Cyclization of Basic Amide Hydrochlorides. A New Synthesis of Substituted Lactams

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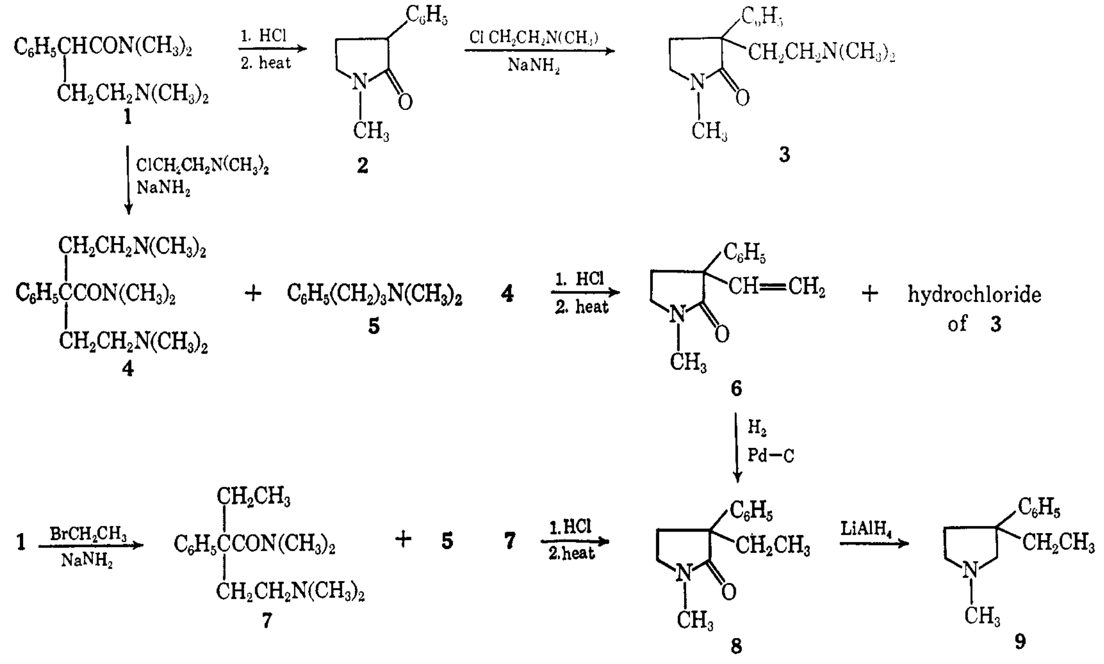
Hydrochlorides of certain basic amides were cyclized by heat to form a 2-pyrrolidinone or 2-piperidone in high yields. N,N-Dimethyl-4-dimethylamino-2-phenylbutyramide (**1**) hydrochloride, pyrolyzed at 280–285°, gave 1-methyl-3-phenyl-2-pyrrolidinone (**2**, 86%). The 3-ethyl and 3-phenyl derivatives of **2** and 1-methyl-3-phenyl-2-piperidone were similarly prepared. N,N-Dimethyl-4-dimethylamino-2-(2-dimethylaminoethyl)-2-phenylbutyramide dihydrochloride yielded a mixture of the 3-(2-dimethylaminoethyl) and 3-vinyl derivatives of **2**. Compounds **1** and **2** were converted into Ivanov-like reagents which, by reaction with formaldehyde, formed the 2- and 3-hydroxymethyl derivatives, respectively.

Discovery in this laboratory that Ivanov-like reagents can be prepared from suitably substituted β-lactams[2] was extended to the γ-lactam series. A suitable lactam for this purpose is 1-methyl-3-phenyl-2-pyrrolidinone[3,4] (**2**). An attempt to prepare **2** by treating 4-dimethylamino-2-phenylbutyric acid[5] with phosphorus trichloride to form the acid chloride as an intermediate and then heating the reaction mixture yielded only a gummy product, although other 2-pyrrolidinones have been prepared in this manner.[6-10]

The desired pyrrolidinone was prepared instead from the hydrochloride of the N,N-dimethylamide of the above acid. Thus, **2** was synthesized in 86% yield by heating N,N-dimethyl-4-dimethylamino-2-phenylbutyramide (**1**) hydrochloride for a short time at 280–285° (see Scheme I). Trimethylamine hydrochloride, which also formed, partially decomposed liberating trimethylamine.

