Analogues of Sparteine. 3. Synthesis and Conformational Studies of Some 2,3-Substituted 7-Methyl-3,7-diazabicyclo[3.3.1]nonanes

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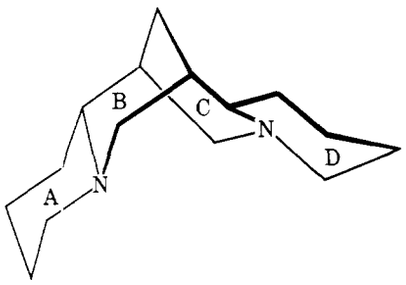
Three 3,7-disubstituted 3,7-diazabicyclo[3.3.1]nonanes having 2-exo alkyl substituents (**4a–c**) were found to adopt boat conformations with respect to the rings bearing the 2 substituents. The first two compounds were synthesized by addition of Grignard reagents to aldimmonium ion **5**, the last by similar addition to aldimine **10** followed by introduction of the N-3 benzyl group. Evidence in favor of the configurational assignments was obtained from the IR and NMR spectra, and in the case of **4a**, by comparison of its spectral and physical properties with those of its epimer (**8**). The conformational preference of **4a–c** was compared to that of other 3,7-diazabicyclo[3.3.1]-nonanes and to that of the alkaloid sparteine (**1**).

By various approaches, the C rings of sparteine (**1**) and α-isosparteine (**2**) have been shown to prefer the boat and chair conformations, respectively.[1] Together, the B and C rings of these alkaloids constitute the 3,7-diazabicyclo[3.3.1]-nonane (bispidine) moiety (**3**). Interest in the structure of this and other bicyclo[3.3.1]nonanes has centered mainly on variants at the 3,7 and 9 positions,[2] with less attention focused on variants at the 2 position.



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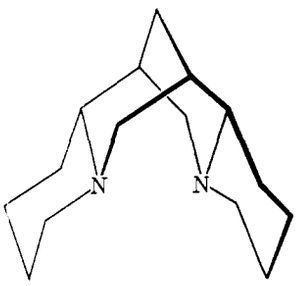

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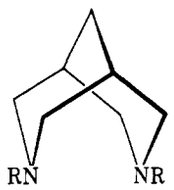
N,N'-Dimethylbispidine (**3**, R = CH_3) has been shown to exist in a double-chair conformation, qualitatively similar to that of the inner rings of **2**, based on NMR spectral features, physical properties (dipole moment, basicity), and on LCAO–MO calculations.[3] Our attention was directed toward the influence of 2-alkyl substituents on the conformation of this ring system. It was anticipated that 2-exo alkyl systems (**4**),[4] being configurationally similar to **1**, would adopt chair–boat conformations similar in respect to the inner rings of **1**. In this paper, we describe synthetic routes which furnished several 2-alkyl derivatives of **3**, and some conformational features of these compounds.

Results and Discussion

Oxidation of **3** (R = CH_3) followed by reaction of the resulting aldimmonium ion (**5**) with methylmagnesium iodide



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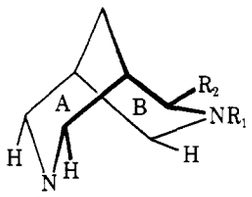
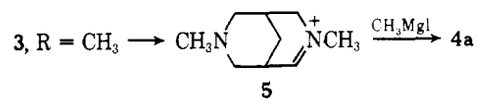


	R_1	R_2
4a	CH_3	CH_3
b	CH_3	i-C_3H_7
c	CH_2Ph	CH_3

had been expected to give **4a** (Scheme I). However, oxidation of *N,N'*-dimethylbispidine with excess mercuric acetate in

Scheme I



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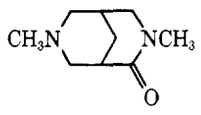
5% aqueous acetic acid[5] gave 71% of a waxy solid that had strong IR absorption at 6.10 μ and a molecular ion of *m/e* 168.1261 in its mass spectrum. From these spectral features, we concluded that the product was bicyclic lactam **6**, rather than **5**.[4] Oxidation of other cyclic diamines to lactams under these conditions has been reported.[6] Treatment of **3** (R =



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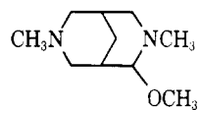

