Compounds in the Pyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole Series (1)

Joseph P. Yevich, John R. Murphy, Richard F. Dufresne and Philip L. Southwick

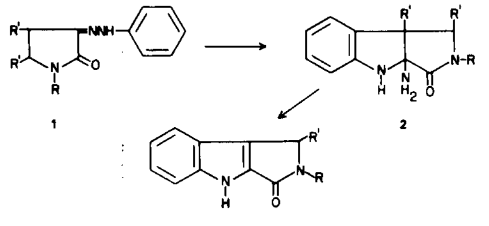
Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received April 19, 1978

Compounds in the new pyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole series have been produced by an imide cyclization of appropriate derivatives of pyrrolo[3,4-*b*]indole.

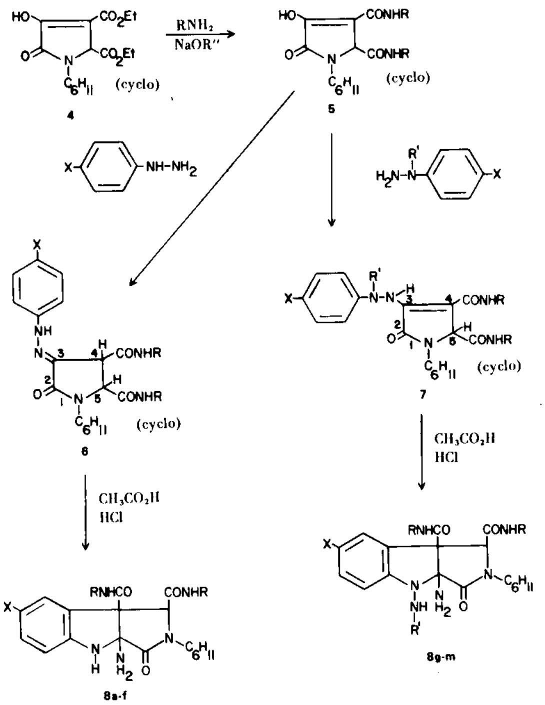
J. Heterocyclic Chem., 15, 1463 (1978)

The synthesis of pyrrolo[3,4-*b*]indole derivatives has been reported in prior publications from these laboratories (2). Acid-catalyzed cyclization of 2,3-dioxopyrrolidine-3-arylhydrazones (**1**) gave the *b*-fused indolines (**2**) as stable, easily isolable compounds. Base-catalyzed or thermal fragmentation of indolines (**2**) bearing an 8b-carbamoyl group (R' = substituted carbamoyl) afforded the aromatized pyrrolo[3,4-*b*]indoles (**3**) as the sole heterocyclic product. An extension of this previous work has revealed that appropriate derivatives of the angularly-substituted indoline type (**2**) undergo a facile cyclization leading to derivatives in the novel pyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole system illustrated in formulas **11** and **12** (Chart II). The folded arrangement of four fused rings present in these compounds would be expected to be quite rigid; the degree of conformational change that would be possible for such molecules should be very limited. It was felt that it would be worthwhile to make such compounds available for examination of possible specific physiological effects.



As shown in Chart I, the 4,5-*bis*-dicarbamoyl compounds (**5**) were prepared by amide-ester interchange of diethyl 1-cyclohexyl-2,3-dioxopyrrolidine-4,5-dicarboxylate (**4**) with ammonia or the appropriate primary amine. Reaction of **5** with arylhydrazines or unsymmetrical alkylarylhydrazines gave the corresponding phenylhydrazones which are listed in Table 1. Whereas those compounds derived from phenylhydrazine (or ring-substituted derivatives) exist in the expected hydrazone form (**6**), the products obtained from unsymmetrical alkylarylhydrazines have the tautomeric structure **7**. As a result of the π-p-π conjugation of the C=NNHAryl chromophore, compounds of type **6** display their major ultraviolet absorption at wavelengths greater than 300 mμ. In the nuclear magnetic resonance (nmr) spectra of **6** the heterocyclic ring protons at position 4 and 5 are seen as one-proton doublets (J = 2-3 Hz) at τ 5.9-6.0 and τ 4.8-5.0 respectively. In contrast, compounds of type **7** have no ultraviolet absorption above 300 mμ and their nmr spectra show a one-proton singlet at τ 4.7-5.0 for the heterocyclic ring proton at position 5. The existence of the enehydrazines (**7**) may be attributable to stabilization *via* intramolecular hydrogen bonding between the hydrazine NH and either the 2-oxo or 4-carbamoyl oxygen atoms. Such hydrogen bond stabilization could not occur in the hydrazone form of these compounds. Enehydrazines are formed as transient intermediates in the Fischer indole synthesis (3) and have been trapped as *N,N'*-diacetyl derivatives (4). Enehydrazines have been isolated and characterized as the products of carbonyl compounds with various 1,2-disubstituted and trisubstituted hydrazines (5,6,7). However, there appears to be no previous account of the isolation of stable enehydrazines derived from hydrazines having an unsubstituted nitrogen.

Chart I

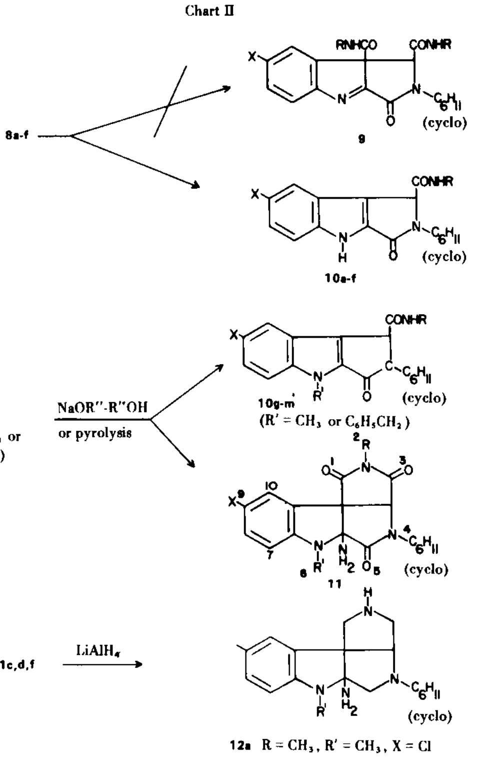


Brief heating of **6** or **7** in a hydrochloric-acetic acid mixture effected their cyclization to the *b*-fused indolines **8**. The failure of such compounds to yield indolenines **9** by loss of ammonia has been rationalized in terms of the considerable strain energy associated with such compounds (2).