Cyclization of other basic amide hydrochlorides is summarized in Table I. Pyrolysis of **4a** yielded a mixture of 3-(2-dimethylaminoethyl)-1-methyl-3-phenyl-2-pyrrolidinone[9] (**3**) hydrochloride and 1-methyl-3-phenyl-3-vinyl-2-pyrrolidinone (**6**); **3** was also prepared from **2**. The reaction was extended to the piperidone series by cyclization of **15a** to give 1-methyl-3-phenyl-2-piperidone (**17**). Other reactions are shown in Scheme I.

SCHEME I



N,N-Dimethyl-3-phenylpropylamine (**5**) was formed in substantial yield owing to elimination of the amide group from **1** when **4** and **7** were prepared. A similar cleavage has been reported during the second alkylation of the 2 position of related substituted phenylacetamides using sodium amide.[11]

Reaction of formaldehyde with Ivanov-like reagents[12] prepared from **1** and **2** gave the corresponding 2- and 3-hydroxymethyl derivatives (**10** and **12**, repectively,

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(2) P. E. Wright, *Dissertation Abstr.*, **21**, 3642 (1961).

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(4) F. F. Blicke, A. J. Zambito, and R. E. Stenseth, *J. Org. Chem.*, **26**, 1826 (1961).

(5) F. F. Blicke and E.-P. Tsao, *J. Amer. Chem. Soc.*, **75**, 5587 (1953).

(6) J. H. Gardner, N. R. Easton, and J. R. Stevens, *ibid.*, **70**, 2906 (1948).

(7) D. J. Dupré, J Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

(8) E. Walton, P. Ofner, and R. H. Thorpe, *ibid.*, 648 (1949).

(9) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949).

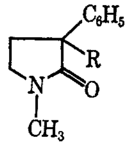
(10) See also W. Wilson, *J. Chem. Soc.*, 3524 (1952), and F. F. Blicke and E.-P. Tsao, *J. Amer. Chem. Soc.*, **75**, 4334 (1953).

(11) O. Mårtensson and E. Nilsson, *Acta Chem. Scand.*, **15**, 1026 (1961).

(12) Hydrolysis of the reagents with HCl regenerated **1** and **2** in 92% and 87% yield, respectively.

TABLE I

SUBSTITUTED 1-METHYL-3-PHENYL-2-PYRROLIDINONES[a]

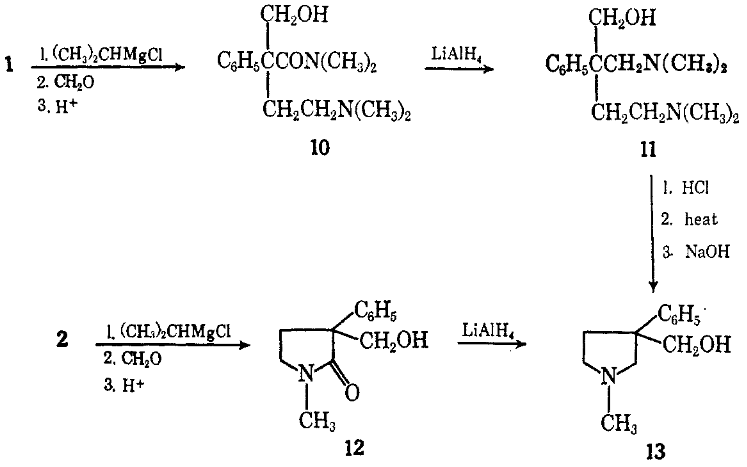


Product	R	Base or salt	Compound cyclized	Bath temp, °C	Yield, %	Bp (mm), °C	Mp, °C
2	H		**1a**	280–285	86	120–124 (0.4)	60–61[b]
3	$CH_2CH_2N(CH_3)_2$	Base	**4a**	280–285	38	137–141[c] (0.6)	68–69[d]
3a	$CH_2CH_2N(CH_3)_2$	Hydrochloride					191–192
3b	$CH_2CH_2N(CH_3)_2$	Acid oxalate					161–162
6	$CH{=}CH_2$		**4a**	280–285	36	110–113[e] (0.2)	
8	CH_2CH_3		**7a**	265–270	93	106–108[e,f] (0.15)	
16	C_6H_5		**14a**	250	88		144–145[g]