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CH_3) as before, except using 33% acetic anhydride in acetic acid as solvent, furnished **5**, which was isolated (31%) as the diperchlorate salt. It exhibited C=N^+ absorption at 5.90 μ in its IR spectrum,[5a] and a broad signal at 8.97 ppm,[1c] due to the presence of the HC=N^+ group, in its NMR spectrum. Conversion of **5** to its free base in the presence of methanol gave the *N,O*-acetal **7** as evidenced by spectral features. Its NMR spectrum had an OCH_3 singlet and an NCHO doublet centered at 3.30 and 3.90 ppm, respectively, and no signals at lower field. Its IR spectrum had no bands in the C=N^+ region. Treatment of **5** with excess methylmagnesium iodide (Scheme I) gave a product (89%) tentatively assigned as that of exo addition (**4a**). Its NMR spectrum displayed one CCH_3 doublet centered at 1.00 ppm, signifying the presence of a single diastereomer. In order to substantiate this configurational assignment, the endo diastereomer (**8**) was required for comparison.

Reaction of **6** with excess methylmagnesium iodide in re-

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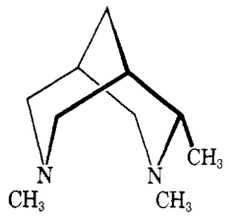
† Professor Smissman died on July 14, 1974.



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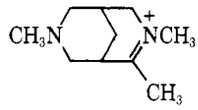

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fluxing ether, followed by treatment of an ethereal solution of the base with excess perchloric acid, furnished ketimmonium salt **9** (40%) which had a characteristic C=N$^+$ band at 5.90 μ in its IR spectrum. Sodium borohydride reduction of **9** in water gave 98% of a single diastereomer **8** as evidenced by the appearance of a single CCH_3 doublet centered at 1.10 ppm in its NMR spectrum. Inspection of molecular models of **9** indicated much less hinderance to exo relative to endo nucleophilic addition. This, along with the known[7] sensitivity of sodium borohydride to steric factors, was the basis for the *endo*-2-methyl configurational assignment.

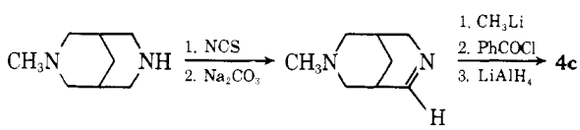
Compound **8** had a GLC retention time of 1.39 relative to **4a.** Also, **8** and **4a** differed in their IR spectral "fingerprint" regions, NMR spectra, and melting points as dihydrobromide salts. By deduction, we concluded that **4a** was the 2-exo isomer, and that addition of Grignard reagents to **5** proceeded stereospecifically. Since **4b** was prepared in the same manner as **4a** (Scheme I), it too was assigned the 2-exo configuration.[4]

Information regarding the conformations of the 2-alkyl substituents of **4a,b** and **8** was provided by inspection of the respective IR and NMR spectra. The NMR spectrum of each compound exhibited signals between 2.60 and 3.10 ppm which integrated for three protons (Table I). Protons in this region of the NMR spectra of related compounds have been postulated to be gauche to the nitrogen lone pairs, with other N- and C-aliphatic protons appearing upfield from these.[8] This suggested an equatorial orientation of the 2-alkyl groups in each of these compounds. Comparison of the IR spectra of *N,N'*-dialkylbispidines (**3**)[9] with those of **4a,b** and **8** indicated considerable similarity in regard to appearance and intensity of Bohlmann (trans) bands, centered at ca. 3.6 μ. The intensity of these has been shown to be proportional to the number of C–H bonds anticoplanar to the nitrogen lone pairs.[10] This indicated that **3, 4a, 4b,** and **8** all had the same number of these bonds, and that the alkyl groups in the last three were equatorial, in agreement with the NMR spectral findings.

