121 (23), 95 (100), 67 (36), and 43 (66).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.15.

Rearrangement of Dienone 38. Using procedure B, crude dienone **38** (220 mg, 1.0 mmol) furnished 180 mg (96%) of conjugated tricyclic dienone **41**, which was identified by comparison of spectral data (IR and NMR) with authentic material.

Rearrangement of α,β-Unsaturated Ketone 39. Using the general conditions described in procedure A and a reaction time of 2 h, ketone **39** (200 mg, 1.0 mmol) yielded 150 mg (78%) of a mixture which was shown by VPC (10% SE 30) to contain nonconjugated enone **33j** and conjugated enone **35j** in a ratio of 1:3. Exposure of product **33j** to identical conditions and reaction time resulted in a 1:1 mixture of **33j** and **35j**, thus suggesting that **33j** is a primary rearrangement product of **39**. Using procedure B, ketone **39** (1.1 g, 5.3 mmol) yielded 850 mg (85%) of conjugated enone **35j**.

Stability of Bicyclo[3.2.1]octene Products. Exposure of the nonconjugated enones **32g** and **33j** to procedure B conditions resulted in complete rearrangement to the conjugated products **41** and **35j**, respectively, as judged by IR and NMR. The nonconjugated bicyclo[3.2.1]octenones **32b, 32h, 33c–e,** and **42** did not rearrange to the corresponding conjugated analogues under these conditions.

Registry No.—**11**, 2220-40-8; **12**, 38258-84-3; **13**, 67316-12-5; **14**, 20023-36-3; **15** (isomer 1), 67337-34-2; **15** (isomer 2), 67337-35-3; **16**, 13697-84-2; **18a**, 64918-89-4; **18b**, 67337-36-4; **18c** (isomer 1), 67316-13-6; **18c** (isomer 2), 67337-37-5; **19**, 67316-14-7; **21**, 67316-15-8; **22a**, 67315-86-0; **22f**, 67316-02-3; **22h**, 67316-03-4; **23a**, 67337-29-5; **23f**, 67337-31-9; **23h**, 67337-32-0; **24a**, 67375-28-4; **24b**, 67337-38-6; **24c**, 67315-87-1; **24d**, 67315-88-2; **24e**, 67315-89-3; **24i**, 67316-04-5; **25a**, 67316-16-9; **25b**, 67315-90-6; **25i**, 67337-33-1; **26**, 67315-91-7; **27**, 67315-92-8; **28**, 67315-93-9; **29**, 67315-94-0; **30**, 67337-30-8; **32a**, 67316-17-0; **32b**, 67315-95-1; **32g**, 67316-07-8; **32h**, 67316-08-9; **33a**, 67316-18-1; **33b**, 67315-99-5; **33c**, 67315-96-2; **33d**, 67315-97-3; **33e**, 67315-98-4; **33j**, 67316-09-0; **34a**, 67316-19-2; **34b**, 67316-01-2; **34g**, 67316-20-5; **34h**, 67316-21-6; **35b**, 67316-00-1; **35j**, 67316-11-4; **36**, 67316-22-7; **36**, methyl ester, 67316-24-9; **38**, 67316-05-6; **39**, 67316-06-7; **41**, 67316-10-3; **42**, 67316-23-8; *p*-methylanisole, 104-93-8; 2-chloroacrylonitrile, 920-37-6; *m*-methylanisole, 100-84-5; acrylonitrile, 107-13-1; *tert*-butyl 2-bromopropionate, 39149-80-9; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; 3-bromopropyl phenyl sulfide, 3238-98-0; acetic acid, 64-19-7; propionic acid, 79-09-4; phenylacetic acid, 103-82-2; *m*-methoxyphenylacetic acid, 1798-09-0; methyl acetoacetate, 105-45-3.

References and Notes

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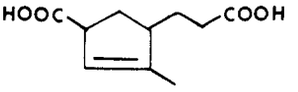
(9) The major product isolated under these conditions is tentatively assigned as diacid A: R. Chen, unpublished observation.