As depicted in Chart II, base-promoted fragmentation of the compounds unsubstituted on the indoline nitrogen resulted in cleavage of the 4a-amino and 8b-carbamoyl groups to afford 1,4-dihydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (**10**) as the exclusive products. A synthesis of 3-substituted indoles described by Bourdais and Germain may also involve fragmentation of a transient 2-aminoindoline intermediate (8). The conversion of **8** to **10** required heating to 140-170° in ethylene glycol in which several gram-atom equivalents of sodium had been dissolved. Heating in lower-boiling solvents (methanol or ethanol) in the presence of the corresponding alkoxide failed to effect conversion to **10**.

Certain of the 4-alkylindolines (**8g**, **8k**, **8m**) also gave indoles upon base treatment and/or pyrolysis of the hydrochloride salts. However, in most cases the predominant if not exclusive product was a tetracyclic imide (**11**), a derivative in the novel pyrrolo[3′,4′:4,5]pyrrolo[3,4-*b*]indole system. Retention of the indoline chromophore was verified by the ultraviolet spectra which were essentially identical with the spectra of compounds of type **8**. In addition to lactam bands, the carbonyl region in the infrared spectra of compounds of type **11** showed characteristic imide carbonyl doublets consisting of strong bands at 5.85-5.9 μ and less intense absorptions at *ca.* 5.6 μ. Further, the nmr spectra of the compounds of type **11** were consistent with the tetracyclic structure.

Chart II

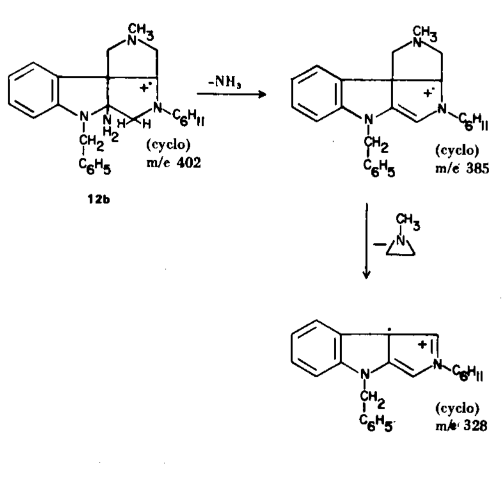


12a R = CH3, R′ = CH3, X = Cl
b R = CH3, R′ = C6H5CH2, C = H
c R = C6H5CH2, R′ = C6H5CH2, X = H

Table 3 summarizes the product distributions arising from the 4-alkylindolines. While reaction conditions and yields were not optimized in all cases, the conversion of **8k** (R = CH_3, R′ = $C_6H_5CH_2$) under various conditions was evaluated by nmr analysis of the crude product mixtures. The ratio of products **10h** and **11d** was determined by integrating the areas of their *N*-methyl signals at τ 7.23 and τ 6.89 respectively. The mildest conditions employed, *i.e.* sodium ethoxide in ethanol at room temperature gave an 80% yield of **11d** to the total exclusion of **10h**. In refluxing sodium ethoxide solution the ratio of **11d**:**10h** was 6.25; treatment with sodium in ethylene glycol at 135° gave a product ratio of 1.21 and pyrolysis of the hydrochloride salt of **8k** afforded a ratio of 0.69.

The base-catalyzed formation of compounds of type **11** is not surprising since amides are known to undergo condensation to imides at a rate inversely proportional to hydrogen ion concentration (9). The deamination of **8** to **11** under pyrolytic conditions might also have been anticipated. It is unclear why those indolines of type **8** having no 4-substituent, unlike the 4-alkylated derivatives, undergo exclusively the fragmentation reaction leading to indoles, but the result may point to abstraction of the proton on the indoline nitrogen as the initiating step in the fragmentation.

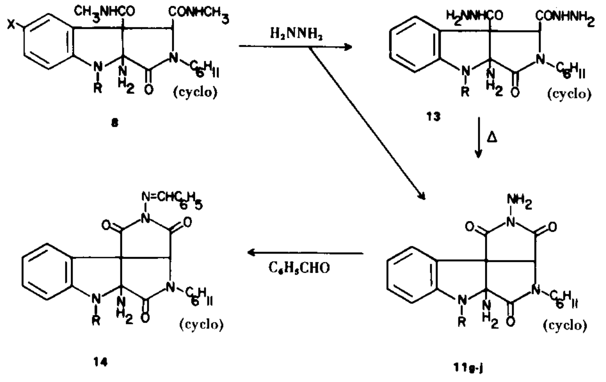
Several of the tetracyclic imides were reduced with lithium aluminum hydride to the octahydro derivatives of type **12** (Table 2). Compounds **12a** and **12b** were obtained as crystalline solids which gave satisfactory elemental analyses; their infrared spectra showed NH bonds and absence of carbonyl absorption. The nmr spectra of both compounds were consistent with the assigned structures although unequivocal assignments were not made for all ring protons. Compelling evidence for structure **12b** was afforded by the high resolution mass spectrum which affirmed the empirical formula $C_{28}H_{34}N_4$ (calculated m/e 402.2783; measured m/e 402.2795). Significant fragment ions were observed at m/e 385 and 328. Elimination of ammonia from the parent ion accounts for the m/e 385 fragment, which can then undergo heterolytic cleavage to eliminate 57 mass units as *N*-methylaziridine and thus form the m/e 328 fragment.



The latter fragmentation is analogous to that observed for *N*-methyl pyrrolidine (10).

Compound **12c** was obtained as an oil which could not be induced to crystallize. However, derivitization of the 5a-amino group by reaction with phenylisocyanate and phenylisothiocyanate gave crystalline products with satisfactory spectral and elemental analysis data.

To further evaluate the scope of the indoline fragmentation, we endeavored to prepare and evaluate the reactivity of a number of *bis*-hydrazides (**13**). Treatment of various *bis*-di-*N*-methylcarbamoyl compounds of type **8** did indeed afford the corresponding hydrazides. However, in a number of cases hydrazine treatment of **8** directly afforded the 2-aminotetracyclic imides (**11g-j**). Those *bis*-hydrazides which were isolated were readily cyclized to the corresponding compound of type **11** by brief heating above their melting points or even upon attempted recrystallization. Reaction of one of the compounds of type **11** with benzyldehyde to yield a derivative of type **14** confirmed spectroscopic indications that the cyclization products were correctly represented as having a 5-membered imide ring with an external amino group, as in formulas **11g-j**.



