Hydrochloride. A solution of 55 mg (0.2 mmol) of Va HCl·H_2O in 10 ml of ethanol was warmed at 60 °C for 5 min and the mixture was concentrated to about 2 ml under reduced pressure. To the concentrate was added 3 ml of ether and the solution was allowed to stand for 1 day. The resulting precipitates were collected by filtration, washed with 5 ml of ether, and dried over phosphorus pentoxide under reduced pressure to give 45 mg (80%) of VIIa HCl·H_2O, colorless needles: mp 119 °C dec; ir 3350 and 3150 (vs and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1095 (vs, C–O–C), 770 and 700 cm^{-1} (m and s, C_6H_5); NMR (CF_3COOD) δ 1.36 (t, J = 7 Hz, 3, OCH_2CH_3), 3.75 (s, 3, NCH_3), 4.70 (s, 2, $CH_2OC_2H_5$), 4.85 (q, J = 7 Hz, 2, OCH_2CH_3), 7.60 (s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (16, M^+), 186 (100, $M^+ - OC_2H_5$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·H_2O: C, 54.63; H, 7.05; N, 14.70. Found: C, 54.58; H, 7.24; N, 14.48.

2-Amino-4-ethoxymethyl-1-methyl-5-phenylimidazole (VIIb) Hydrochloride. In the same manner as VIIa 0.258 g (1 mmol) of Vb HCl gave 0.150 g (57%) of VIIb, pale yellow needles, mp 164 °C effervescence, 246–250 °C dec. Two recrystallization from ethanol and ether afforded colorless plates: mp 171 °C effervescence, 249 °C dec; ir 3260 and 3100 (s and vs, NH_2), 1675 (vs, imidazolium ring), 1540 (m, NH_2), 1100 (s, C–O–C), 775 and 700 cm^{-1} (m and s, C_6H_5); NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3, OCH_2OH_3), 3.50 (q, J = 7 Hz, 2, OCH_2CH_3), 3.55 (s, 3, NCH_3), 4.28 (s, 2, $CH_2OC_2H_5$), 7.10–7.70 (broad s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (44, M^+), 186 (100, $M^+ - C_2H_5O$), 103 (23, $C_6H_5C{\equiv}N^+$), 45 (76, $CH_3CH{=}O^+H$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·½H_2O: C, 56.43; H, 6.91; N, 15.14. Found: C, 56.88; H, 6.53; N, 15.23.

2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) Hydrochloride. Compound Va HCl·H_2O (0.552 g, 2 mmol) was dissolved in 6.0 ml of 2% hydrochloric acid at 60 °C. After standing for 1 day in a refrigerator, the precipitates were collected and washed twice with 0.3 ml each of 2% hydrochloric acid to give 0.373 g (72%) of VIIIa HCl, pale pink needles, mp 70 °C sinter, 96 °C. One recrystallization from 2% hydrochloric acid gave colorless needles: mp 70 °C sinter, 102 °C; ir 3300 and 3120 (vs and vs, NH_2), 1675 (vs, imidazolium ring), 1555 (m, NH_2), 1025 or 1000 (s and s, C–O), 785 and 710 cm^{-1} (s and s, C_6H_5); NMR (Me_2SO-d_6) δ 3.60 (s, 3, NCH_3), 4.46 (s, 2, CH_2OH), 5.50 (broad, about 1, CH_2OH), 7.50 (s, 5, C_6H_5), 7.80 (s, 2, NH_2).

Anal. Calcd for $C_{11}H_{13}N_3O$·HCl·2H_2O: C, 47.91; H, 6.57; N, 15.24. Found: C, 47.02; H, 6.20; N, 15.52.

Registry No.—I, 579-07-7; II, 471-29-4; II ½H_2SO_4, 598-12-9; IIIa, 58325-27-2; IIIb, 58325-28-3; IIIb HCl, 58325-29-4; Va HCl, 58325-30-7; Vb HCl, 58325-31-8; VIa HCl, 58325-32-9; VIb HCl, 58325-33-0; VIc HCl, 58325-34-1; VIIa HCl, 58325-35-2; VIIb HCl, 58325-36-3; VIIIa HCl, 58325-37-4.