		Analyses, %					
		Carbon		Hydrogen		Nitrogen	
Product	Formula	Calcd	Found	Calcd	Found	Calcd	Found
2	$C_{11}H_{13}NO$	75.40	75.42	7.48	7.41	7.99	8.24
3	$C_{15}H_{22}N_2O$	73.13	72.86	9.00	8.95	11.37	11.43
3a	$C_{15}H_{23}ClN_2O$[h]	63.70	63.49	8.20	8.29	9.91	10.13
3b	$C_{17}H_{24}N_2O_5$	60.70	60.74	7.19	7.19	8.33	8.49
6	$C_{13}H_{15}NO$	77.58	77.43	7.51	7.83	6.96	6.96
8	$C_{13}H_{17}NO$	76.81	76.82	8.43	8.63	6.89	6.97

[a] All of the salts were prepared in ether. Compound **2** was recrystallized from ether; **3** from petroleum ether (bp 30–40°); **3a** from acetone–absolute ethanol; **3b** from isopropyl alcohol; **16** from benzene–cyclohexane. [b] Lit.[3] mp 58–59°; lit.[4] mp 60–61°. [c] Crystalline **3** was obtained by being converted to **3a** (27% yield from **4a**), liberating **3**, and redistilling: bp 128–130° (0.4 mm); 27% yield of **3a** from **4a**; **3**, bp 123–126° (0.2 mm). [d] Lit.[9] bp 137–138° (0.25 mm), mp 66.5–68°, ir (Nujol) 1685 cm^{-1} (C=O). The ir spectra of **3** prepared from **4a** and from **2** (Table II) were identical. [e] Ir (neat) 1685 cm^{-1} (C=O) and, for **6**, ir 918 and 1000 (C=C bend) and 1635 cm^{-1} (C=C stretch). [f] F. J. Marshall [*J. Org. Chem.*, **23**, 503 (1958)] reported bp 130–132° (0.75 mm). [g] Lit.[7] mp 146.5–147°. The mixture melting point with an authentic sample[7] (mp 144–145°) was 144–145°. [h] Calcd: Cl, 12.54. Found: Cl, 12.64.

SCHEME II



Scheme II). The 2-(1-hydroxypropyl) derivative (**18**) of **1** and the 3-(1-hydroxycyclohexyl) derivative (**19**) of **2** were similarly prepared. Other reactions are shown in Scheme II.

Experimental Section

Melting points are corrected and boiling points uncorrected.

Basic Amides (Table II).—The general procedure is illustrated in the case of **1**; modifications for **3**, **4**, **7**, and **14** are given below.

N,N-Dimethyl-4-dimethylamino-2-phenylbutyramide (1).—N,N-Dimethylphenylacetamide (163.2 g, 1.0 mol) in dry toluene was added dropwise to a stirred, refluxing suspension of 58.5 g (1.5 mol) of sodium amide in toluene and the mixture was refluxed for 4 hr. The temperature was lowered slightly and 161.4 g (1.5 mol) of 2-dimethylaminoethyl chloride[13] in toluene was added dropwise. The mixture was refluxed for 6 hr and cooled, and water was added. The toluene phase and a toluene extract of the aqueous phase were extracted with HCl. Crude **1** was liberated with NaOH, extracted with ether, dried ($MgSO_4$), and distilled.

For **3**, **4**, **7**, and **14**, the mole ratio of sodium amide to alkylating agent to organic amide was 1.2:1.2:1. For **14**, the organic amide was added as a suspension in hot toluene to the sodium amide suspension; ether removal gave crude **14** as a solid.

The crude oils of **4** and **7** yielded **5**, bp 35–36° (0.2 mm) (24%)

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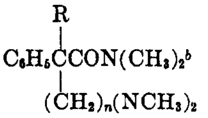
[13] Liberated from the hydrochloride just before use by R. R. Burtner's method [*J. Amer. Chem. Soc.*, **71**, 2578 (1949)] and the toluene solution was kept ice cold to minimize cyclization.