EXPERIMENTAL (11)

1-Cyclohexyl-4,5-*bis*-carbamoyl-2,3-dioxopyrrolidine (**5a**).

A mixture of 65.8 g. (0.2 mole) 1-cyclohexyl-4,5-dicarbethoxy-2,3-dioxopyrrolidine (**4**) (2c), sodium methoxide (prepared from 14.5 g., 0.63 mole of sodium) and 38.0 g. (2.23 moles) of anhydrous ammonia in 200 ml. of absolute methanol was shaken and heated at 70° for 8 hours in a 1 liter high-pressure bomb. The reaction mixture was concentrated under reduced pressure to *ca.* one-fourth the initial volume, diluted to 300 ml. with methanol and acidified with concentrated hydrochloric acid. The precipitated solid was collected by filtration, washed with water and recrystallized twice from 95% ethanol to provide 17.0 g. (32%) of **5a** as a white crystalline solid, m.p. 251-252° (dark red ferric chloride test); ir (potassium bromide): 3.05, 3.25, 6.15, 10.12, 11.04, 11.31, 11.80, 12.86, 13.64 μ; uv (ethanol): λ max 245 mμ (ε, 8,900).

Anal. Calcd. for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.85; H, 6.57; N, 15.56.

1-Cyclohexyl-4,5-*bis*-*N*-methylcarbamoyl-2,3-dioxopyrrolidine (**5b**).

A mixture of 8.0 g. (24.6 mmoles) of diester **4**, 6-8 g. (200-250 mmoles) of anhydrous methylamine and sodium methoxide (from 4.5 g., 195 mmoles of sodium in 50 ml. of absolute methanol) was shaken and heated at 60° for 16 hours under 500 psig nitrogen. The mixture was concentrated under reduced pressure, diluted with ice water and acidified with concentrated hydrochloric acid. The crude product was collected by filtration, washed with water and recrystallized from 95% ethanol to afford yields of 4.0-6.5 g. (55-90%) of **5b** as fluffy white crystals, m.p. 242-244° (dark red ferric chloride test); ir (potassium bromide): 2.94, 3.10, 6.0, 6.05, 8.18, 11.02, 11.97, 12.78, 13.60 μ, uv (ethanol): λ max 235 mμ (ε, 8,450), 273 (sh) (ε, 6,800).

Anal. Calcd. for $C_{14}H_{21}N_3O_4$: C, 56.93; H, 7,16; N, 14.23. Found: C, 57.09; H, 6.93; N, 14.08.

1-Cyclohexyl-4,5-*bis*-*N*-ethylcarbamoyl-2,3-dioxopyrrolidine (**5c**).

A mixture of 16.4 g. (50 mmoles) of diester **4**, 11.0 g. (245 mmoles) of anhydrous ethylamine and sodium methoxide (from 3.6 g., 167 mmoles of sodium in 60 ml. of absolute methanol) was shaken and heated at 60-65° for 8 hours in a bomb under 500 psig nitrogen. The mixture was worked up as described above for **5b** and the crude product recrystallized from 95% ethanol to afford 2.0 g. (20%) of **5c** as white needles, m.p. 217-219° (dark red ferric chloride test); ir (potassium bromide): 3.00, 3.19, 6.00, 6.48, 8.20, 8.74, 10.08, 10.90, 11.26, 12.47, 12.83, 13.90; uv (ethanol): λ max 239 mμ (ε, 10,950).

Anal. Calcd. for $C_{16}H_{25}N_3O_4$: C, 59.42; H, 7.79; N, 12.99. Found: C, 59.35; H, 7.48; N, 13.17.

Preparation of Aryhydrazone (**6**) and Enehydrazine (**7**) Derivatives of 1-Cyclohexyl-4,5-*bis*-dicarbamoyl-2,3-dioxopyrrolidines.

The compounds of type **6** and **7** listed in Table 1 were prepared by refluxing a solution of the appropriate pyrrolidinedione (**5**), a slight excess of arylhydrazine and glacial acetic acid (0.2-0.25 ml./g. of **5**) in 95% ethanol (20-30 ml./g. of **5**) for 30-45 minutes. The precipitated products were collected by filtration and washed with ether and were generally suitable for subsequent use without further purification. The following examples are illustrative.

1-Cyclohexyl-4,5-*bis*-*N*-methylcarbamoyl-2,3-dioxopyrrolidine Phenylhydrazone (**6b**).

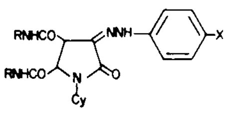
Refluxing a solution of 4.1 g. (13.9 mmoles) of **5b**, 1.6 g. (14.8 mmoles) of phenylhydrazone and 1.0 ml. of glacial acetic acid in 100 ml. of 95% ethanol for 0.5 hour afforded 3.6 g. (68%) of **6b**. An analytical sample was obtained by recrystallization from 95% ethanol as pale yellow prisms, m.p. 224-225°; ir (potassium bromide): 3.00, 6.00, 6.10, 6.56, 8.11, 8.63, 10.30, 11.20, 12.55, 13.03, 13.71, 14.38 μ; uv (ethanol): λ max 230 mμ (ε, 12,900), 328 (ε, 29,800), sh 293 mμ (ε, 11,850), λ min 250 mμ (ε, 3,980); nmr (pyridine): τ 4.79 (1H, d, J = 2.0 Hz, 5-C*H*), 5.96 (1H, d, J = 2.0 Hz, 4-C*H*), 6.0-6.3 (1H, broad, tertiary cyclohexyl proton, 7.11 (3H, d, J = 3.8 Hz, 4- or 5-CONHCH_3, collapses to singlet at 7.11 upon deuteration), 7.18 (3H, d, J = 3.8 Hz, collapses to singlet at 7.17 upon deuteration), 7.9-9.2 (10H, broad m, cyclohexyl protons), (aromatic region obscured by solvent).

1-Cyclohexyl-4,5-*bis*-*N*-methylcarbamoyl-2-oxo-3-(2-methyl-2-phenylhydrazino)-3-pyrroline (**7c**).