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(7) R. A. Turner, C. F. Huchner, and C. R. Scholz, *J. Am. Chem. Soc.*, **71**, 2801 (1949).
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Analogues of Sparteine. II. Synthesis of *N*-Monoalkylbispidines and *N,N'*-Dialkylbispidines

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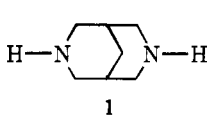
The structural and physiochemical similarity of the bicyclic diamine bispidine (1) to the antiarrhythmic–oxytocic agent sparteine (2) prompted the development of synthetic routes to bispidines containing substituents on one or both nitrogens, for studies directed toward elucidation of optimum molecular characteristics required for sparteine-like bioactivity. Condensation of N-substituted 4-piperidones with benzylamine and formaldehyde, followed by modified Wolff–Kishner reduction of the resulting diamino ketones (8) furnished hydrogenolytically labile intermediates (11) which were converted to *N*-alkylbispidines (12). Alkylation of these last compounds by formation and reduction of amides (15) or by selective alkylation of the secondary amine functions afforded several *N,N'*-dialkylbispidines (3).

Investigations concerning the synthesis and reactivity of the bicyclic amine bispidine (1) have been reported by a number of groups.[1] Although bispidine itself is not naturally occurring, the bispidine moiety constitutes the B and C rings of the C-15 lupine alkaloid sparteine (2).[2] As a result, both compounds have similar physical properties: they are strong bases[3] and form complexes with certain divalent metal cations.[1b,4]



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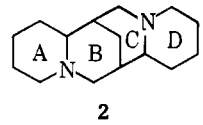

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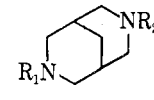
Sparteine has been shown to affect muscular activity, especially the myocardium (heart) and myometrium (uterus).[5] Its chemical and physical similarity to bispidine prompted our efforts to develop facile synthetic routes to *N*-alkylbispidines (3, R_2 = H) and *N,N'*-dialkylbispidines (3) for pharmacologic studies.



3

Bispidine was originally prepared in six steps from pyridine-3,5-dicarboxylic acid ester.[1a] Difficulties encountered in attempted conversion of 1 to 3 (R_1 = R_2 = CH_3)[1e] and the number of steps required prompted us to investigate alternate routes for preparation of 3.

The syntheses of various 1,5-dicarboalkoxybispidinones[6] and 1,5-diarylbispidinones[7] (4) and 2,4,6,8-tetraarylbispidinones[8] (5) via Mannich condensations have been reported (Scheme I). Reductive removal of the carbonyl group in the N-substituted condensation products (e.g., 4, R_1 = H, or 5, R_3 = R_4 = H) would constitute a two-step synthesis of 3. Alternatively, formation of 4 (R_1 = $COOC_2H_5$) followed by hy-

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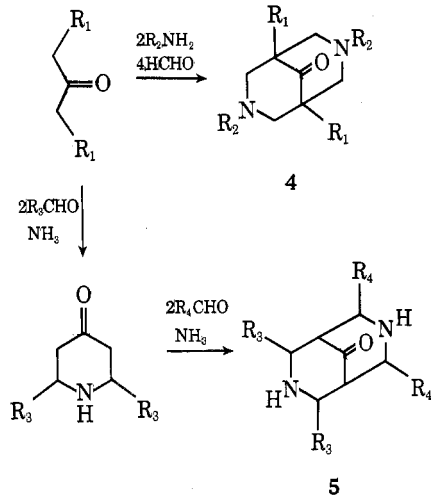
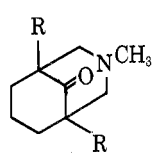
Scheme I

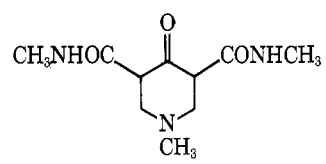


R_1 = aryl, $COOC_2H_5$; R_2 = aryl, alkyl; R_3 = aryl; R_4 = aryl

drolysis and decarboxylation would furnish the intermediate diamino ketones which could then be reduced to the desired compounds. [Decarboxylation of the related base (**6a**) in boiling 20% HCl gave amino ketone **6b** in 67% yield.[9]] How-



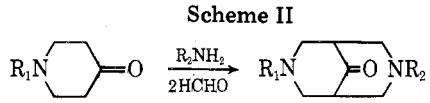
6a, R = $COOC_2H_5$
b, R = H



7

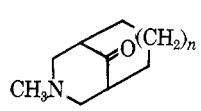
ever, condensation of acetonedicarboxylic acid ester with formaldehyde and methylamine (Scheme I, R_1 = $COOCH_3$; R_2 = CH_3) afforded a small amount of the piperidone **7** accompanied by polymeric products; the respective bicyclic diamine **4** was not detected. Use of acetone itself in this condensation failed to give any tractable products. In contrast, the condensation of *N*-methyl-4-piperidone with paraformaldehyde and methylamine furnished diamino ketone **8a** in low yield (Scheme II).[10] Comparable yields of some closely