In order to substantiate further the equatorial conformational assignment of the 2-exo alkyl substituents in **4a,b,** we wished to prepare the *N*-benzyl analogue (**4c**) for NMR spectral analysis. In the related *N*-benzyl-2-alkylpiperidines, the benzylic methylene protons appear as a singlet if the 2-alkyl substituent is axial, and as an AB quartet if it is equatorial.[11,12]

Compound **4c** was prepared as shown in Scheme II. Oxidation of *N*-methylbispidine with *N*-chlorosuccinimide[13]

Scheme II



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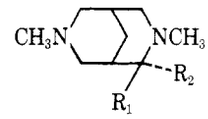
followed by treatment of the unstable *N'*-chloro intermediate with base gave a product thought to be aldimine **10,** as the monoperchlorate salt in 67% yield. While this product had the expected elemental composition, it lacked spectral features characteristic of the presence of an aldimine moiety. When it was converted to the free base, it exhibited a one-proton

Table I. NMR Spectral Features of *N,N'*-Dimethylbispidine and 2-Alkyl Derivatives[a]



Compd	R_1	R_2	CCH_3, δ	NCH_3, δ	Protons gauche to N[b]
3	H	H		2.15, 2.15	4
4a	CH_3	H	1.00 (d, J = 6 Hz)	2.08, 2.17	3
4b	i-C_3H_7	H	0.77, 0.88 (d, J = 6 Hz)	2.08, 2.12	3
8	H	CH_3	1.10 (d, J = 6 Hz)	2.11, 2.11	3

[a] Spectra were taken using benzene as solvent. Chemical shifts are in parts per million relative to internal tetramethylsilane. [b] Calculated from the relative integrated intensity of the spectrum between 2.60 and 3.10 ppm.[8]

multiplet centered at 7.86 ppm (HC=N)[14] and absorbance at 6.00 μ (C=N) in its NMR and IR spectra, respectively. This suggested that the initially isolated salt was nonmonomeric, but that the free base was monomer **10.** Other features in the above spectra and in the mass seectrum of the free base were consistent with this structural assignment. In contrast to **10,** monocyclic aldimines **11** and **12** have been shown to exist

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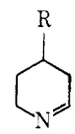

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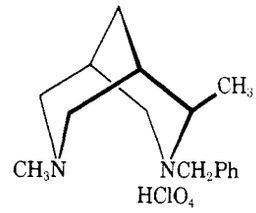
predominantly and exclusively as trimers, respectively.[13b,15]

Treatment of **10** with methyllithium, followed by benzoylation of the resulting secondary amine and subsequent reduction of the benzamide with lithium aluminum hydride, gave **4c** (Scheme II). The low overall yield (6%) of this sequence was due primarily to the difficulty encountered in reduction of the benzamide—this proceeded in only 17% yield.[16] Other approaches to the synthesis of **4c** proved even less satisfactory.

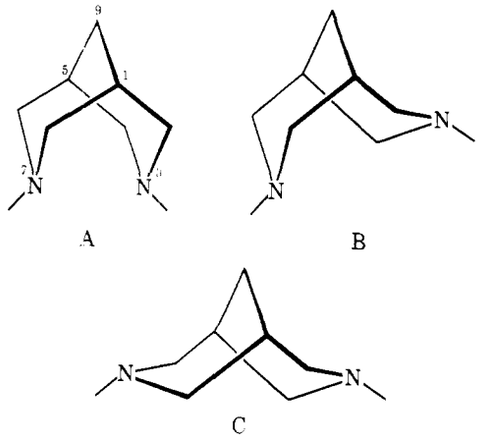
The NMR spectrum of **4c** monoperchlorate exhibited a singlet at 3.77 ppm, representative of the *N*-benzylic methylene protons. The lack of observable nonequivalence of these protons signified an axial orientation of the 2-methyl group.[11] In addition, this indicated that **4c** resulted from exo addition of methyllithium to **10,** since the ring system of this salt was assumed to adopt the double chair conformation (Chart I).

Chart I. Conformation of 4c Monoperchlorate

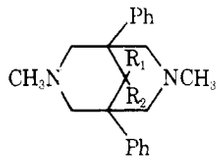


(The inner rings of **1** monoperchlorate have been shown to adopt a similar conformation.[17]) Conversion of **4c** monoperchlorate to the free base caused the *N*-benzylic methylene protons to appear as an AB quartet in the NMR spectrum, which indicated that the 2-methyl group was now equatorial.[11]

Conformation of the Ring Systems in 4a–c. The 3,7-diazabicyclo[3.3.1]nonane (bispidine) ring system may assume any of three nondistorted orientations (A–C). Its 3,7-dimethyl



derivative (**3**, R = CH_3) has been shown to exist as A.[3] However, structural modifications of this system have been found to alter this preference. Its 9-phenyl-9-hydroxy derivative has been shown to exist in the chair–boat form (B), on the basis of strong transannular hydrogen bonding seen in its IR spectrum.[2c] The 1,5-diphenyl derivatives (**13a,b**) have also been



	R_1	R_2
13a	(=O)	
b	H	OH

postulated to prefer this conformation, based on spectral and dipole moment studies.[18] The spectral evidence described above indicated that the 2-exo-alkyl groups in **4a–c** were all equatorial. Thus, the 2-substituted ring of each of these compounds exists in the boat conformation, and either B or C may represent their ring systems. Of these, B appears to be favored owing to unfavorable steric interactions present in C; however, the spectral characteristics we observed do not rule out the presence of the latter conformer.