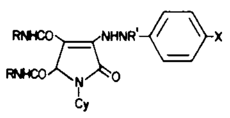
A mixture of 15.0 g. (51.0 mmoles) **5b**, 6.4 g. (52.0 mmoles) of 1-methyl-1-phenylhydrazine and 4 ml. of glacial acetic acid in 300 ml. of 95% ethanol was stirred and refluxed for 45 minutes.

Table 1

Arylhydrazone (**6**) and Enehydrazine (**7**) Derivatives of 1-Cyclohexyl-2,3-dioxo-4,5-bis-dicarbamoylpyrrolidines



6

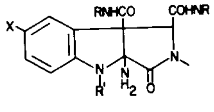


7

No.	R	R'	X	M.p. °C	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N
6a	H	--	H	234-235	98	$C_{18}H_{23}N_5O_3$	60.48	6.49	19.60	60.32	6.54	19.60
6b	CH_3	--	H	224-225	68	$C_{20}H_{25}N_5O_3$	62.32	7.06	18.17	62.38	7.15	18.10
6c	CH_3	--	Cl	212-213	73	$C_{20}H_{26}ClN_5O_3$	57.20	6.24	16.68	57.17	6.13	16.68
6d	CH_3CH_2	-	H	158-160	38	$C_{22}H_{31}N_5O_3$	64.05	7.33	16.98	63.89	7.44	16.85
6e	$C_6H_5CH_2$	--	Cl	189-191	93	$C_{32}H_{34}ClN_5O_3$	67.18	5.99	12.24	67.27	5.87	12.01
6f	$C_6H_5CH_2$	--	OCH_3	181-183	49	$C_{33}H_{37}N_5O_4$	69.81	6.57	12.34	69.57	6.50	12.47
7a	H	CH_3	H	144-147	49	$C_{19}H_{25}N_5O_3$	61.38	6.78	18.85	61.07	7.02	18.65
7b	H	$C_6H_5CH_2$	H	188-191	35	$C_{25}H_{29}N_5O_3$	67.09	6.53	15.65	67.34	6.43	15.38
7c	CH_3	CH_3	H	174-177	62	$C_{21}H_{29}N_5O_3$	63.13	7.32	17.53	62.08	7.32	17.09
7d	CH_3	CH_3	Cl	193-194	76	$C_{21}H_{28}ClN_5O_3$	58.12	6.50	16.14	58.19	6.60	15.92
7e	CH_3	$C_6H_5CH_2$	H	130-133	14	$C_{27}H_{33}N_5O_3$	68.18	6.99	14.73	68.05	7.20	14.95
7f	$C_6H_5CH_2$	CH_3	H	184-185	37	$C_{33}H_{37}N_5O_3$	71.87	6.72	12.72	71.66	6.98	12.47
7g	$C_6H_5CH_2$	$C_6H_5CH_2$	H	148-150	54	$C_{39}H_{41}N_5O_3$	74.61	6.58	11.16	74.77	6.68	11.13

Table 2

3a-Amino-1,8b-bis-carbamoyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)ones (**8**)



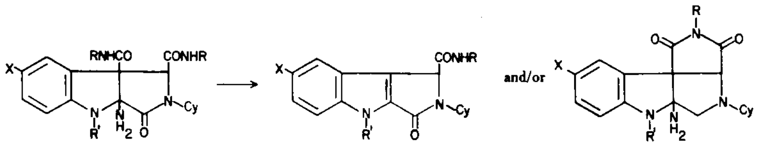
8

No.	R	R'	X	M.p. °C	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N
8a	H	H	H	237-239	61	$C_{18}H_{23}N_5O_3$	60.48	6.49	19.60	60.53	6.31	17.45
8b	CH_3	H	H	251-252	60	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17	62.19	7.23	18.02
8c	CH_3	H	Cl	244-246	75	$C_{20}H_{26}ClN_5O_3$	57.20	6.24	16.68	57.13	6.20	16.41
8d	CH_3CH_2	H	H	225-236 (a)	65	$C_{22}H_{31}N_5O_3$						
8e	$C_6H_5CH_2$	H	Cl	265-267	38	$C_{32}H_{34}ClN_5O_3$	67.18	5.99	12.24	67.19	6.05	11.96
8f	$C_6H_5CH_2$	H	OCH_3	260-262	5	$C_{33}H_{37}N_5O_4$	69.81	6.57	12.34	70.01	6.88	12.60
8g	H	CH_3	H	228-230	23	$C_{19}H_{25}N_5O_3$	61.38	6.78	18.85	61.07	7.08	18.84
8h	H	$C_6H_5CH_2$	H	204-206	60	$C_{25}H_{29}N_5O_3$	67.09	6.53	15.65	66.81	6.67	15.33
8i	CH_3	CH_3	H	213-215 (b)	53	$C_{21}H_{30}N_5O_3$-HCl	57.85	6.94	16.07	57.56	7.13	16.27
8j	CH_3	CH_3	Cl	248-249	55	$C_{21}H_{28}ClN_5O_3$	58.12	6.50	16.14	57.86	6.40	16.36
8k	CH_3	$C_6H_5CH_2$	H	228-230 (b)	82	$C_{27}H_{33}N_5O_3$-HCl	63.32	6.69	13.69	63.31	6.64	13.62
8m	$C_6H_5CH_2$	CH_3	H	175-177	66	$C_{33}H_{37}N_5O_3$-HCl- -1/2 H_2O	66.37	6.58	11.73	66.59	7.10	11.41
	$C_6H_5CH_2$	$C_6H_5CH_2$	H	210-211 (b)	79	$C_{39}H_{41}N_5O_3$-HCl	70.52	6.37	10.54	70.50	6.39	10.25

(a) Compound **8d** was obtained as a crude product and was not purified or analyzed. (b) These compounds were isolated and characterized as monohydrochloride salts.