Scheme II



8a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$
c, $R_1 = n$-C_4H_9; $R_2 = CH_2C_6H_5$

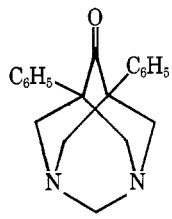
related bicyclic amino ketones (**9**) have been obtained utilizing analogous double Mannich condensations starting with cy-



9, n = 0–2

cloalkanones instead of *N*-methyl-4-piperidone.[11] The use of benzylamine as the primary amine (Scheme II, R_2 = $CH_2C_6H_5$) resulted in a decrease in reaction time and more satisfactory yields of bicyclic amino ketones **8b,c** without the production of significant amounts of other condensation products. This is consistent with earlier work which showed that benzylamine reacts more readily with formaldehyde and ketones than do most primary amines.[12,13]

Amino ketones **8a,b** failed to react with carbonyl reagents, and reacted with hydrazine only under vigorous conditions. This relative inertness may be due to an amide-like character of these compounds. The 1,3-diazadamantanone **10** is of similar reactivity for this postulated reason.[14] Amino ketones **8a,b** were, however, reduced without difficulty under modified Wolff–Kishner conditions[15] to give bicyclic amines **11a,b.**



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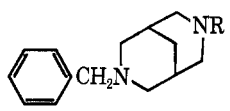
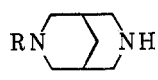


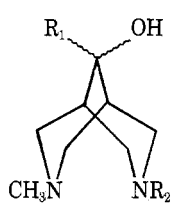
11a, R = CH_3
b, R = n-C_4H_9



12a, R = CH_3
b, R = n-C_4H_9

Hydrogenolytic removal of the benzyl groups in **11a,b** utilizing 10% palladium on carbon[16] afforded the *N*-monoalkylbispidines **12a,b.**

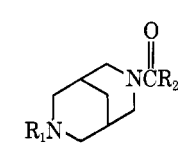
Attempted catalytic debenzylation of bridge-substituted bispidine **8b** gave amino alcohol **13,** and similar treatment of **14**[17] gave only the product of C–O bond cleavage.[18] This suggested that *N*-benzylbispidines are adsorbed exo prior to C–N bond fission, as expected from inspection of molecular models of these compounds.



13, $R_1 = R_2$ = H
14, $R_1 = C_6H_5$; $R_2 = CH_2C_6H_5$

The *N*-alkylbispidines **12a,b** were converted to the N,N′-disubstituted analogues by (a) acylation followed by lithium aluminum hydride reduction of the resulting amides or (b) selective alkylation of the secondary amine groups.

It had been anticipated that hydride reduction of *N*-acyl-*N*′-alkylbispidines (**15**), prepared readily from the appropriate *N*-alkylbispidines and acid chlorides or anhydrides, would not constitute a feasible approach owing to the demonstrated susceptibility of the probable reduction intermediates, immonium ions **16,** to cyclization.[1c] Reductive alkylation of **12a,b** was not attempted for this reason. However, *N*-benzoyl-*N*′-*n*-butylbispidine (**15c**) was reduced with $LiAlH_4$ to afford **11b** cleanly in 83% yield. Less favorable results were obtained in the reductions of amides **15a,b** with $LiAlH_4$. Reduction of **15b** gave a mixture of products containing the desired diamine and a substantial amount of deacylated starting material (**12a**). Reduction of formamide **15a** gave a low yield of diamine ac-



15a, R_1 = CH_3; R_2 = H
b, $R_1 = R_2 = CH_3$
c, R_1 = n-Bu; R_2 = C_6H_5

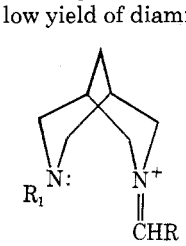


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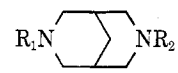
Table I. Products of Alkylation of Amide Anions of *N*-Alkylbispidines