Assuming that B represents the preferred conformer of **4a–c**, these compounds are not only configurationally similar to the inner rings of (±)-sparteine, but are qualitatively similar to them conformationally.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were taken on a Beckman IR 33 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained using a Varian T-60 spectrometer with tetramethylsilane as internal standard. Electron impact mass spectra (EIMS) were recorded using a Varian CH5 spectrometer, at 70 eV. The chemical ionization mass spectrum (CIMS) was obtained using a Finnegan 1015 spectrometer with isobutane as ionizing gas. Elemental analyses were obtained on a Hewlett-Packard 185, C, H, N analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind. Analytic gas–liquid chromatography (GLC) was performed with a F & M 810 gas chromatograph using flame ionization detection; carrier gas helium (30 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).

General Methods. All reactions involving air-sensitive reagents were carried out under dry nitrogen. Workup of organic extracts: solutions of products were dried with anhydrous sodium sulfate, filtered, and concentrated at a rotary evaporator using a Buchler water aspirator (10–40 mm) at water bath temperatures of 40 °C or less. Free bases were prepared from salts by partitioning them between ether and 10% aqueous sodium hydroxide. Ethanol was added to increase the rate of equilibration in the case of water-insoluble salts.

***N*-Methylbispidine** and ***N,N'*-dimethylbispidine** were obtained as described previously.[9]

3,7-Dimethyl-3-azonia-7-azabicyclo[3.3.1]non-2-ene (5). To 100 ml of cold 33% v/v acetic anhydride in glacial acetic acid were added 1.3 g (8.4 mmol) of *N,N'*-dimethylbispidine and 10 g (31 mmol) of mercuric acetate. The solution was heated to 40 °C for 5 min, then allowed to stand for 96 h at room temperature. The suspension was filtered and the filtrate was saturated with hydrogen sulfide, filtered, and concentrated at the oil pump. The residual viscous yellow oil was dissolved in 25 ml of chloroform, and the solution cooled in ice and equilibrated with 20 ml of ice-cold 20% aqueous sodium hydroxide. The aqueous phase was extracted three more times with 30-ml portions of cold chloroform. The combined extracts were concentrated, leaving a light yellow oil. This was dissolved in ether, cooled, and treated with excess aqueous ethanolic perchloric acid. The diperchlorate salt separated from alcohol as white crystals: 1.30 g (31%); mp 251–253 °C dec; IR (KBr) 3.23 (s), 3.34 (w), 3.55 (w), 5.90 (s, $C{=}N^+$), 6.85 (s), 9.22 μ (s, ClO_4^-); NMR (D_2O) δ 2.20 (t, J = 2 Hz, 2, CH_2 bridge) 3.01 (s, 6, $^+NCH_3$), 4.67 (s, 2, HDO), 8.97 (m, $W_{1/2}$ = 9 Hz, 1, $HC{=}N^+$).

Anal. Calcd for $C_9H_{18}Cl_2N_2O_8$: C, 30.61; H, 5.14; N, 7.93. Found: C, 30.84; H, 4.80; N, 7.21.

Reactivity of 5. A. With Methanol. The perchlorate salt of **5** (100 mg) was converted to the base by partition between 30 ml of alcohol-free chloroform and 3 ml of 15% aqueous sodium hydroxide. The concentrated residue was dissolved in 5 ml of methanol, the solution reduced to dryness, the residue taken up in 5 ml of benzene, and this solution reduced to dryness at the oil pump. This afforded methyl acetal **7** as a yellow oil: NMR (CD_3OD) δ 2.11 and 2.33 (s, 6, NCH_3), 3.30 (s, OCH_3), 3.88 (d, J = 2 Hz, 1, carbinolamine CH), 1.30–3.10 (10, remaining protons).