Table 3

Products from Base-Catalyzed and Pyrolytic Fragmentation of 1,8b-bis-Dicarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)ones



8 10 11

Starting Material	R	R'	X	Method	Products		Yield, %		Calcd., % C	H	N	Found, % C	H	N
8a	H	H	H	A	**10a**	304-306	30	$C_{17}H_{19}N_3O_2$	68.67	6.44	14.13	68.80	6.62	14.13
8b	CH_3	H	H	A	**10b**	299-300	50	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.50	69.65	6.62	12.50
8c	CH_3	H	Cl	A	**10c**	313-315	47	$C_{18}H_{20}ClN_3O_2$	62.51	5.83	12.15	62.43	5.60	12.04
8d	CH_3CH_2	H	H	A	**10d**	281-284	30	$C_{19}H_{23}N_3O_2$	70.13	7.12	12.91	70.26	7.28	12.68
8e	$C_6H_5CH_2$	H	Cl	A	**10e**	300-302	52	$C_{24}H_{24}ClN_3O_2$	68.23	5.73	9.96	68.13	5.75	9.81
8f	$C_6H_5CH_2$	H	OCH_3	A	**10f**	240-242	43	$C_{25}H_{27}N_3O_3$	71.91	6.52	10.06	71.38	6.43	10.58
8g	H	CH_3	H	A	**10g**	295-297	51	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.50	69.10	6.74	13.36
				B	**10g**		34							
8h	H	$C_6H_5CH_2$	H	A	**11a**	215-217	81	$C_{25}H_{26}N_4O_3$	69.75	6.09	13.02	69.46	6.10	13.05
8i	CH_3	CH_3	H	B	**11b**	189-191	83	$C_{20}H_{24}N_4O_3$	65.20	6.57	15.21	65.18	6.74	14.91
8j	CH_3	CH_3	Cl	C	**11c**	189-190	86	$C_{20}H_{23}ClN_4O_3$	59.62	5.75	13.91	59.67	5.72	13.79
8k	CH_3	$C_6H_5CH_2$	H	A	**10h**	253-255	13	$C_{25}H_{27}N_3O_2$	74.78	6.78	10.47	74.57	6.73	10.48
					11d	212-213	51	$C_{26}H_{28}N_4O_3$	70.25	6.35	12.60	70.39	6.24	12.50
				B	**10h**		47							
					11d		24							
				C	**11d**		80							
8l	$C_6H_5CH_2$	CH_3	H	A	**11e**	183-185	24	$C_{26}H_{28}N_4O_3$	70.25	6.35	12.60	70.21	6.93	12.32
8m	$C_6H_5CH_2$	$C_6H_5CH_2$	H	A	**10i**	218-221	4	$C_{31}H_{31}N_3O_2$	77.96	6.54	8.80	77.80	6.48	8.80
					11f	202-203	44	$C_{32}H_{32}N_4O_3$	73.82	6.20	10.75	73.60	6.39	10.58

Method A: Indoline **8** heated in a sodium in ethylene glycol solution to 140-170°. Method B: Pyrolysis of hydrochloride salt of **8**. Method C: Sodium ethoxide solution at room temperature.

The cooled reaction mixture was diluted with sufficient water to form a cloudy suspension which upon standing overnight yielded a crystalline precipitate. The latter was collected by filtration and air dried to give 12.2 g. (62%) of **7c**. Recrystallization from 50% ethanol gave white prisms, m.p. 174.5-177° dec.; ir (potassium bromide): 3.10, 6.00, 6.15, 6.60, 8.10, 8.29, 11.10, 11.83, 12.75, 13.20, 14.42 μ; uv (ethanol: λ max 235 mμ (ϵ, 15,900), 295 (ϵ, 7,150), min. 268 mμ (ϵ, 6,230); nmr (pyridine): τ 4.68 (1H, s, 5-C*H*), 6.85 (3H, s, $\mathrm{NHNC}\mathit{H}_3\mathrm{C_6H_5}$), 7.12 (3H, d, J = 4.6 Hz, 4-$\mathrm{CONHC}\mathit{H}_3$, 7.9-9.1 (10H, broad m, cyclohexyl protons), (aromatic region obscured by solvent).

Preparation of 3a-Amino-1,8b-*bis*-carbamoyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)ones.

The compounds listed in Table 2 were prepared by the following general procedure: A suspension of the appropriate phenylhydrazone precursor in a 3:2 mixture of glacial acetic acid and concentrated hydrochloric acid (5 ml. acid mixture per gram) was heated to boiling and the resulting solution was poured into water. In several cases the indoline hydrochlorides precipitated but in most cases remained in solution and the free base was isolated by neutralization with aqueous alkalai. The following examples are typical.

3a-Amino-2-cyclohexyl-1,8b-*bis*-*N*-methylcarbamoyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)one (**8b**).

A suspension of 10.0 g. (26.2 mmoles) of phenylhydrazone **6b** in 30 ml. of glacial acetic acid and 20 ml. of concentrated hydrochloric acid was magnetically stirred and heated to boiling. The hot solution was poured into water and the aqueous mixture neutralized with 20% potassium hydroxide. The precipitated solid was collected by filtration, water-washed and air-dried to afford 6.0 g. (60%) of **6b** as a white solid. Recrystallization from benzene-petroleum ether (b.p. 30-60°) gave an analytical sample, m.p. 251-252°; ir (potassium bromide): 2.96, 6.0, 6.42, 8.07, 9.77, 10.21, 10.75, 11.20, 11.85, 13.40 μ; uv (ethanol): λ max 245 mμ (ϵ, 3,850), 297 (ϵ, 2,220), λ min 273 mμ (ϵ, 900).

3a-Amino-2-cyclohexyl-4-methyl-1,8b-*bis*-*N*-methylcarbamoyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)one (**8i**).

A mixture of 8.5 g. (21.3 mmoles) of enehydrazine **7c** in 25 ml. of glacial acetic and 17 ml. of concentrated hydrochloric acid was heated to boiling and poured into water. A solid which precipitated during neutralization with 20% potassium hydroxide was collected by filtration, air dried and recrystallized from 95% ethanol to yield 4.9 g. (53%) of **8i** as the monohydrochloride salt, m.p. 213.5-215°; ir (potassium bromide): 2.98, 5.97, 6.06, 6.47, 8.11, 8.69, 9.52, 10.62, 12.67, 13.37, 13.57, 13.88 μ; uv (ethanol): λ max 257 mμ (ϵ, 4,540), 310 (ϵ, 1,930), λ min 238 mμ (ϵ, 3,960), 284 (ϵ, 905).

Base-catalyzed and Pyrolytic Fragmentation of 1,8-b-*bis*-Carbamoylindolines (**8**).

Method A.

A mixture of the indoline (**8**) in a solution of sodium (3-4 g.-atom per mole of indoline) in ethylene glycol (25-30 ml. per gram of indoline) was magnetically stirred and heated to 140-170° at the rate of *ca.* 5° per minute. The hot reaction mixture was poured into ice and acidified to precipitate the product. The following examples are typical.

2-Cyclohexyl-1,4-dihydropyrrolo[3,4-*b*]indol-3(2*H*)one-1-*N*-methylcarboxamide (**10b**).