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Association Phenomena. 5. Synthesis and Properties of 1,4-Dipolar Substituted Cyclohexenes

Te C. Kung and C. David Gutsche*

Department of Chemistry, Washington University, St. Louis, Missouri 63130

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To study the intramolecular association between oppositely charged centers, several cyclohexenes substituted at the 1 and 4 positions with groups capable of carrying positive and negative charges have been synthesized. Included among these are the cis and trans isomers of 3-(methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic acid (**7** and **9**), 6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (**8** and **10**), 2,3-dimethyl-6-(methylamino)cyclohexenecarboxylic acid (**17a** and **19**), and 3-carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (**18a** and **20**) and the cis isomers of 3-methyl-6-(methylamino)cyclohexenecarboxylic acid (**17b**) and 3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**). However, the expectation that the zwitterions of these compounds should, to a greater extent than the anionic or cationic species, exist in the boat conformation failed to be clearly demonstrable by ^1H and ^{13}C NMR measurements. It is postulated that the apparent lack of conformational response to changing pH is due to the rather large nonbonded interactions arising from the groups at C-2 (i.e., CH_2 in **7–10**, CH_3 in **17a–20**, and H in **17b** and **18b**) and at C-4 (i.e., $NHCH_3$ or $N(CH_3)_3^+$), which favor the half-chair conformation, and the rather small coulombic interaction of the carboxylate and ammonium centers in the zwitterion (calculated to be 3–5 kcal/mol), which favors the boat conformation.

Papers 1–4 of this series[1] deal with intermolecular association phenomena involving interactions between positively and negatively charged moieties. The present paper represents an intramolecular counterpart of these systems and involves an attempt to measure the extent of intramolecular association in cyclohexenes substituted at the 1 and 4 positions with

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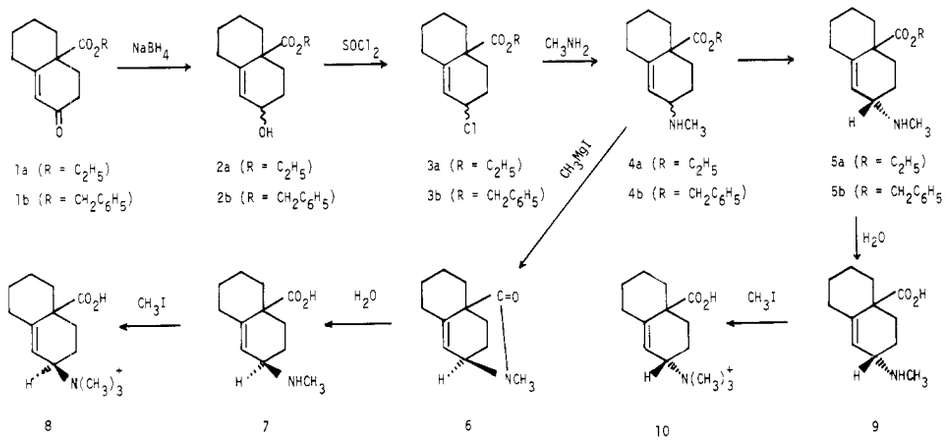


Figure 1. Synthesis of *cis*- and *trans*-6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (8 and 10).