TABLE II

BASIC AMIDES[a]



$$\mathrm{C_6H_5\underset{(CH_2)_n(NCH_3)_2}{\overset{R}{C}}CON(CH_3)_2}^{b}$$

Compd	n	R	Base or salt	Yield, %	Bp (mm), °C	Mp, °C
1	2	H	Base	84	109–115 (0.3)	
1a	2	H	Hydrochloride			159–160
1b	2	H	Acid oxalate			155–156
4	2	$CH_2CH_2N(CH_3)_2$	Base	39	154–155 (1)	64–66
4a	2	$CH_2CH_2N(CH_3)_2$	Dihydrochloride			242–243
7	2	CH_2CH_3	Base	41	106–109 (0.2)	
7a	2	CH_2CH_3	Hydrochloride			209–210
14	2	C_6H_5	Base	44		95–97[c]
14a	2	C_6H_5	Hydrochloride			226–228[c]
15	3	H	Base	89	132–135 (0.6)	
15a	3	H	Hydrochloride			134–135
3[b]	Prepared from **2**		Base	70	133–135[d] (0.5)	68–69[e]
3a			Hydrochloride			192–193
3b			Acid oxalate			161–162

		Analyses, %							
		Carbon		Hydrogen		Nitrogen		Chlorine	
Compd	Formula	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
1	$C_{14}H_{22}N_2O$	71.75	71.65	9.46	9.36	11.96	11.90		
1a	$C_{14}H_{23}ClN_2O$	62.09	62.07	8.56	8.47	10.35	10.55	13.09	13.22
1b	$C_{16}H_{24}N_2O_5$	59.24	59.35	7.46	7.49	8.64	8.81		
4	$C_{18}H_{31}N_3O$	70.78	70.76	10.23	10.10	13.76	13.99		
4a	$C_{18}H_{33}Cl_2N_3O$	57.13	57.13	8.79	8.69	11.11	11.17	18.74	18.64
7	$C_{16}H_{26}N_2O$	73.24	73.08	9.99	9.93	10.68	10.77		
7a	$C_{16}H_{27}ClN_2O$	64.30	63.98	9.11	8.91	9.38	9.52	11.86	11.99
15	$C_{15}H_{24}N_2O$	72.54	72.36	9.74	9.59	11.28	11.00		
15a	$C_{15}H_{25}ClN_2O$	63.25	63.27	8.85	8.87	9.84	10.04	12.45	12.50

[a] All of the salts were prepared in ether. Compounds **1a** and **1b** were recrystallized from absolute ethanol; **4a** from absolute ethanol–ether; **7a, 14a,** and **3b** from isopropyl alcohol; **14** from cyclohexane; **15a** from acetone; **3** from petroleum ether (bp 30–40°); **3a** from acetone–absolute ethanol. Compound **4** was triturated with petroleum ether (bp 30–40°). [b] Compound **3** does not conform to the general formula. [c] R. B. Moffett and B. D. Aspergren [*J. Amer. Chem. Soc.*, **79**, 4462 (1957)] reported mp 97–99°, hydrochloride mp 228–230°. [d] Crystalline **3** was obtained by being converted to **3a** (62% yield from **2**), liberating **3**, and redistilling: bp 128–130° (0.4 mm). [e] Lit.[9] bp 137–138° (0.25 mm), mp 66.5–68°. Ir (Nujol) 1685 cm^{-1} (C=O); the ir spectra of **3** prepared from **2** and from **4a** (Table I) were identical.

and bp 42° (0.3 mm) (17%), respectively [lit.[14] bp 117–118° (26 mm)]. The positive identification of **5** was established by mixture melting points of picrates,[15] hydrochlorides,[14] acid oxalates,[16] and methiodides,[14] using an authentic sample of **5**.[14]

Substituted 1-Methyl-3-phenyl-2-pyrrolidinones (Table I).—The general procedure is illustrated in the case of **2**; modifications for **3**, **6**, and **16** are given below.

1-Methyl-3-phenyl-2-pyrrolidinone (2).—The salt **1a** (13.5 g, 0.05 mol) was heated at 280–285° under a stream of dry N_2 connected to an ether scrubber. When gas evolution had almost ceased (about 20 min), **2** was extracted with anhydrous ether, leaving a residue of trimethylamine hydrochloride. The extract was dried ($MgSO_4$), concentrated, and distilled.

Picric acid in ether was added to the trimethylamine solution in the scrubber to give 1.1 g of the picrate, mp 215–216° (from absolute ethanol) (lit.[16] mp 216°).

Compounds **3** and **6** were separated by adding water to the reaction mixture and extracting crude **6** with ether; **3** was liberated from the aqueous phase with NaOH and extracted with ether. Mixture melting points of **3**, **3a**, and **3b**, Table I, with their counterparts from Table II verified the structure of **3**. Compound **6** decolorized instantly solutions of Br_2 and $KMnO_4$.