To a solution of 3.4 g. (0.148 g.-atom) of sodium in 500 ml. of ethylene glycol was added 18.5 g. (48.0 mmoles) of **8b**. The mixture was magnetically stirred and heated to 160°, the dark colored solution poured onto *ca.* 2 l. crushed ice and the aqueous mixture acidified with concentrated hydrochloric acid. The precipitated product was collected by filtration, water washed and dried to afford 7.5 g. (50%) of **10b** as an off-white solid. An analytical sample was recrystallized from 95% ethanol; ir (potassium bromide): 3.10, 5.97, 6.03, 6.47, 8.23, 8.63, 9.93, 10.32, 10.94, 11.71, 12.23, 12.92, 13.67 μ; uv (ethanol): λ max 200 mμ (ϵ, 30,700), 294 (ϵ, 18,100), λ min 257 mμ (ϵ, 3,070).

4-Benzyl-2-cyclohexyl-1,4-dihydropyrrolo[3,4-*b*]indol-3(2*H*)one-1-*N*-methylcarboxamide (**10h**) and 5a-Amino-6-benzyl-4-cyclohexyl-3a,4,5a,6-tetrahydro-2-methylpyrrolo[3:4′:4,5]pyrrolo-[3,4-*b*]indole-1,3,5(2*H*)trione (**11d**).

A mixture of 12.6 g. (24.5 mmoles) of **8k** and 1.75 g. (0.075 g.-atom of sodium) in 350 ml. of ethylene glycol was stirred and heated to 140°, quenched in ice and acidified. The crude product was collected by filtration, water washed and fractionally recrystallized from 95% ethanol to yield 5.6 g. (51%) of **11d** as the first fraction and 1.3 g. (13%) of **10h** from the mother liquor. Both compounds were recrystallized again from ethanol to provide analytical samples. Spectral data for **10h**: ir (potassium bromide): 2.95, 5.93, 6.00, 6.53, 8.23, 8.41, 8.74, 10.45, 11.19, 13.15, 13.48, 14.36 μ; uv (ethanol): λ max 229 mμ (ϵ, 33,400), 301 (ϵ, 18,900), λ min 265 mμ (ϵ, 4,950); nmr (5:1 deuteriochloroform:trifluoroacetic acid): τ 2.1-3.1 (9H, m, Ar*H*), 4.56 (3H, s, overlap of 1-C*H* and 4-CH_2Ph), 5.8-6.1 (1H, b, tertiary cyclohexyl proton), 7.23 (3H, d, J = 4.8 Hz, -$\mathrm{CONHC}\mathit{H}_3$, 7.85-9.0 (10H, b, cyclohexyl protons). Spectral data for **11d**: ir (potassium bromide): 2.86, 5.58, 5.84, 5.94, 8.34, 8.75, 9.36, 11.62, 11.34, 13.44, 13.67, 14.33 μ; uv (ethanol): λ 243 mμ (sh) (ϵ, 6,680), 260 (ϵ, 7,600), 312 (ϵ, 2,495); λ min 228 mμ (ϵ, 5,650), 287 (ϵ, 1,680); nmr (deuteriochloroform): 2.70 (5H, s, benzyl Ar*H*), 2.85-3.85 (4H, m, Ar*H*), 5.26 (2H, q, J = 17.4 Hz, 6-CH_2Ph), 5.64 (1H, s, 3a-C*H*), 6.0-6.5 (1H, b, tertiary cyclohexyl proton), 6.89 (3H, s, 2-CH_2P, 7.82 (2H, bs, 5a-NH_2), 7.9-9.0 (10H, bm, cyclohexyl protons).

Method B.

The hydrochloride salts of several of the 4-alkylated derivatives of type **8** were pyrolyzed by heating in an oil bath at the rate of *ca.* 10°/minute until the salt began to fuse. Heating was continued until fusion was complete and the temperature was maintained at *ca.* 10-15° above the melting point of the salt for 3-5 minutes.

Pyrolysis of **8k**.

The indoline monohydrochloride **8k** (550 mg., 1.07 mmoles) was heated at the rate of *ca.* 10°/minute to a temperature of 240°. After 5 minutes the pyrolysate was cooled and the resolidified mass fractionally recrystallized from 95% ethanol to give 205 mg. (47%) of **10h** and 120 mg. (24%) of **11d**.

Method C.

Several of the 4-alkylated indolines gave high yields of imide (**11**) by treatment with sodium ethoxide at room temperature. E.g.: A mixture of indoline monohydrochloride **8k** (700 mg., 1.36 mmoles) in a solution of 120 mg. (5.4 mmoles) sodium in 30 ml. of absolute ethanol was stirred at room temperature for 24 hours. The mixture was neutralized with 20% hydrochloric acid, concentrated by evaporation to a volume of *ca.* 10 ml. and diluted with 100 ml. water. The resulting precipitate was collected by filtration and recrystallized from 95% ethanol to afford 485 mg. (80%) of **11d**.

5a-Amino-6-benzyl-4-cyclohexyl-1,2,3,4a,4,5,5a,6-octahydro-2-methylpyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole (**12b**).

A mixture of 5.0 g. (11.3 mmoles) of **11d** and 5.0 g. of lithium aluminum hydride in 250 ml. of dry ether was magnetically stirred and refluxed for 18 hours. The cooled mixture was treated with saturated sodium sulfate solution, the organic phase separated, dried (sodium sulfate) and concentrated under reduced pressure. The solid residue was recrystallized from petroleum ether (b.p. 30-60°) to afford 1.95 g. (43%) of **12b** as a white solid, m.p. 135-137°. An analytical sample recrystallized from 95% ethanol melted at 136-138.5°; ir (potassium bromide): 2.90, 6.22, 7.96, 8.15, 8.57, 9.75, 10.59, 11.35, 11.76, 13.59, 13.86, 14.39 μ; uv (ethanol): λ max 255 mμ (ϵ, 14,050), 307 (ϵ, 4,980); λ min 280 mμ (ϵ, 1,850); nmr (deuteriochloroform): τ 2.73 (5H, d, benzyl Ar*H*), 2.8-4.0 (4H, m, Ar*H*), 5.55 (2H, q, J = 16.8 Hz, 6-CH_2Ph), 6.3-8.0 (7H, m, heterocyclic ring protons), 7.69 (3H, s, 2-CH_3), 8.10 (2H, s, 5*a*-NH_2), 8.0-9.2 (10H, b, cyclohexyl portons); ms: m/e 402.2795 (calculated for $C_{26}H_{34}N_4$: 402.2783); significant fragmentations: m/e 138, 155, 170, 235, 328, 385.