Anion of	Alkyl halide	Yield, %	EIMS, *m/e* M	EIMS, *m/e* B	Monoacid salts Mp, °C	Crystn solvent	Ref	Registry no.
12a	CH_3I	100	154	58	227–229 dec[a]	Ethanol	10, 22	14789-40-3
12a	C_2H_5Br	74	168	58	189–190[a]	Acetone	23, *d*	
12a	*n*-C_4H_9Br	100			129–131[b]	Ethyl acetate–ether	*d*	
12a	c-$C_6H_{11}CH_2Br$	75	236	58	163.5–166 dec[c]	Acetone	*d*	
12b	*n*-C_4H_9Br	100			94.5–95.5[a]	Ethyl acetate–petroleum ether	*d*	

[a] Perchlorate salt. [b] Hydrobromide salt. [c] Hydrochloride salt. [d] Elemental analysis agreed within 0.4% in carbon, hydrogen, and nitrogen.

Table II. Proton Magnetic Resonance Spectral Analysis of *N,N'*-Dialkylbispidines[a]

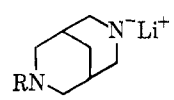


R_1, R_2			
C_2H_5, CH_3	*n*-C_4H_9, CH_3	c-$C_6H_{11}CH_2$, CH_3	*n*-C_4H_9, *n*-C_4H_9
1.00, 3 H, t (7)	0.9, 3 H, t (6)	0.83–1.91, 15 H, m	0.93, 6 H, t (6)
1.45, 2 H, t (3)	1.15–1.60, 8 H, m		1.17–1.63, 10 H, m
1.75, 2 H, m		2.08, 2 H, d (6)	1.82, 2 H, m
2.15, 3 H, s	2.1, 3 H, s	2.15, 3 H, s	
2.2, 4 H, dd (10.5, 4)	2.1–2.45, 6 H, m	2.2–2.8, 8 H, m	2.1–2.3, 8 H, m
2.3, 2 H, q (7)			
2.7, 4 H, dd (10.5, 3)	2.5–2.9, 4 H, m		2.68, 4 H, dd (10, 3)

[a] Spectra were taken using benzene as solvent. Chemical shifts are in parts per million relative to internal tetramethylsilane.

companied by several impurities. Diborane reduction[19] of **15c** proceeded with complete reaction of starting material. However, the borane–amine complex that had formed could not be readily decomposed.[20]

Since it appeared that *N,N'*-dialkylbispidines could not be synthesized from alkyl amides **15** without complications, an alternate method was used to prepare these compounds. Treatment of **12a** or **12b** with an equimolar amount of methyllithium in the cold[21] generated amide anions **17**, which



17, R = CH_3, *n*-C_4H_9

reacted readily with various alkyl halides to afford *N*-*n*-butyl-*N'*-alkylbispidines and *N*-methyl-*N'*-alkylbispidines (**3**) in 74–100% yields (Tables I and II).

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were taken on Beckman IR 10, IR 33, and Perkin-Elmer 727 spectrophotometers. Nuclear magnetic resonance spectra (NMR) were obtained using Varian A-60A and T-60 spectrometers with tetramethylsilane as internal standard. Electron impact mass spectra (EIMS) were recorded using Finnegan 1015 and Varian CH5 spectrometers, at 70 eV unless otherwise indicated. Elemental analysis were obtained on a Hewlett-Packard 185 C, H, N analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind. Analytical gas–liquid chromatography (GLC) was performed with a F & M 810 gas chromatograph using dual column flame ionization detection; carrier gas helium (55 ml/min); detector gases hydrogen (55 ml/min), compressed air (250 ml/min); columns 6 ft × 0.125 in. stainless steel containing Dowfax 9N9 KOH supported on 80–100 mesh acid-washed DMCS-treated HP Chromosorb G; instrument temperatures, injection port (210 °C), detector (225 °C), oven (125–170 °C isothermal). The GLC–EIMS experiment was conducted using the columns and conditions described above, on a Varian Aerograph 1700 gas chromatograph interfaced with the Varian CH5 mass spectrometer.

Free bases were prepared from salts by partitioning the salt between ether and 10% aqueous sodium hydroxide. In the case of water-insoluble salts (perchlorates of aromatic ring containing bispidines) ethanol was added to the mixture to increase the rate of equilibration.

Perchlorate salts were prepared by treating ice-cold ethereal solutions of the amines with excess 70% perchloric acid–ethanol (1:1); the resulting precipitates were filtered and washed with ether. This method afforded diperchlorate salts, except in the case of the aromatic-ring-containing bispidines which yielded monoperchlorates. Monoperchlorates (and other monoacid salts) were prepared by the procedure of Leonard and co-workers.[3]

Workup of Organic Extracts. Unless otherwise stated, solutions were dried with anhydrous sodium sulfate, filtered, and concentrated at a rotary evaporator using a Buchler water aspirator at water bath temperatures of 40 °C or less.

