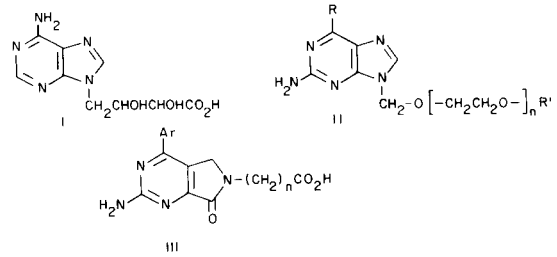
Department of Chemistry, Carnegie-Mellon University,
4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Received February 11, 1980

1-(ω-Carboxyalkyl)-4-carboethoxy-2,3-dioxopyrrolidines were prepared by a one-pot synthesis from β-alanine or γ-aminobutyric acid, ethyl acrylate and diethyl oxalate. In a second one-pot process these products were hydrolyzed, decarboxylated and condensed with aromatic aldehydes under the influence of hydrochloric acid to yield 1-(ω-carboxyalkyl)-4-arylidene-2,3-dioxopyrolidines, which yielded 2-amino-4-aryl-6-(ω-carboxyalkyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)-ones upon treatment with guanidine. It was shown that 3,4-dihydro derivatives of certain 2-amino-4-aryl-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)ones, formed initially in the guanidine reaction, readily undergo conversion to 5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)ones.

J. Heterocyclic Chem., **17**, 1231 (1980).

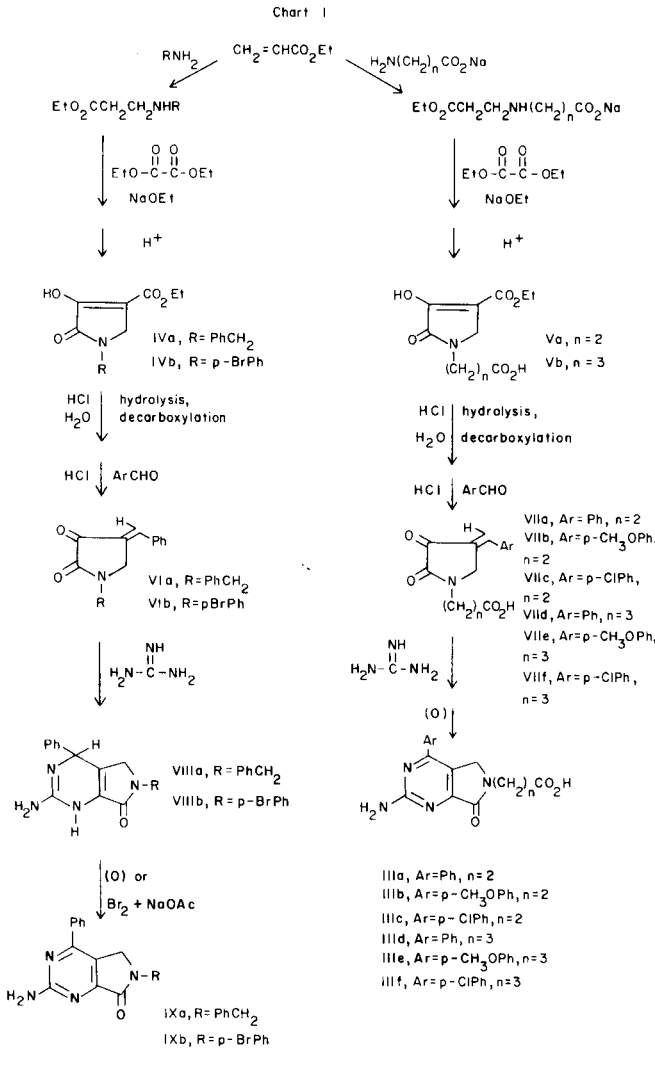
The mushroom metabolite eritadenine (I) and some of its synthetic analogues have been reported to exhibit anticholesteremic activity (1,2), and antiviral activity



has been claimed for another series of related compounds (II) (3). These indications of physiological activity in purine derivatives having a side chain of the fatty-acid or polyether types suggest the possibility of finding biological effects from somewhat similarly constituted pyrrolo[3,4-*d*]pyrimidine derivatives (III). The present work, an aspect of a continuing search for biological activity among pyrrolo[3,4-*d*]pyrimidine derivatives (4), has led to the synthesis of a series of compounds of type III.