Anal. Calcd. for $C_{26}H_{34}N_4$: C, 77.61; H, 8.46; N, 13.93. Found: C, 77.55; H, 8.37; N, 13.69.

5a-Amino-9-chloro-4-cyclohexyl-1,2,3,3a,4,5,5a,6-octahydro-2,6-dimethylpyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole (**12a**).

A mixture of 1.0 g. (2.5 mmoles) of **11c** and 1.0 g. of lithium aluminum hydride in 100 ml. of ether and 25 ml. of tetrahydrofuran was refluxed 3.5 hours; isolation was similar to **12b**. The crude product thus obtained was recrystallized from ethanol-water to give 585 mg. (65%) of **12a** as white needles, m.p. 167-168°; ir (potassium bromide): 3.25, 6.20, 8.00, 8.18, 8.56, 11.80, 13.66, 14.55; uv (ethanol): λ max 261 mμ (ϵ, 14,000), 321 (ϵ, 3,080); λ min 232 mμ (ϵ, 3,380), 284 (ϵ, 798).

Anal. Calcd. for $C_{20}H_{29}ClN_4$: C, 66.55; H, 8.10; N, 15.62. Found: C, 66.47; H, 8.29; N, 15.49.

5a-Amino-2,6-dibenzyl-4-cyclohexyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole (**12c**) and its 5a-Phenylurea and Phenylthiourea Derivatives.

Reduction of 1.0 g. (1.9 mmoles) of **11f** with 1.0 g. of lithium aluminum hydride in 50 ml. of absolute ether provided after workup 410 mg. (46%) of **12c** as a water-white oil which could not be induced to crystallize. A solution of 40 mg. of **12c** and 2 drops of phenyl isocyanate in 5 ml. of absolute ether was refluxed for 30 minutes then diluted with peteroleum ether (b.p. 30-60°). The precipitated phenylurea was collected by filtration and recrystallized from ether-petroleum ether to afford the 5a-phenylurea derivative as a white powder, m.p. 106-109°; ir (potassium bromide): 2.95, 6.05, 6.50, 7.69, 8.16, 8.65, 9,75, 14.45 μ.

Anal. Calcd. for $C_{39}H_{43}N_5O$: C, 78.36; H, 7.25; N, 11.72. Found: C, 78.21; H, 7.21; N, 11.79.

A solution of 50 mg. of **12c** and 2 drops phenyl isothiocyanate in 5 ml. of absolute ether was refluxed 30 minutes and diluted with petroleum ether (b.p. 30-60°). The precipitated product was recrystallized from ether-petroleum ether to give the 5a-phenylthiourea derivative as a white solid, m.p. 135-136°; ir (potassium bromide): 2.95, 6.75, 7.89, 8.24, 8.67, 8.76, 13.40, 13.59, 14.30, 14.45 μ.

Anal. Calcd. for $C_{39}H_{43}N_5S$: C, 76.31; H, 7.06; N, 11.41. Found: C, 76.41; H, 7.14; N, 11.27.

3a-Amino-2-cyclohexyl-1,8b-*bis*-hydrazido-4-methyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)one (**13a**).

A mixture of 1.0 g. (2.5 mmoles) of the *bis*-methylcarbamoyl compound **8i** and 1.0 ml. of 95% hydrazine in 20 ml. of 1-butanol was refluxed for 16 hours. After removal of solvent *in vacuo* the residual solid was slurried with water and collected by filtration to give 830 mg. (83%) of **13a**. An analytical sample recrystallized from THF-ether melted at 216-217°; ir (potassium bromide): 2.94, 3.01, 5.92, 6.04, 6.51, 7.30, 8.10, 8.77, 9.41, 10.08, 10.40, 11.60, 13.44, 14.14, 14.50 μ.

Anal. Calcd. for $C_{19}H_{27}N_7O_3$: C, 56.84; H, 6.78; N, 24.43. Found: C, 56.58; H, 6.82; N, 24.25.

3a-Amino-4-benzyl-2-cyclohexyl-1,8b-*bis*-hydrazido-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)one (**13b**).

A mixture of 500 mg. (1.05 mmoles) of **8k** and 0.5 ml. of hydrazine in 25 ml. of ethanol was refluxed for 16 hours. The solvent was removed *in vacuo* to afford a gummy residue which solidified upon trituration with water to afford 425 mg. (85%) of **13b** as a white solid, m.p. *ca.* 150°. Attempts to recrystallize this material resulted in cyclization.

Anal. Calcd. for $C_{25}H_{31}N_7O_3$: C, 62.87; H, 6.54; N, 20.53. Found: C, 62.70; H, 6.40; N, 20.33.

2,5a-Diamino-4-cyclohexyl-3a,4,5a,6-tetrahydro-6-methyl-pyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole-1,3,4(2*H*)trione (**11i**).

The *bis*-hydrazide **13a** (500 mg., 1.25 mmoles) was heated in a test tube to *ca.* 225° for about 1 minute. The semi-solid material was cooled and recrystallized from 95% ethanol to yield 375 mg. (81.5%) of **11i** as white needles, m.p. 162-163°; ir (potassium bromide): 2.94, 3.01, 5.57, 5.85, 6.22, 6.89, 7.64, 8.43, 9.33, 10.48, 11.81, 13.30, 13.41; uv (ethanol): λ max 240 mμ (7,350), 259 (ϵ, 7,330), 316 (ϵ, 2,220); min 231 mμ (ϵ, 6,940), 250 (ϵ, 6,960), 293 (ϵ, 1,460).

Anal. Calcd. for $C_{19}H_{23}N_5O_3$: C, 61.77; H, 6.28; N, 18.96. Found: C, 61.53; H, 6.15; N, 18.83.

2,5a-Diamino-6-benzyl-4-cyclohexyl-3a,4,5a,6-tetrahydropyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole-1,3,5(2*H*)trione (**11j**).

Bis-hydrazide **13b** (500 mg., 1.05 mmoles) was heated for several minutes at 160°. The cooled solid was recrystallized from ethanol-water to give 425 mg. (91.4%) of **11j** as white needles, m.p. 221-223°.