Compound **16** was extracted with benzene after water was added to the reaction mass.

1-Methyl-3-phenyl-2-piperidone (17).—This compound was prepared from **15a** at 285–290° by the pyrrolidinone general procedure: 79% yield; bp 120–123° (0.3 mm).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.83; H, 7.94; N, 7.18.

3-Ethyl-1-methyl-3-phenyl-2-pyrrolidinone (8) (Prepared from 6).—A mixture of 6.0 g (0.03 mol) of **6**, 0.06 g of 5% palladium on carbon, and absolute ethanol was hydrogenated under an initial pressure of 50 psi for 2 hr. Filtration and distillation of the filtrate gave 5.9 g (97%) of **8**: bp 108–111° (0.4 mm); ir (neat) 1685 cm^{-1} (C=O). The ir spectrum was identical with that of **8** prepared from **7a**.

3-Ethyl-1-methyl-3-phenylpyrrolidine (9). A.—Compound **8** (8.1 g, 0.04 mol, prepared from **7a**) in ether was reduced with 2.3 g (0.06 mol) of $LiAlH_4$ to give 7.5 g of crude **9** (not distilled because of foaming).

The hydrochloride was prepared in ether: mp 164–165° (from acetone).

Anal. Calcd for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93; N, 6.20; Cl, 15.71. Found: C, 69.29; H, 8.99; N, 6.30; Cl, 15.89.

The acid oxalate was prepared in ether: mp 132–133° (from acetone).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.84; H, 7.72; N, 5.17.

B.—Compound **9** was similarly prepared from **8** prepared from

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[14] M. Tiffeneau and K. Fuhrer, *Bull. Soc. Chim. Fr.*, (4) **15**, 162 (1914).

[15] P. M. G. Bavin, C. R. Ganellin, J. M. Loynes, P. D. Miles, and H. F. Ridley, *J. Med. Chem.*, **9** (5), 790 (1966).

[16] M. Delépine, *Ann. Chim.* (Paris), (7) **8**, 439 (1896).

6. The hydrochloride melted at 164–165°, mmp 164–165°. The acid oxalate melted at 132–133°, mmp 132–133°.

Compounds Obtained from Ivanov-Like Reactions (Table III).—The general procedure is illustrated in the case of **10**; modifications for **12**, **18**, and **19** are given below.

TABLE III

COMPOUNDS OBTAINED FROM IVANOV-LIKE REACTIONS[a]

	Base or salt	Yield, %	Mp, °C
	Basic Amides		
10	Base	61	121–122
10a	Hydrochloride		180–181
10b	Acid oxalate		162–163
18	Base	84[b]	
18a	Acid oxalate	64	200–201
	Pyrrolidinones		
12		15	103–104
12a	*p*-Nitrobenzoate		172–173
19		12	133–134

		Analyses, %					
		Carbon		Hydrogen		Nitrogen	
Compd	Formula	Calcd	Found	Calcd	Found	Calcd	Found
10	$C_{15}H_{24}N_2O_2$	68.15	68.24	9.15	9.13	10.60	10.72
10a	$C_{15}H_{25}ClN_2O_2$[c]	59.88	59.77	8.38	8.40	9.31	9.39
10b	$C_{17}H_{26}N_2O_6$	57.61	57.69	7.39	7.38	7.91	8.16
18a	$C_{19}H_{30}N_2O_6$	59.67	59.64	7.91	7.90	7.33	7.56
12	$C_{12}H_{15}NO_2$	70.21	70.36	7.37	7.44	6.83	6.91
12a	$C_{19}H_{18}N_2O_6$	64.40	64.44	5.12	5.32	7.91	7.70
19	$C_{17}H_{23}NO_2$	74.69	74.85	8.48	8.59	5.12	5.17

[a] The salts **10a** and **10b** were prepared in ether–absolute ethanol and **18a** in ether. Compounds **10**, **10b**, **18a**, and **12a** were recrystallized from absolute ethanol; **10a** from absolute ethanol–ether; **12** and **19** from benzene–petroleum ether (bp 60–75°). [b] Crude yield. [c] Calcd: Cl, 11.79. Found: Cl, 11.78.