The first step in the synthesis of pyrrolo[3,4-*d*]-pyrimidines of type III was carried out by modification of the one-flask version (5) of the method of Southwick and Crouch (6), in which oxalate esters are condensed *in situ* with esters of *N*-substituted β-alanines prepared from addition of primary amines to acrylate esters. In this instance the requisite *N*-substituted β-amino esters were obtained in solution by addition of the sodium salts of β-alanine or γ-aminobutyric acid to ethyl acrylate in absolute ethanol. Condensation of these intermediates with ethyl oxalate in the presence of sodium ethoxide yielded the enolic 4-carboethoxy-2,3-dioxopyrrolidines

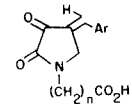
Chart I



0022-152X/80/061231-05$02.25

Table I

Benzylidene Derivatives

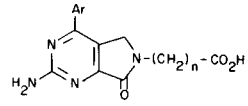


VII

Compound No.	Ar	n	Yield %	M.p.	Molecular Formula	Analysis	C	H	N	Uv Data λ max nm	(log ε)
VIIa	Ph-	2	61.1	201-202	$C_{14}H_{13}NO_4$	Calcd.	64.86	5.05	5.40	229	(3.83)
						Found	64.75	5.12	5.30	239	(3.77)
										329	(4.41)
VIIb	*p*-CH_3OPh-	2	64.4	238-240	$C_{15}H_{15}NO_5$	Calcd.	62.28	5.28	4.84	247	(4.09)
						Found	61.98	5.31	4.84	370	(4.59)
VIIc	*p*-ClPh-	2	45.5	249-250	$C_{14}H_{12}NO_4Cl$	Calcd.	57.34	4.10	4.78	233	(3.89)
						Found	57.28	4.26	4.67	334	(4.39)
VIId	Ph-	3	57.8	206-207	$C_{15}H_{15}NO_4$	Calcd.	65.92	5.53	5.13	229	(3.83)
						Found	65.80	5.74	5.05	235	(3.79)
										328	(4.43)
VIIe	*p*-CH_3O-Ph-	3	62.3	195-196	$C_{16}H_{17}NO_5$	Calcd.	63.36	5.65	4.62	246	(3.92)
						Found	63.25	5.61	4.53	370	(4.41)
VIIf	*p*-ClPh-	3	43.1	206-207	$C_{15}H_{14}NO_4Cl$	Calcd.	58.54	4.58	4.55	233	(3.88)
						Found	58.88	4.68	4.32	333	(4.45)

Table II

2-Amino-4-aryl-6-(ω-carboxyalkyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)ones



III

Compound No.	Ar	n	Yield %	M.p.	Molecular Formula	Analysis	C	H	N	Uv Data λ max nm	(log ε)
IIIa	Ph-	2	26.5	290-291	$C_{15}H_{14}N_4O_3$	Calcd.	60.39	4.73	18.78	248	(4.32)
						Found	60.08	4.73	18.71	265	(4.22)
										347	(4.05)
IIIb	*p*-CH_3OPh-	2	31.1	254-256	$C_{16}H_{16}N_4O_4$	Calcd.	58.53	4.91	17.07	234	(4.49)
						Found	58.01	5.01	16.80	295	(4.12)
										349	(4.17)
IIIc	*p*-Cl-Ph	2	18.3	273-274	$C_{15}H_{13}N_4O_3Cl$	Calcd.	54.14	3.94	16.84	254	(4.23)
						Found	54.44	4.03	16.93	268	(4.23)
										350	(3.92)
IIId	Ph-	3	28.5	228-229	$C_{16}H_{16}N_4O_3$	Calcd.	61.53	5.16	17.94	249	(4.19)
						Found	61.54	4.92	18.06	268	(4.09)
										348	(3.77)
IIIe	*p*-CH_3OPh-	3	29.1	240-241	$C_{17}H_{18}N_4O_4$	Calcd.	59.64	5.30	16.37	235	(4.48)
						Found	59.66	5.43	16.20	298	(4.23)
										350	(4.26)
IIIf	*p*-ClPh-	3	20.3	253-255	$C_{16}H_{15}N_4O_3Cl$	Calcd.	55.41	4.36	16.16	255	(4.29)
						Found	55.44	4.28	16.08	269	(4.29)
										349	(3.99)

(Va and b) in moderate yield. The method did not succeed, however, when applied to sodium salts of α-amino acids in place of the salts of β- or γ-amino acids.