Anal. Calcd. for $C_{25}H_{27}N_5O_3$: C, 67.40; H, 6.11; N, 15.72. Found: C, 67.29; H, 6.10; N, 15.80.

2,5a-Diamino-4-cyclohexyl-3a,4,5a,6-tetrahydropyrrolo[3',4':4,5]-pyrrolo[3,4-*b*]indole-1,3,5(2*H*)trione (**11g**).

A mixture of 600 mg. (1.55 mmoles) of the *bis*-*N*-methylcarbamoyl compound **8b** and 1.0 ml. (30 mmoles) of 95% hydrazine in 25 ml. 1-butanol was refluxed for 14 hours. The mixture was concentrated *in vacuo* and the residue triturated with water to afford 390 mg. (69.5%) of **11g** as a white solid. An analytical sample recrystallized from ethanol-water melted at 216-218°.

Anal. Calcd. for $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.96; H, 19.71. Found: C, 60.55; H, 5.86; N, 19.57.

2,5a-Diamino-9-chloro-4-cyclohexyl-3a,4,5a,6-tetrahydropyrrolo[3',4':4,5]pyrrolo[3,4-*b*]indole-1,3,5(2*H*)trione (**11h**).

A mixture of 500 mg. (1.2 mmoles) of **8c** and 0.75 ml. (95%) of hydrazine in 20 ml. of absolute ethanol was refluxed for 16 hours, the solvent removed *in vacuo* and the gummy residue triturated with water to afford 385 mg. (83%) of **11h** as a white granular solid, m.p. 232-234°; ir (potassium bromide): 2.95, 3.00 and 3.07 (NH), 5.58 (symmetrical imide C=O), 5.81 (asymmetrical imide C=O), 5.91 (lactam C=O), 6.22, 6.70, 6.80, 6.88, 7.06, 7.28, 7.78, 8.26, 8.50, 10.60, 11.31, 13.31, 14.90 μ; uv λ max (ethanol): 239 (ϵ, 8,620), 258 (ϵ, 8,400), and 315 (ϵ, 2,800).

Anal. Calcd. for $C_{18}H_{20}ClN_5O_3$: C, 55.45; H, 5.17; N, 17.95. Found: C, 55.18, H, 5.31; N, 18.13.

5a-Amino-6-benzyl-2-benzylideneamino-4-cyclohexyl-3a,4,5a,6-tetrahydropyrrolo[3′,4′:4,5]pyrrolo[3,4-*b*]indole-1,3,5(2*H*)trione (**14**).

A mixture of 50 mg. (0.11 mmoles) of **11j**, 50 mg. (0.47 mmoles) of benzaldehyde, and 5 ml. of 95% ethanol was refluxed for 4 hours. The ethanol was allowed to evaporate. The remaining white solid was slurried with ether and collected by filtration to yield 55 mg. (94%) of **14**. Recrystallization from absolute ethanol provided an analytically pure sample, m.p. 240-242°; ir (potassium bromide): 2.93, 3.00, and 3.11 (NH), 5.58 (symmetrical imide C=O), 5.79 (asymmetrical imide C=O), 5.88, 5.94 (lactam C=O), 6.00, 6.22 (C=N and aromatic), 6.72, 6.83, 6.89, 7.09, 7.26, 7.30, 7.58, 7.64, 7.70, 8.25, 8.44, 13.38, 13.68, and 14.38 μ; uv λ max (ethanol): 262 (ϵ, 21,000) and *ca.* 297 (sh) (ϵ, 10,800); nmr (deuteriochloroform): τ 0.82 (1H, s, $C_6H_5C\mathit{H}$), 2.0-2.7 (5H, m, 2-$C_6\mathit{H}_5CH$), 2.72 (5H, s, 6-$C_6\mathit{H}_5CH_2$), 2.8-4.0 (4H, m, Ar*H*), 5.30 (2H, q, 6-$C_6H_5C\mathit{H}_2$), 5.52 (1H, s, 3a-C*H*), 6.0-6.6 (1H, b, tertiary cyclohexyl proton), 7.76 (2H, s, 5a-$N\mathit{H}_2$), and 7.9-9.1 (10H, b, cyclohexyl protons).

Anal. Calcd. for $C_{32}H_{31}N_5O_3$ (mol. wt. 533.61): C, 72.02, H, 5.86; N, 13.13. Found: C, 71.74; H, 6.11; N, 12.88.

REFERENCES AND NOTES

(1) Supported in part by Research Grant GM-04371 from the National Institutes of Health, U. S. Public Health Service. This paper is based on theses submitted by Joseph P. Yevich, John R. Murphy, and Richard F. Dufresne in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie-Mellon University.

(2a) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, 25, 1133 (1960); (b) P. L. Southwick, B. McGrew, R. R. Engel, O. E. Milliman, and R. J. Owellen, *ibid.*, **28**, 3058 (1963); (c) P. L. Southwick, J. A. Vida, B. M. Fitzgerald, and S. K. Lee, *ibid.*, **33**, 2051 (1968).

(3a) B. Robinson, *Chem. Rev.*, **63**, 373 (1963); (b) B. Robinson, *ibid.*, **69**, 227 (1969).

(4) N. N. Suvorov and N. P. Sorokina, *Dokl. Adad. Nauk SSSR*, **136**, 840 (1961); *Chem. Abstr.*, **55**, 17621f (1961).

(5) G. Zinner, W. Kliegel, W. Ritter, and H. Bohlke, *Chem. Ber.*, **99**, 1678 (1966).

(6) P. Schiess and A. Greider, *Tetrahedron Letters*, 2097 (1969).

(7) W. Sucrow and E. Wiese, *Chem. Ber.*, **103**, 1767 (1970).

(8) J. Bouvdais and C. Germain, *Tetrahedron Letters*, 195 (1970).

(9) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1900 (1963).

(10) A. M. Duffield, H. Budzidiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 810 (1965).

(11) Micronanlyses are by M-H-W Laboratories, Phoenix, Arizona, Galbraith Laboratories, Knoxville, Tennessee or Drs. G. Weiler and F. B. Strauss, Oxford, England. Melting points were taken in capillary tubes with a Thomas-Hoover melting point apparatus, and are corrected. Mass spectral data were obtained with an AEI-MSO high-resolution mass spectrometer by James Boal. In nmr spectra s stands for singlet, d for doublet, t for triplet, q for quartet, m for multiplet and b for broad signal.