N,N-Dimethyl-4-dimethylamino-2-hydroxymethyl-2-phenylbutyramide (10).—Compound 1 (23.4 g, 0.1 mol) in anhydrous ether was added dropwise to a stirred solution of isopropylmagnesium chloride prepared from 11 ml (0.12 mol) of isopropyl chloride, 2.7 g (0.11 g-atom) of magnesium, 0.5 ml of ethyl bromide, and ether. The mixture was refluxed for 2 hr. Formaldehyde (approximately 0.11 mol), prepared by depolymerization[17] at 200° of 3.5 g of paraformaldehyde (dried over P_2O_5), was swept by dry N_2 into the cooled mixture over a 1-hr period, followed by an additional 10 hr at room temperature. Water and HCl were added to extract **10**, which was liberated with NaOH, extracted with benzene, and dried ($MgSO_4$). Solvent removal gave crude **10**, which was triturated with ether.

For **18**, propionaldehyde in ether was added to the Ivanov-like reagent and the mixture was refluxed for 3 hr.

When preparing **12**, a black oil precipitated midway through addition of **2**. Benzene addition failed to dissolve it. After hydrolysis with HCl, the aqueous layer was extracted with ether. This extract and the ether–benzene layer were dried ($MgSO_4$) and concentrated and the residue was refrigerated in ether–petroleum ether (bp 60–75°) to yield **12**; **2** was recovered (58%) from the mother liquor.

For **19**, **2** was added in benzene to the Grignard reagent. A black oil separated during addition of cyclohexanone in benzene. The mixture was stirred for 5 hr and treated as given above for **12**. The residue was triturated with ether–petroleum ether (bp 30–40°) to give crude **19**; **2** was recovered (53%) from the mother liquor.

4-Dimethylamino-2-(dimethylaminomethyl)-2-phenyl-1-butanol (11) Dihydrochloride.—Compound **10** (26.4 g, 0.1 mol), in a modified Soxhlet extractor,[18] was reduced with 5.7 g (0.15 mol) of $LiAlH_4$ in ether to give 24 g (96%) of crude **11**.

The dihydrochloride was prepared in ether: mp 211–212° (from absolute ethanol); 90% yield of **11** based on the salt.

Anal. Calcd for $C_{15}H_{28}Cl_2N_2O$: C, 55.72; H, 8.73; N, 8.66; Cl, 21.93. Found: C, 55.56; H, 8.53; N, 8.47; Cl, 21.67.

3-Hydroxymethyl-1-methyl-3-phenylpyrrolidine (13). A. Prepared from 11 Dihydrochloride.—The cyclization procedure was used except that after treatment (290–295°) water was added and the base was liberated with NaOH, extracted with ether, and distilled to give **13** (67%): bp 110–114° (0.6 mm); mp 59–60° (from 30–40° petroleum ether).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.19; H, 8.98; N, 7.40.

The acid oxalate was prepared in ether: mp 112–113° (from absolute ethanol).

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.97; H, 6.95; N, 5.09.

B. Prepared from 12.—Compound **12** (0.95 g, 0.0046 mol) in ether was reduced with 0.26 g (0.0069 mol) of $LiAlH_4$ to give **13** in pure form: mp and mmp 59–60°. The acid oxalate was prepared in ether and recrystallized from absolute ethanol–ether: mp and mmp 112–113°.

Registry No.—**1**, 20538-19-6; **1a**, 20538-20-9; **1b**, 20555-20-8; **3**, 20538-18-5; **3a**, 20555-21-9; **3b**, 20538-27-6; **4**, 20538-43-6; **4a**, 20555-26-4; **6**, 20538-28-7; **7**, 20538-29-8; **7a**, 20555-22-0; **8**, 20555-23-1; **9** (HCl), 20538-30-1; **9** (oxalate), 20538-31-2; **10**, 20538-32-3; **10a**, 20555-24-2; **10b**, 20555-25-3; **11** (2HCl), 20538-33-4; **12**, 20538-34-5; **12a**, 20538-44-7; **13**, 20538-35-6; **13** (oxalate), 20538-36-7; **15**, 20538-37-8; **15a**, 20538-38-9; **16**, 20538-39-0; **17**, 20538-40-3; **18a**, 20538-41-4; **19**, 20538-42-5.

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[17] See F. F. Blicke, H. Raffelson, and B. Barna, *J. Amer. Chem. Soc.*, **74**, 253 (1952).

[18] No siphon tube. Liquid from the condenser dropped directly into the reaction mixture.