The benzylidene derivatives of type VII (Table I) were obtained by the method of Southwick and Barnas (7) using the one-pot version in which acid catalyzed hydrolysis and decarboxylation of 4-carboalkoxy-2,3-dioxopyrrolidines is combined with acid-catalyzed condensation with aryl aldehydes.

For the formation of the pyrimidine ring by addition of guanidine to the 4-benzylidine derivatives (VII), a procedure was used which was developed following a detailed reexamination of the addition of guanidine to 4-benzylidine derivatives of type VI. Reaction of guanidine with VIa had been described in an earlier paper (8). The new derivative VIb was first made and studied in the present investigation. The earlier experiments yielded derivatives of 3,4- or 1,4-dihydro-2-amino-4-phenyl-5*H*-pyrrolo[3,4-*d*]pyrimidine-7-(6*H*)one (VIII) (8). The dihydropyrimidine structure had not undergone a spontaneous dehydrogenation or oxidation with removal of the hydrogens at the 1 or 3 and 4 positions leading to the more aromatized 5*H*-pyrrolo-[3,4-*d*]pyrimidine ring system of compounds of type IX. In the present extension of the earlier work it was found that either a longer reaction period or addition of bromine and sodium acetate to the reaction mixtures can result in dehydrogenation at the 1 or 3 and 4 positions.

The more aromatized products (IX) are clearly distinguishable from their precursors (VIII) on the basis of expected differences in nuclear magnetic resonance and ultraviolet spectra, as well as other properties. The structures assigned to compounds of types VIII and IX were confirmed by their nmr spectra. Compound IXa showed two-proton singlets at δ 4.68 and δ 4.48 arising from methylene groups of ring position 5 and the 6-benzyl group, whereas the undehydrogenated precursor VIIIa showed the pairs of doublets expected from methylene protons situated in compounds having a nearby chiral center (at ring position 4 in this compound) (8). A signal from the 4-proton of VIIIa (δ 5.47) was absent, as expected, from the spectrum of IXa.

The 2-amino-4-aryl-(6-ω-carboxyalkyl)-5*H*-pyrrolo-[3,4-*d*]pyrimidin-7-(6*H*)ones (III) which were obtained are listed in Table II. Their ultraviolet spectra show that they contain the same heterocyclic structure as the aromatized derivatives IXa and IXb.

EXPERIMENTAL

All melting points are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee and M. H. W. Laboratories, Phoenix, Arizona. All infrared spectra were taken as Nujol mulls on a Perkin-Elmer Infracord spectrophotometer. All nmr spectra were determined on a Varian A-60 spectrometer in a variety of solvents with tetramethylsilane as the reference standard. Ultraviolet spectra were determined on Cary Model 11 or Perkin-Elmer Model 202 spectrophotometers.

1-*p*-Bromophenyl-4-carbethoxy-2,3-dioxopyrrolidine (IVb).

A solution of 100 g. (0.58 mole) of *p*-bromoaniline, 222 ml. (2.2 moles) of ethyl acrylate and 50 ml. of acetic acid was refluxed for 10 hours. The solution was concentrated on a rotary evaporator over steam to yield a tan oil. The tan oil was dissolved in 600 ml. of absolute ethanol. To this solution were added 87 ml. (0.64 mole) of diethyl oxalate and a sodium ethoxide solution prepared by dissolving 37 g. (1.6 moles) of sodium in 1400 ml. of absolute ethanol. The mixture was heated over a hot plate until a thick paste developed. The paste was dissolved by the addition of *ca.* 1500 ml. of water. The resultant solution was acidified with 500 ml. of 20% hydrochloric acid, causing a tan solid to precipitate. The precipitate was filtered, washed with ether and recrystallized from a mixture of 95% ethanol and dimethyl formamide to give 43.4 g. (25%) of white fibrous crystlas, m.p. 178-180°; ir: 2.93 (OH), 5.79, 5.90 and 6.00 (C=O), 6.29 μ (C=C).

Anal. Calcd. for $C_{13}H_{12}BrNO_4$: C, 47.86; H, 3.71; N, 4.29. Found: C, 47.94; H, 3.82; N, 4.09.