B. With Grignard Reagents. 2-*exo*,3,7-Trimethyl-3,7-diazabicyclo[3.3.1]nonane (4a) was made by addition of 0.35 g (1 mmol) of **5** diperchlorate to 1 ml of a cold (−20 °C) 2.7 M solution of methylmagnesium iodide in ether. After stirring for 24 h at room temperature, the excess Grignard reagent was destroyed with 30% aqueous ammonium chloride. The mixture was treated with excess 20% aqueous potassium fluoride and centrifuged. The supernatant was decanted, made strongly basic with 20% aqueous sodium hydroxide (5 ml), and extracted with four 15-ml portions of ether. The combined ethereal extracts were worked up to give 0.15 g (89%) of a colorless liquid: IR (neat) 3.40, 3.58, 7.84, 8.10, 8.70, 9.05, 9.26, 9.52, 9.76 μ; NMR (Table I); EIMS *m/e* 168 (M), 58 (B). Treatment of a cold ether solution of this base with a 24% solution of hydrobromic acid in aqueous acetone afforded the dihydrobromide salt as a white powder which separated from alcohol–acetone as white plates, mp 266–270 °C dec.

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; N, 8.48. Found: C, 36,54: H, 6.75; N, 8.22.

The free base was prepared from a portion of this salt: GLC (130 °C) retention time 5.6 min, ca. 100% purity.

2-*exo*-Isopropyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (4b) was prepared by addition of a suspension of 1.3 g (3.7 mmol) of **5** diperchlorate in 5 ml of dry tetrahydrofuran to 8 ml of a stirred 1.25 M solution of isopropylmagnesium bromide in tetrahydrofuran. The mixture was stirred and refluxed for 42 h and cooled, and the excess Grignard reagent destroyed as above. The solvent was removed in vacuo. To the residue was added 5 ml of water. The mixture was adjusted to pH 7 by addition of 10% aqueous hydrochloric acid, treated with 20% aqueous potassium fluoride, and centrifuged. The supernatant was made strongly basic by addition of sodium hydroxide pellets and extracted with four 10-ml portions of ether. The combined organic extracts were washed with 30 ml of fresh 1 M aqueous sodium bicarbonate and worked up to give a light amber liquid, 0.3 g, GLC (140 °C) 88% purity. This was dissolved in 10 ml of ether, cooled, and treated with excess ethereal hydrochloric acid to precipitate 0.25 g of the crude dihydrochloride. Crystallization from alcohol–ethyl acetate afforded 0.2 g (25%) of **4b** as white crystals, mp 255–257 °C *dec*.

Anal. Calcd for $C_{12}H_{26}N_2Cl_2$: C, 53.53; H, 9.73; N, 10.40. Found: C, 53.14; H, 9.89; N, 10.18.

The free base was prepared from this salt as a colorless oil: IR (neat) 3.40 and 3.59 μ (s, aliphatic CH); NMR (Table I); EIMS *m/e* 196 (M), 58 (B).

3,7-Dimethyl-3,7-diazabicyclo[3.3.1]nonan-2-one (6). To 70 ml of cold 5% aqueous acetic acid was added 2.2 g (14.3 mmol) of *N,N'*-dimethylbispidine and 18.2 g (57.2 mmol) of mercuric acetate. The solution was heated at 47 °C for 6 h, during which time a copious white precipitate of mercurous acetate formed. The mixture was saturated with hydrogen sulfide, filtered, and concentrated at the oil

pump. The residue was dissolved in 16 ml of ice-cold 20% aqueous sodium hydroxide, and extracted with four 16-ml portions of chloroform. The combined extracts were concentrated to give 1.7 g (71%) of a waxy, yellowish solid: mp 62–64 °C; IR (KBr) 3.38 (s), 3.57 (s), 6.10 μ (s, NC=O); NMR (CCl_4) δ 2.10 (s, 3, NCH_3), 2.85 (s, 3, $CONCH_3$), 1.50–3.50 (remaining protons); EIMS *m/e* 168 (M) 58 (B), M 168.1261 (calcd for $C_9H_{16}N_2O$, 168.1314); CIMS *m/e* (rel intensity) 169 (qm, 100), 71 (14).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.51; H, 9.71; N, 16.67.