***N*-Benzyl-*N'*-alkylbispidinones (8b,c). A. General Procedure.** The synthesis of *N*-benzyl-*N'*-methylbispidinone (**8b**) is typical. To a suspension of 45 g (1.5 mol) of paraformaldehyde in 500 ml of methanol was added 21.5 g (0.2 mol) of benzylamine in 100 ml of methanol, which had previously been neutralized with 12 g (0.2 mol) of glacial acetic acid. A solution of 22.5 g (0.2 mol) of *N*-methyl-4-piperidone (freshly distilled) in 100 ml of methanol was neutralized with 12 g (0.2 mol) of glacial acetic acid and added in increments to the magnetically stirred contents of the reaction flask over a period of 5 days. After stirring for an additional 15 days, the solvent was distilled in vacuo and the residual oil partitioned between 250 ml of water and 200 ml of chloroform. The chloroform was removed and discarded and the aqueous phase was reextracted with 100 ml of chloroform which was also discarded. To the aqueous phase was added 100 ml of ice-cold 20% aqueous sodium hydroxide, and the resulting suspension was extracted with five 200-ml portions of ether. The combined extracts gave 21.6 g (44%) of an amber oil which crystallized on standing. A small amount of this material was placed in a microsublimator and evacuated at 20 mm (70 °C) for 48 h. The product was collected (15 mg) as white crystals: mp 60–61 °C; ir (KBr) 3.24 (w, aromatic CH), 3.38 (s), 3.56 (s, Bohlmann bands), 5.76 (s), 5.83 (s, C=O), 6.85, 7.41, 9.17, 9.62, 13.7, 14.5 μ; NMR ($CDCl_3$) δ 2.3 (s, 3, NCH_3), 3.5 (s, 2, NCH_2Ph), 7.2 (s, 5, C_6H_5), 2.2–3.2 (m, 10, remaining protons); EIMS *m/e* 244 (M), 58 (B).

The monoperchlorate salt was precipitated from ether, washed with water, and crystallized from acetone–ethyl acetate, mp 110–112 °C.

Anal. Calcd for $C_{15}H_{21}ClN_2O_5 \cdot H_2O$: C, 49.66; H, 6.39; N, 7.71. Found: C, 49.30; H, 6.53; N, 7.30.

B. N-Benzyl-N'-n-butylbispidinone (8c) was prepared in 38% yield by the above procedure. It could not be induced to crystallize: ir (CCl_4) 3.24 (w), 3.40 (s), 3.62 (s), 5.71 (s), 5.83 μ (shoulder); NMR (CCl_4) δ 0.92 (t, J = 6 Hz, 3, CCH_3), 1.06–1.67 (m, 6, CCH_2CH_2C), 2.23–3.33 (m, 12, NCH_2 and bridgehead CH), 3.47 (s, 2, NCH_2Ph), 7.30 (s, 5, C_6H_5).

Catalytic Debenzylation of 8b. To a solution of 2.5 g (10 mmol) of **8b** in 20 ml of glacial acetic acid containing 1 ml of 70% aqueous perchloric acid was added 0.2 g of 10% palladium on carbon. The suspension was stirred under 1 atm of hydrogen for 8 h, filtered, and the filtrate concentrated, giving 2.5 g of **13** as a cream-colored powder. The free base was prepared from 0.3 g of this salt: ir (NaCl) 3.03 μ (s, broad, NH and OH), no absorption between 5.7 and 5.9 μ; NMR (CCl_4) δ 2.1 (s, 3, NCH_3), no peaks are seen further than 3.1 ppm downfield.

Attempted Synthesis of 1,5-Dicarbomethoxy-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (4). The method for the preparation of **6a** from 1,3-dicarbethoxycyclohexan-2-one was used,[24] starting instead with acetonedicarboxylic acid dimethyl ester and twice the molar quantities of methylamine and formaldehyde. The crude product, analyzed by GLC–EIMS, consisted primarily of the starting keto diester accompanied by a small quantity of monoamino ketodiamide **7** (m/e 229).