1-*p*-Bromophenyl-4-benzylidene-2,3-dioxopyrrolidine (VIa).

A mixture of 9.78 g. (0.03 mole) of 1-*p*-bromophenyl-4-carbethoxy-2,3-dioxopyrrolidine, 3 ml. (0.03 mole) of benzaldehyde, 200 ml. of 20% hydrochloric acid and 70 ml. of 95% ethanol was refluxed with stirring for 1 hour. A solution of 10 ml. (0.1 mole) of benzaldehyde dissolved in 20 ml. of 95% ethanol was added dropwise to the refluxing mixture over a period of 2 hours. After the aldehyde had been added, the mixture was refluxed for 3 hours. The mixture was then filtered, while hot, using a preheated funnel and flask. The filtrate was refluxed an additional 5 hours. At the end of this reflux period, the filtering process was repeated and the filtrate refluxed an additional 5 hours. During this last reflux period, a solution of 4 ml. (0.035 mole) of benzaldehyde and 11 ml. of 95% ethanol was added dropwise. After the reaction had been cooled in an ice bath, all solids were filtered and combined with the previously filtered solids. These solids were recrystallized from acetone. Partial evaporation of the mother liquor increased the total yield of purified product to 6.91 g. (67%) of yellow needles, m.p. 231-232°; ir: 5.79 and 5.88 (C=O), 6.16 μ (C=C); nmr (trifluoroacetic acid/carbon tetrachloride): τ 2.56 (m, 9, C_6H_5 and *p*-Br-C_6H_4), 5.10 (s, 2, C-5 CH_2); uv (ethanol): max 232 nm (log ε 4.07), 336 nm (log ε 4.26).

Anal. Calcd. for $C_{17}H_{12}BrNO_2$: C, 59.67; H, 3.51; N, 4.09. Found: C, 59.80; H, 3.42; N, 3.99.

2-Amino-6-*p*-bromophenyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo-[3,4-*d*]pyrimidin-7-(6*H*)one (VIIIb).

A solution of guanidine in absolute ethanol was prepared from 2.5 g. (0.025 mole) of guanidine hydrochloride and 0.6 g. (0.025 mole) of sodium each dissolved in 25 ml. of absolute ethanol. The precipitated sodium chloride was filtered. The guanidine solution was added dropwise to a stirring suspension of 1.72 g. (0.005 mole) of 1-*p*-bromophenyl-4-benzylidene-2,3-dioxopyrrolidine and 75 ml. of absolute ethanol. After the guanidine had been added, the solution was refluxed with

stirring until a white solid precipitated (*ca.* 1 hour). The mixture was cooled in an ice bath and the precipitate collected by filtration to give 0.68 g. (35%) of a white, microcrystalline solid which melted at 251-256° dec. The filtrate was returned to reflux temperature for 24 hours, cooled in an ice bath and the precipitate filtered to give 0.55 g. (29%) of the same microcrystalline solid for a total yield of 1.23 g. (64%). Recrystallization from a dimethylformamide-water mixture changed the melting point to 249-251° dec.; ir: 2.85-3.00 (NH, NH_2), 5.95 and 6.03 (H bonded C=O), 6.18 μ (C=C); nmr (trifluoroacetic acid/deuteriochloroform): τ 2.56 (m, 9, *p*-Br-C_6H_4 and C_6H_5), 4.21 (s, 1, CHC_6H_5), 5.66 (q, 2, J = 19.5 Hz, C-5 CH_2); uv (ethanol): max 270 nm (log ϵ 4.34), 320 nm (log ϵ 3.45).

Anal. Calcd. for $C_{18}H_{15}BrN_4O$: C, 56.40; H, 3.95; N, 14.62. Found: C, 56.30; H, 3.89; N, 14.52.

2-Amino-6-*p*-bromophenyl-4-phenyl-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)one (IXb).