2,3,7-Trimethyl-3-azonia-7-azabicyclo[3.3.1]non-2-ene (9). A solution of 2.0 g (11.9 mmol) of **6** in 15 ml of dry benzene was added to an ice-cold 1.8 M solution of methylmagnesium iodide in ether. The mixture was stirred, refluxed for 43 h, and cooled, and excess Grignard reagent was removed (see above). The ether was decanted from precipitated solids. The precipitate was treated with excess 20% aqueous potassium fluoride and centrifuged. The supernatant was made strongly basic with 20% aqueous sodium hydroxide and the resulting mixture (15 ml) was extracted with four 15-ml portions of chloroform. Workup of the combined extracts furnished 1.0 g (45%) of a yellow oil which darkened readily on exposure to air: NMR ($CDCl_3$) δ 2.15 (s, 3, NCH_3), 2.30 (s, 3, CCH_3), 2.40 (s, 3, NCH_3), 1.30–3.30 (10, remaining protons). To 60 mg of this oil dissolved in 5 ml of ether was added excess aqueous ethanolic perchloric acid. The product was recrystallized three times from ethanol to give yellow needles: mp 223–225 °C dec; IR (KBr) 5.97 (s, C=N^+), 9.17 μ (s, ClO_4^-).

Anal. Calcd for $C_{10}H_{20}Cl_2N_2O_8$: C, 32.71; H, 5.49; N, 7.63. Found: C, 32.43; H, 5.42; N, 7.59.

2-*endo*,3,7-Trimethyl-3,7-diazabicyclo[3.3.1]nonane (8). To a solution of 0.95 g (6.2 mmol) of **9** in 25 ml of water was added 0.5 g (13 mmol) of sodium borohydride. After stirring for 24 h, the suspension was extracted with three 50-ml portions of ether. The combined extracts were concentrated to give 0.9 g (98%) of a colorless, mobile liquid, NMR (Table I). This was dissolved in 20 ml of acetone and treated with an ice-cooled solution of 25% hydrobromic acid in water–acetone. The white precipitate was filtered, washed with acetone, and crystallized from ethanol–acetone to give 1.1 g of the dihydrobromide salt: mp 251–253 °C dec; EIMS *m/e* 168 (M), 58 (B).

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.42; N, 8.48. Found: C, 36.12; H, 6.86; Br, 48.68; N, 8.42.

The free base was prepared from a portion of this salt: GLC (130 °C) retention time 7.8 min; ca. 100% purity; IR (neat) 3.39, 3.58, 7.84, 8.77, 9.26, 9.57, 9.80 μ.

7-Methyl-3,7-diazabicyclo[3.3.1]non-2-ene (10). To a solution of 1.1 g (7.85 mmol) of *N*-methylbispidine in 40 ml of dry ether was added 1.1 g (7.85 mmol) of *N*-chlorosuccinimide. The suspension was stirred at room temperature for 24 h. About 5 ml of ethanol was added and the solution was concentrated. The residue was dissolved in 5 ml of ethanol, and 2 g of anhydrous sodium carbonate was added. The suspension was stirred for 0.5 h and then filtered. The filtrate was cooled in ice and treated with excess 35% perchloric acid in ethanol–water. The resulting fine white precipitate was filtered, yielding 1.25 g (67%) of the monoperchlorate: mp 232–233 °C dec; IR (KBr) 3.25, 3.31, 3.37, 6.7, 9.22 μ (s, ClO_4^-); NMR (Me_2SO-d_6) δ 1.92 (m, 2, CH_2 bridge), 2.82 (m, 2, bridgehead CH), 3.35 (s, 3, NCH_3), 3.52 (m, 7, remaining protons).

Anal. Calcd for $C_8H_{15}ClN_2O_4$: C, 40.26; H, 6.33; N, 11.73. Found: C, 40.39; H, 6.40; N, 11.60.

The salt (0.202 g, 0.85 mmol) was suspended in 10 ml of methanol, and sufficient Bio-Rad AG2-X8, 50–100 mesh (OH^-) was added to dissolve the product. The mixture was then placed on a 4-g column of the above resin and eluted with 50 ml of methanol. The eluent was concentrated and residual solvent was removed azeotropically with benzene, in vacuo. This left a low-melting white solid: IR (neat) 3.39 and 3.57 (s, aliphatic CH), 5.90 μ (s, C=N); NMR (CD_3OD) δ 1.48 (m, 2, CH_2 bridge), 3.50 (m, 2, $CNCH_2$), 7.7 (m, 1, HC=N), 1.62–3.30 (remaining protons); EIMS *m/e* 138 (M), 44 (B).