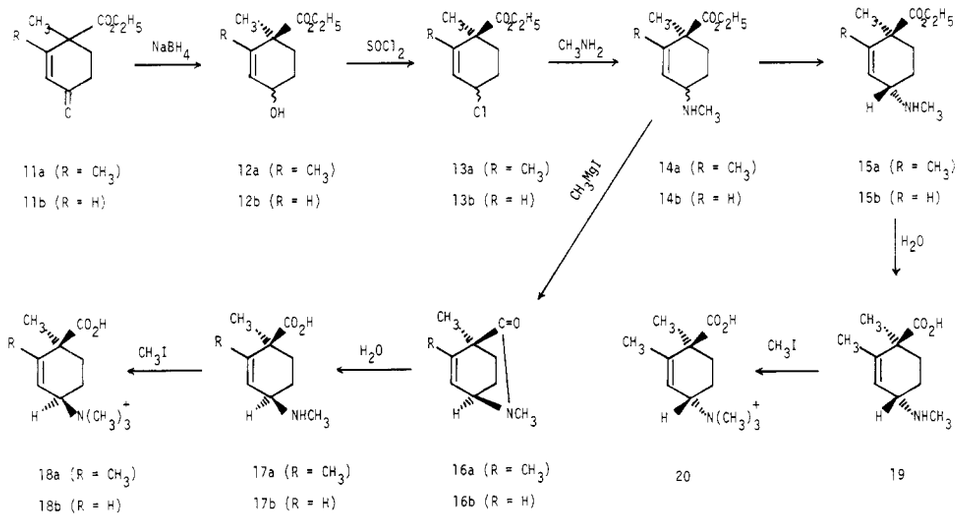
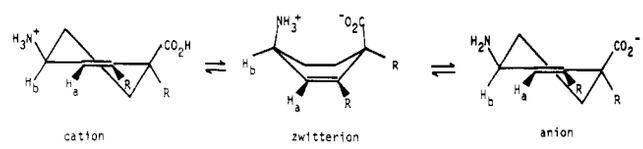


Figure 2. Synthesis of *cis*- and *trans*-3-carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (18a and 20) and *cis*-3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (18b).

groups capable of carrying positive and negative charges, respectively. To this end, several *cis*-4-amino-2-cyclohexene-1-carboxylic acids have been synthesized to test whether the conformation of the cyclohexene ring is a function of the extent of protonation of the amino and carboxyl groups. At high and low pH the aminocarboxycyclohexenes are singly charged (i.e., negatively and positively, respectively), and the ring might be expected to exist predominately in the half-chair conformation; at intermediate pH regions, however, the compounds are zwitterions and, as a result, should be more likely to assume the boat conformation because of electrostatic attraction between the oppositely charged groups, viz., Scheme I. It was hoped that the conformation of the cyclohexene ring could be discerned from the line shape of the NMR resonances arising from the vinyl hydrogen (H_a) that is coupled with the hydrogen α to the amino function (H_b). Although the results fell short of expectation, some observations requiring explanation have been obtained and some useful syntheses have been achieved.

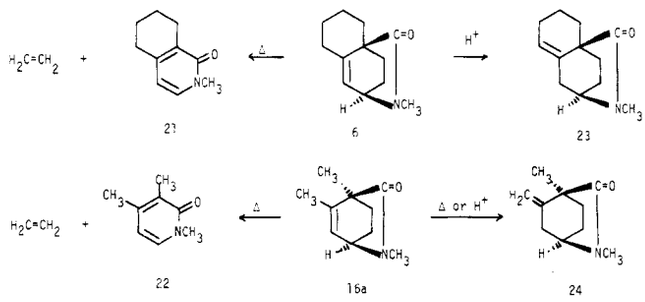
Synthesis of Compounds Containing the 4-Amino-2-cyclohexene-1-carboxylic Acid Moiety. Three series of compounds containing the 4-amino-2-cyclohexene-1-carboxylic acid moiety were synthesized. The first of these, the cis and trans isomers of 6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (8 and **10**), involved the sequence of reactions outlined in Figure 1. The second, the cis and trans isomers of 3-carboxy-2,3-dimethyl-6-(trimethylammonio)-cyclohexene chloride (**18a** and **20**), and the third, the cis isomer of 3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**), involved the equivalent sequence of reactions, as outlined in Figure 2. A key step in all cases is the separation of the cis and trans isomers of the amino esters (compounds **4** in Figure 1 and compounds **14** in Figure 2) via methylmagnesium iodide induced conversion[2] to the lactams **6** and **16**, the trans isomers of the amino esters remaining unchanged in the process. Separation of the lactams from the *trans*-amino esters, hydrolysis to the corresponding *cis*- and *trans*-amino acids, and methylation yielded the desired trimethylammonium compounds **8, 10, 18a, 18b, and 20.**