***N*-Benzyl-*N'*-alkylbispidines (11a,b). A. General Procedure.** The reduction of amino ketone **8b** to give *N*-benzyl-*N'*-methylbispidine (**11a**) is typical. A magnetically stirred solution of 50 g (1 mol) of hydrazine hydrate, 49 g (0.2 mol) of **8b**, and 500 ml of triethylene glycol, maintained under nitrogen, was heated to 60 °C, and 50 g of 85% potassium hydroxide (pellets) was added. The yellow solution was stirred and refluxed (145 °C) for 4 h; then a Dean-Stark trap was inserted, and 59 ml of distillate was removed. The cooled contents of the reaction flask were poured into 50 ml of cold water, and the mixture was extracted with four 50-ml portions of ether. The combined extracts afforded 35.9 g (78%) of an amber liquid. Treatment of 2 g of this base with excess perchloric acid furnished the monoperchlorate of **11a**, white plates from acetone–ethyl acetate, 0.4 g, mp 145–147 °C.

Anal. Calcd for $C_{15}H_{23}ClN_2O_4$: C, 54.46; H, 7.01; N, 8.47. Found: C, 54.19; H, 6.97; N, 8.23.

The free base was prepared from this salt as a colorless oil: ir (neat) 3.25 (w, aromatic, CH), 3.40 (s), 3.58 (s, Bohlmann bands), 6.70, 6.85, 7.30, 7.84, 8.85, 9.01, 9.40, 10.0, 13.5, 13.9, 14.5 μ; NMR ($CDCl_3$) δ 1.45 (t, J = 3 Hz, 2, CH_2 bridge), 1.90 (m, 2, bridgehead CH), 2.2–2.6 (m, 4, *exo*-NCH), 2.75 (dd, J_1 = 11 Hz, J_2 not resolved, 4, *endo*-NCH), 3.40 (s, 3, NCH_2Ph), 7.3 (s, 5, C_6H_5); EIMS m/e 230 (M), 58 (B).

B. N-Benzyl-N'-n-butylbispidine (11b). This was prepared in 68% yield from **8c** by use of the general procedure. The monoperchlorate salt crystallized from water–methanol, mp 142–143 °C.

Anal. Calcd for $C_{18}H_{29}ClN_2O_4$: C, 57.99; H, 7.83; N, 7.51. Found: C, 57.67; H, 8.03; N, 7.46.

This salt was converted to the free base: ir (CCl_4) 3.24 (w), 3.40 (s), 3.62 μ (s, trans bands); NMR (CCl_4) δ 0.95 (t, J = 6 Hz, 3, CCH_3), 1.20–1.67 (m, 6, CCH_2CH_2C and CH_2 bridge), 1.85 (m, 2, bridgehead CH), 2.28 (m, 6, *exo*-NCH and NCH_2 of *n*-Bu), 2.73 (d, J = 10 Hz 4, *endo*-NCH), 3.40 (s, 2, NCH_2Ph), 7.03 (s, 5, C_6H_5); EIMS m/e 272 (M), 58 (B).

Catalytic Debenzylation of 11a,b. A. N-Methylbispidine (12a). A suspension of 5 g of 10% palladium on carbon in 30 ml of 85% acetic acid was stirred under 1 atm of hydrogen until uptake ceased. This suspension was then added to a solution of 33.9 g (0.24 mol) of *N*-benzyl-*N'*-methylbispidine in 120 ml of 85% acetic acid. The mixture was shaken under 50 psi of hydrogen until uptake ceased—5 h at ambient temperature. The catalyst was filtered and the solvent was removed at the oil pump. The residual oil was ice cooled and 110 ml of ice-cold 10% aqueous sodium hydroxide was added. The mixture was extracted with four 200-ml portions of ether. The combined extracts afforded 20.05 g (97%) of a mobile yellow liquid: bp 97–99 °C (28 mm); ir (neat) 3.11 (w, NH), 3.45 (s), 3.57 μ (s); NMR (C_6H_6) δ 1.33 (m, 2, CH_2 bridge), 1.50 (m, 2, bridgehead CH), 1.98 (s, 3, NCH_3), 2.18 (d, J = 11 Hz, 2, *exo*-NCH adjacent to NCH_3), 2.75 (d, J = 11 Hz, 2, *endo*-NCH adjacent to NCH_3), 2.93 (m, 4, NCH_2 adjacent to NH); EIMS m/e 140 (M), 44 (B). The monoperchlorate separated from ethanol–benzene–Skellysolve B as fine white crystals, mp 200–205 °C.