3-Benzyl-2-*exo*-7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (4c). To a suspension of 0.55 g (4 mmol) of aldimine **10** in 7 ml of dry tetrahydrofuran at 0 °C was added 4.4 ml of a 1.36 M solution of methyllithium in ether. The stirred solution was maintained at 0–5 °C. GLC analysis (140 °C) indicated the reaction to be 80% complete 0.5 h after completion of addition. Over the next 0.5 h, the reaction suspension was allowed to warm to room temperature, and then the excess methyllithium was destroyed with saturated aqueous ammonium chloride. The product was worked up in ether and 20% aqueous sodium hydroxide affording 0.53 g (86%) of a colorless oil: NMR (C_6H_6) δ 1.23 (d, J = 7 Hz, 3, CCH_3), 1.98 (s, 3, NCH_3); EIMS *m/e* 154 (M) 58 (B). Treatment of 0.33 g (2.1 mmol) of this with benzoyl chloride under previously described conditions[9] afforded 0.23 g (42%) of the benzamide, IR (neat) 6.13 μ (s, NC=O). This was dissolved in 5 ml of dry tetrahydrofuran and added dropwise to a saturated solution of lithium aluminum hydride in 3 ml of tetrahydrofuran. The solution was stirred and refluxed for 21 h, then cooled, and excess hydride was destroyed by addition of 30% aqueous ammonium chloride. The suspension was filtered and the insolubles were washed well with tetrahydrofuran. The filtrate and washings were combined and concentrated. The residue was dissolved in 10 ml of ether. The solution was washed once with 5 ml of 5% aqueous sodium hydroxide, cooled, and treated with excess aqueous ethanolic perchloric acid. The monoperchlorate salt separated from methanol–water, and then alcohol, as light orange needles: 0.053 g (17%); mp 160.5–161.5 °C; NMR (CD_3COCD_3) δ 1.00 (d, J = 6 Hz, 3 CCH_3), 1.70–2.27 (m, 4, CH_2 bridge and bridgehead CH), 2.80 (s, 3, NCH_3), 2.92–3.63 (m, 7, NCH_2), 3.77 (s, 2, $NCH_2C_6H_5$), 7.42 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{25}ClN_2O_4$: C, 55.73; H, 7.31; N, 8.12. Found: C, 55.56; H, 7.39; N, 7.90.

The free base was obtained from the monoperchlorate as a light yellow oil: NMR (C_6D_6) δ 0.93 (d, J = 6 Hz, 3, CCH_3), 1.17–1.75 (m, 4, CH_2 bridge and bridgehead CH), 2.18 (s, 3, NCH_3), 2.03–3.97 (m, 7, NCH_2), 3.39 (d, J = 14 Hz, 1, $NCH_aC_6H_5$), 3.65 (d, J = 14 Hz, 1, $NCH_bC_6H_5$), 6.98–7.58 (m, 5, C_6H_5); EIMS *m/e* 244 (M), 58 (B); GLC (170 °C) retention time 12.5 min, >95% purity.

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Registry No.—**3** (R = CH_3), 14789-33-4; **4a,** 61267-75-2; **4a** di-HBr, 61267-76-3; **4b,** 61267-77-4; **4b** di-HCl, 61267-78-5; **4c,** 61267-79-6; **4c** monoperchlorate, 61267-80-9; **5,** 61267-81-0; **5** diperchlorate, 61267-82-1; **6,** 61267-83-2; **7,** 61267-92-3; **8,** 61267-84-3; **8** di-HBr, 61267-85-4; **9** diperchlorate, 61267-87-6; **10,** 61267-88-7; **10** monoperchlorate, 61267-89-8; **10** 2-methyl derivative, 61267-90-1; **10** 2-methyl-3-benzoyl derivative, 61267-91-2; methyl iodide, 74-88-4; isopropyl bromide, 75-26-3; *N*-methylbispidine, 58324-99-5; *N*-chlorosuccinimide, 128-09-6; methyllithium, 917-54-4; benzoyl chloride, 98-88-4.