A solution of guanidine in absolute ethanol was prepared from 5 g. (0.05 mole) of guanidine hydrochloride, 1.15 g. (0.05 mole) of sodium and a total of 100 ml. of absolute ethanol by the same procedure described previously. The guanidine solution was added dropwise to a stirring suspension of 3.44 g. (0.01 mole) of 1-*p*-bromophenyl-4-benzylidene-2,3-dioxopyrrolidine and 100 ml. of absolute ethanol. After the guanidine had been added, the solution was refluxed with stirring for 24 hours. After the mixture had been cooled in an ice bath, 1.59 g. (42%) of a white precipitate was removed by filtration. Recrystallization from a dimethylformamide-water mixture gave a white, microcrystalline solid, m.p. 291-293° dec.; ir: 3.00-3.11 (NH_2), 5.85 (C=O), 6.20 μ (C=C); nmr (trifluoroacetic acid/deuteriochloroform): τ 2.16 (m, 5, C_6H_5), 2.35 (s, 4, *p*-Br-C_6H_4), 4.68 (s, 2, C-5 CH_2); (ethanol): uv max 240 nm (log ϵ 4.37), 268 nm (log ϵ 4.19), 352 nm (log ϵ 4.06).

Anal. Calcd. for $C_{18}H_{13}BrN_4O$: C, 56.70; H, 3.44; N, 14.69. Found: C, 56.92; H, 3.36; N, 14.92.

2-Amino-6-benzyl-4-phenyl-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)-one (IXa) (9).

A 0.2*M* bromine solution was prepared by dissolving 1 ml. (0.02 mole) of bromine in 100 ml. of acetic acid. A 25 ml. aliquot of the bromine solution (5 mmoles) was added to a solution of 1.59 g. (5 mmoles) of 2-amino-6-benzyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)one (8), 0.84 g. (10 mmoles) of sodium acetate and 25 ml. of acetic acid. The bromine was decolorized immediately and the resultant clear solution was refluxed for 2 hours. After the hot reaction mixture had been poured into 150 ml. of boiling water, the mixture was allowed to come to room temperature and then cooled in a refrigerator for 12 hours. All solids were filtered and recrystallized from a dimethylformamide-water mixture to give 0.65 g. (41%) of a white, microcrystalline solid, m.p. 263-268° dec.; ir: 2.82, 2.98 and 3.08 (NH_2), 5.85 (C=O), 6.20 μ (C=C); nmr (trifluoroacetic acid/deuteriochloroform): τ 2.55 (m, 5, C_6H_5), 2.93 (s, 5, C_6H_5), 5.32 (s, 2, $CH_2C_6H_5$), 5.52 (s, 2, C-5 CH_2); uv (ethanol): max 250 nm (log ϵ 4.28), 342 nm (log ϵ 3.81).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.34; H, 5.07; N, 17.77.

The mother liquor from the reaction mixture was treated with crushed ice and ammonium hydroxide to give 0.39 g. (25%) of starting material which was identified by comparison of its infrared spectrum with the spectrum of an authentic sample.

1-(2-Carboxyethyl)-4-carbethoxy-2,3-dioxopyrrolidine (Va).

To a cooled stirred solution of β-alanine (17.8 g., 0.2 mole) in ethanolic sodium ethoxide prepared from 4.6 g. (0.2 mole) of sodium and 150 ml. of absolute ethanol was added ethyl acrylate (20.0 g., 0.2 mole) in small portions and the mixture was set aside overnight. The resulting solution of the ethyl acrylate adduct was heated with an ethanolic sodium ethoxide solution (prepared from 4.6 g. (0.2 mole) of sodium and 50 ml. of absolute ethanol) mixed with diethyl oxalate (29.2 g., 0.2 mole) under gentle reflux on a water bath for 3 hours. The reaction mixture was poured into ice-cold water and acidified with concentrated hydrochloric acid to precipitate the product. After collection on a filter and washing with water, the yield was 32.5 g. (70.0%). The product crystallized from 95% ethanol as white needles, m.p. 194-195° (red color with alcoholic ferric chloride).

Anal. Calcd. for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.35; N, 5.75. Found: C, 49.35; H, 5.27; N, 5.58.

1-(3-Carboxypropyl)-4-carbethoxy-2,3-dioxopyrrolidine (Vb).

The above procedure was followed starting with γ-aminobutyric acid (0.2 mole). The yield of product was 34.0 g., 75.2%, m.p. 184-185° (from ethanol) (red color with alcoholic ferric chloride).

Anal. Calcd. for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.81; N, 5.45. Found: C, 51.07; H, 5.50; N, 5.40.