Anal. Calcd for $C_8H_{17}ClN_2O_4$: C, 39.92; H, 7.12; Cl, 14.73; N, 11.64. Found: C, 40.12, H, 7.37; Cl, 14.66; N, 11.62.

B. N-n-Butylbispidine (12b). This was synthesized from 29.6 g (0.109 mol) of **11b** in 100% yield via the method described in A. Distillation furnished the pure compound, a water-white, mobile liquid: bp 62–68 °C (0.2 mm); ir (CCl_4) 2.98 (w, NH), 3.41 (s), 3.63 (s), 6.90, 7.78, 9.09, 10.6 μ; NMR (C_6D_6) δ 0.92 (t, J = 6 Hz, 3, CCH_3), 1.33 (m, 6, CCH_2CH_2C and CH_2 bridge), 1.58 (m, 2, bridgehead CH), 2.13 (m, 4, *exo*-NCH adjacent to *N*-*n*-Bu, and $NCH_2C_3H_7$), 2.87 (dd, J_1 = 11 Hz, J_2 not resolved, 2, *endo*-NCH adjacent to *N*-*n*-Bu), 3.00 (m, 4, NCH_2 adjacent to NH); EIMS m/e 182 (M), 58 (B). Addition of saturated ethanolic picric acid to a cold ethereal solution of this base afforded the monopicrate which separated at once as fine yellow needles: mp 98–100 °C (softening at 80 °C).

Anal. Calcd for $C_{17}H_{25}N_5O_7$: C, 49.63; H, 6.13; N, 17.02. Found: C, 49.74; H, 6.30; N, 16.67.

Hydrogenolysis of 3-Methyl-7-benzyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (14). A solution of 390 mg (1 mmol) of **14** in 40 ml of ethanol was adjusted to pH 3 with ethanolic hydrogen chloride and shaken with 0.1 g of 10% palladium on carbon for 22 h. The catalyst was then filtered and the solvent was removed in vacuo. The residue was partitioned between 5 ml of 10% aqueous sodium hydroxide and 25 ml of ether. The aqueous phase was extracted with an additional 25-ml portion of ether, and the combined extracts were worked up to give 0.25 g (79%) of a yellow oil: NMR ($CDCl_3$) δ 3.53 (s, 2, CH_2Ph), 7.2 (m, 10, C_6H_5). Use of 80% aqueous acetic acid as the reaction solvent resulted in no change in the appearance of the NMR spectrum of the product.

Preparation of N,N'-Dialkylbispidines by Selective Alkylation of N-Alkylbispidines. A solution of 6 mmol of **12a** or **12b** in 10 ml of dry tetrahydrofuran, magnetically stirred under nitrogen, was cooled to −10 °C and an equimolar amount of ethereal methyllithium (1.3–1.6 M) was added. After stirring for 2 min, a solution of 6 mmol of the appropriate alkyl halide in 5 ml of dry tetrahydrofuran was added dropwise to the brown reaction solution. Completion of addition discharged the color, and after warming to room temperature and stirring for 2 h, the reaction solution was concentrated in vacuo, and the product was worked up with ether and 5% aqueous sodium hydroxide. Characterization of compounds prepared by this method is summarized in Tables I and II.

Synthesis and Reduction of N-Acyl-N'-alkylbispidines (15a–c). Treatment of *N*-methylbispidine with acetic–formic anhydride[25] or acetic anhydride in dry chloroform under routine conditions gave **15a** and **15b**, respectively. *N*-*n*-Butylbispidine gave **15c** on treatment with benzoyl chloride. Purity of ca. 100% was confirmed by GLC; the ir spectra exhibited strong amide carbonyl absorbtion.

Reduction was carried out as follows. The amide (1–2 mmol) was dissolved in 2–3 ml of tetrahydrofuran. The resulting solution, magnetically stirred and maintained under nitrogen, was treated with 2–3 ml of a ca. 10% solution of lithium aluminum hydride in tetrahydrofuran. The suspension was refluxed for 17–24 h, after which time the excess hydride was destroyed with saturated aqueous ammonium chloride and wet tetrahydrofuran. Filtration and concentration gave the crude products which were analyzed by GLC. Amide **15c** gave a product in 83% yield and >95% purity whose ir and NMR spectra were identical with those of a known sample of bicyclic amine **11b**. Reduction of **15b** resulted in a 90% yield of a product containing eight parts of *N*-ethyl-*N'*-methyl-, one part of *N*-methylbispidine, and one part of an unidentified substance. The identities of *N*-ethyl-*N'*-methyl- and *N*-methylbispidine were verified by simultaneous GLC with authentic samples. The formamide **15a** furnished only 29% of a mixture containing six parts of *N,N'*-dimethylbispidine, one part of *N*-methylbispidine (retention times coincided with those of authentic samples), and a total of three parts of two unknown components.