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Syntheses and Spectral Properties of Substituted Imidazolidones and Imidazolines

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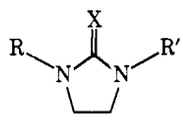
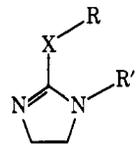
A series of substituted imidazolidones and imidazolines were synthesized as potential model compounds for the coenzyme, biotin. The syntheses and mass, infrared, ^{1}H NMR, and ^{13}C NMR spectral properties for these substrates are described. The ^{1}H NMR spectra for the acetyl substituted imidazolidones and imidazolidinethiones exhibited a characteristic downfield shift for the acetyl methyl proton (ca. δ 2.50 and 2.80, respectively). Surprisingly, the ^{1}H NMR spectra for the acyl substituted thioimidazolines consistently showed a singlet for the ethylene unit rather than the expected AA'BB' pattern. Verification of this unusual accidental equivalence in the ^{1}H NMR spectra was accomplished by the use of ^{13}C NMR. The ^{13}C NMR spectra for these compounds exhibited two distinct resonances which were attributed to the different ring carbon atoms.

Substituted imidazolidones (**1**) and imidazolines (**2**) are compounds of considerable current interest both as model

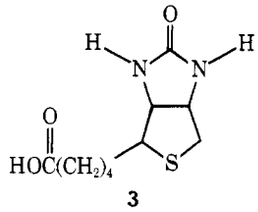


1 (X = O, S)



2 (X = O, S)

substrates for biological processes[1-7] and as chemotherapeutic agents.[8-10] As part of a current project dealing with the mechanism of biotin catalysis,[1] we synthesized a series of imidazolidones (**1**) and imidazolines (**2**) as model substrates. Compounds of types **1** and **2** possess many of the unique structural features found in biotin (**3**).[11]

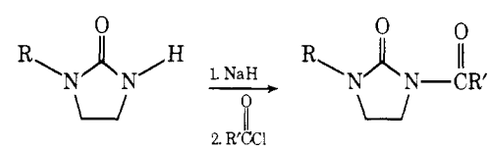


3

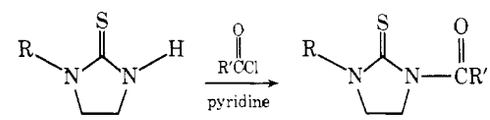
Many of the simple members of these classes of compounds have not been prepared. In this paper, we report the syntheses and characterization of these substrates, as well as a comparison of their properties to those of previously reported congeners.[12,13] Although the acyl substituted thioimidazolines prepared gave satisfactory elemental analyses, mass, and infrared spectral data, the surprising simplicity of their ^{1}H NMR necessitated a ^{13}C NMR study of these compounds. We also examined the ^{13}C NMR spectra of their counterparts, the substituted imidazolidones. The importance of ^{13}C NMR in clarifying the structural assignment of these heterocyclic molecules is outlined. In a subsequent paper, the chemistry of some of these compounds will be described.[14]

Synthesis. Tables I and II list the substrates we have prepared and pertinent infrared and ^{1}H NMR data. The majority of these substrates are new. They were prepared by a variety of synthetic routes. All new compounds gave the appropriate parent peak in the mass spectrum and satisfactory elemental analysis or high-resolution mass spectral characterization. Most of the compounds reported herein were crystalline,[15] with only the dialkyl substituted imidazolines generally being liquids.

Two general synthetic methods were adopted for the preparation of the new acyl-substituted imidazolidones and imidazolidinethiones. The imidazolidones (**9, 10, 12,** and **13**) were synthesized by the prior formation of the corresponding imidazolidone anion, followed by the addition of the acylating



agent. By comparison, in the sulfur series (**16, 18, 19, 20, 21,** and **22**), the acylating agent was introduced to a solution containing both the imidazolidinethione and pyridine. Although the method of choice for the preparation of the substituted imidazolidones was the initial formation of the anion, these substrates could be prepared in lower yields by a method analogous to that used for the imidazolidinethiones. The re-



duced reactivity observed in the oxygen series appears to stem from the decreased nucleophilicity of the imidazolidone's ring carbonyl group as compared to the thione group in the imidazolidinethiones.[16] In an experiment to verify this reactivity pattern, procedures comparable to those employed in the syntheses of **18** and **21** (CH_2Cl_2, reflux) were adopted for the preparation of **8** and **12.** Even though the reaction times were doubled in the imidazolidone series, considerably lower yields were observed for these reactions.[14]

The molecular structure assigned by us for each of these acyl substrates was the N,N'-disubstituted products rather than the isomeric N,O- or N,S-substituted imidazolines.