4-Arylidene-1-(ω-carboxyalkyl)-3,4-dioxopyrrolidines (VII).

The 1-(ω-carboxyalkyl)-4-carbethoxy-2,3-dioxopyrrolidine (0.01 mole) was refluxed with 6*N* hydrochloric acid (50 ml.) for 30 minutes. To the solution was added dropwise the aromatic aldehyde (0.015 mole) in 5 ml. of formic acid. The mixture was refluxed for an additional 2.5 hours. The solution, which had assumed a bright yellow to orange red color, was poured onto crushed ice and the precipitated solid was collected on a filter and washed with water to yield a bright yellow solid, which was then recrystallized from 95% ethanol. Table I summarizes the data recorded on the individual compounds.

2-Amino-4-aryl-6-(ω-carboxyalkyl)-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)ones (III).

A solution of guanidine in absolute ethanol was prepared by addition of 3.8 g. (0.04 mole) of guanidine hydrochloride to 100 ml. of 0.4*N* ethanolic sodium ethoxide, followed by filtration to remove precipitated sodium chloride.

A 0.01-mole quantity of the benzylidene compound (VIII) and 0.5 g. of guanidine hydrochloride were added to the guanidine solution and the mixture was stirred for 100 hours at room temperature. The solution was cooled in an ice bath and the product was collected by filtration, then dissolved in 20 ml. of water. Following precipitation from solution by dropwise addition of 50% acetic acid, the product was collected by filtration, washed with a small volume of ice-cold water, and recrystallized from a dimethylformamide-water mixture. Data for the individual compounds are collected in Table II.

Acknowledgement.

Supported in part by Research Grant GM-04371 from the National Institutes of Health, U. S. Public Health Service.

REFERENCES AND NOTES

(1a) A. Tensho, I. Shimizi, T. Takenawa, H. Kikinchi and

T. Kamiya, *J. Pharm. Soc. Japan*, **94**, 708 (1974); (b) T. Kamiya, Y. Saito, M. Hashimoto and H. Seki, *Tetrahedron Letters*, 4729 (1969); (c) T. Kamitani, *et al.*, Japanese Patent 72 01,936 (1972); *Chem. Abstr.*, 77, 19964d (1972); (d) I. Chibata, K. Okumura, S. Takeyama and K. Kotera, *Experientia*, **25**, 1237 (1969); (e) T. Kamiya, *et al.*, German Patent 2,047,973 (1971); *Chem. Abstr.*, **75**, 36132g (1971); (f) T. Okumura, *et al.*, German Patent 2,041,222 (1971); *Chem. Abstr.*, **75**, 36134 (1971).

(2) Other names which have been applied to eritadenine are lentinacin (1d) and lentysine (1b).

(3) H. J. Schaeffer, German Patents 2,708,828 and 2,708,827 (1971); *Chem. Abstr.*, **88**, 6940v, 6941w (1978).

(4) See preceding paper in this series, P. L. Southwick, V. Amarnath and R. Madhav, *J. Heterocyclic Chem.*, **11**, 723 (1974).

(5) P. L. Southwick, E. P. Previc, J. Casanova, Jr. and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(6) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953). See also, P. L. Southwick and L. L. Seivard, *ibid.*, **71**, 2532 (1949).

(7) P. L. Southwick and E. F. Barnes, *J. Org. Chem.*, **27**, 98 (1962).

(8) P. L. Southwick and G. H. Hofmann, *ibid.*, **28**, 1332 (1963).

(9) Details of the preparation and characterization of additional derivatives of types VIII and IX with other substituents in the 4 and/or 6 positions are included in the Ph.D. thesis of Carroll A. Snyder, Carnegie-Mellon University, 1969. The melting points found for these derivatives were as follows: VIIIc, 4-*p*-methoxyphenyl-6-benzyl-, m.p. 284-286° dec.; VIIId, 4-*p*-chlorophenyl-6-benzyl-, m.p. 270-271° dec.; IXc, 4-*p*-methoxyphenyl-6-benzyl-, m.p. 248-252°; IXd, 4-*p*-chlorophenyl-6-benzyl-, m.p. 309-311°; IXe, 4-*p*-methoxyphenyl-6-*p*-bromophenyl-, m.p. 340-341°; IXf, 4-*p*-chlorophenyl-6-*p*-bromophenyl-, m.p. 336-341°.