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Registry No.—**3** (R_1 = C_2H_5; R_2 = CH_3) $HClO_4$, 14789-41-4; **3** (R_1 = *n*-C_4H_9; R_2 = CH_3) HBr, 58324-88-2; **3** (R_1 = CH_2-c-C_6H_{11}; R_2 = CH_3) HCl, 58324-89-3; **3** (R_1 = R_2 = *n*-C_4H_9) $HClO_4$, 58324-91-7; **8b**, 58324-92-8; **8b** $HClO_4$, 58324-93-9; **8c**, 58324-94-0; **11a**, 58324-95-1; **11a** $HClO_4$, 58324-96-2; **11b**, 58324-97-3; **11b** $HClO_4$, 58324-98-4; **12a**, 58324-99-5; **12a** $HClO_4$, 58325-00-1; **12b**, 58325-01-2; **12b** picrate, 58375-24-9; **13**, 58904-53-3; **14**, 58325-03-4; **15a**, 58325-04-5; **15b**, 58374-89-3; **15c**, 58325-05-6; CH_3I, 74-88-4; C_2H_5Br, 74-96-4; *n*-

C_4H_9Br, 109-65-9; c-$C_6H_{11}CH_2Br$, 2550-36-9; benzylamine, 100-46-9; *N*-methyl-4-piperidone, 1445-73-4; acetic–formic anhydride, 2258-42-6; acetic anhydride, 108-24-7; benzoyl chloride, 98-88-4.

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Reactions of Cytidine with 7-Bromomethylbenz[*a*]anthracene, Benzyl Bromide, and *p*-Methoxybenzyl Bromide. Ratio of Amino to 3 Substitution[1]

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Alkylation of cytidine in dimethylacetamide by 7-bromomethylbenz[*a*]anthracene (1), benzyl bromide, and *p*-methoxybenzyl bromide afforded the 3-substituted cytidines in good yield. The identity of these products has been confirmed by spectroscopic studies and chemical transformations. Deamination of 3-(benz[*a*]anthryl-7-methyl)cytidine by nitrous acid or sodium bisulfite afforded the corresponding uridine derivative, which was also prepared from uridine and 1. Alkylation of cytidine by the above halides in aqueous solution led to the formation of 3- and N^4-substituted products. The structure of the latter was established by unequivoval synthesis from 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine and the appropriate benzylic amines. The alkylation reactions in aqueous solution went in low overall yield. 3-Substitution of cytidine predominated in the case of benzyl bromide, and N^4 substitution with *p*-methoxybenzyl bromide, while both types of product were formed in almost equal amounts with 1. Substitution at N^4 of cytidine appears to be correlated with the ability of the reagent to accommodate a positive charge, which leads to thermodynamic rather than kinetic control of the reaction.

Alkylation of the heterocyclic bases of the nucleic acids generally proceeds most rapidly at the pyridine-type ring nitrogen atoms. The most reactive positions in nucleosides are the 7 position of guanosine, 1 position of adenine, and 3 position of cytosine. Similar results are obtained in single stranded nucleic acids.[2,3] One striking exception to this rule was reported by Dipple and co-workers in studies with the carcinogenic alkylating agent, 7-bromomethylbenz[*a*]anthracene.[4] Alkylation by this reagent in dimethylacetamide was in accord with the usual pattern described above. In aqueous solution, however, alkylation of nucleosides and polynucleotides proceeded mainly on the amino group of guanine, adenine, and possibly cytosine. The possible importance of amino group alkylation to carcinogenesis was pointed out by the above authors. More recently, another author has suggested that amino group substitution is a significant process in the reaction of another carcinogen, *N*-acetoxy-*N*-acetyl-2-aminofluorene, with DNA.[5]

We have further investigated the reactions of cytidine with 7-bromomethylbenz[*a*]anthracene (1) and with benzyl bromide and *p*-methoxybenzyl bromide. One objective was to confirm the structure of the reaction product formed by 1 in an aqueous solution and in dimethylacetamide. The position of substitution on alkylation of a nucleic acid component is usually assigned on the basis of ultraviolet spectroscopy.[2] This technique is inapplicable in reactions in-