Scheme I



The major difficulty in the syntheses involved the formation of the lactams **6** and **16** and their subsequent conversion to the *cis*-amino acids. Attempts to form lactam **6** by heating **4a** resulted in the formation of the pyridone **21**, presumably the result of a $_{\pi}4_s + {}_{\pi}2_s$ cycloreversion reaction of the initially formed lactam. In similar fashion **14a** yields the pyridone when heated. Hydrolysis of lactam **6** proved to be particularly difficult, and prolonged treatment with 4 N sodium hydroxide

Scheme II



in ethanol was necessary to achieve optimum, although low, yields of **7**. Acid-catalyzed hydrolysis of the lactams was precluded, for **6** and **16a** were both shown to isomerize to **23** and **24**, respectively, in the presence of acid (Scheme II).

In an attempt to achieve a stereoselective synthesis of **7**, the benzyl ester (**1b**) was used as the starting material and was converted to *cis*-**2b** with lithium tri-*tert*-butoxyaluminum hydride. Treatment of *cis*-**2b** with thionyl chloride in pyridine yielded a mixture of *cis*- and *trans*-**3b**, however, thereby negating the stereoselective character of the sequence. Amination of this mixture with methylamine in benzene solution gave a mixture of *cis*- and *trans*-**4b**; amination in the absence of a solvent produced *trans*-**4b** in 95% yield.

Conformations of the Anionic, Cationic, and Zwitterionic Forms of the 4-Amino-2-cyclohexene-1-carboxylic Acids. Examination of the Dreiding models of the cis isomers of the monocyclic and bicyclic compounds containing the 4-amino-2-cyclohexene-1-carboxylic acid moiety indicates that there are four limiting conformations, viz., two boat forms (B_{aa} and B_{ee}) and two half-chair forms ($C_{a'e'}$ and $C_{e'a'}$), as illustrated in Figure 3. Measurement of the distance between the center of the amino function and a point extending 1.45 Å beyond the carbon atom of the carboxyl group along an axis midway between the oxygen atoms[3] shows that the amino and carboxyl functions can be as close as 2.7 Å (in B_{aa}) and as far apart as 7.2 Å (in B_{ee}), as indicated in Figure 3. Also shown in Figure 3 are the dihedral angles between the H_a and H_b hydrogens in the four conformations and the magnitude of the NMR coupling constant between these hydrogens that might be expected for the various dihedral angles.

The magnitude of the coupling constant between the vinyl hydrogen and the adjacent allylic hydrogens in cycloalkenes is a function of the dihedral angle between the hydrogens,[4] and it changes, for example, from 1.8 Hz for cyclobutene (dihedral angle 66°) to 5.7 Hz for cycloheptene (dihedral angle 11°).[5] The relation between the coupling constant and the dihedral angle has been used to assign a conformation to 3,4,5-trihydroxy-1-cyclohexenecarboxylic acid (shikimic acid),[6] and it was expected that it could be used in similar fashion in the present case. When the resonances arising from H_a in compounds **7**, **8**, **9**, **10**, **17a**, **18a**, **19**, and **20** were measured, however, essentially unresolved envelopes were obtained. That this can be attributed, at least in part, to long-range coupling with the homoallylic hydrogens is indicated by the ^1H NMR spectra of the lactams **6** and **16a** (constrained in the boat conformation), which show multiplet rather than doublet patterns for H_a. Compound **6**, for example, shows a doublet of triplets for which coupling constants of 5.5 (for J_{ab}) and 1.5 Hz (long-range coupling) can be determined. To gain a rough estimate of the coupling constants, therefore, the widths of the envelopes at half-height were measured; the differences in these widths with and without spin decoupling with the adjacent hydrogen (i.e., H_a or H_b) were taken as measures of the coupling constants J_{ab}, as shown in Table I. Although the uncertainties in this procedure are large and the significance of small differences is questionable, it does turn out that the widths at half-height for H_a, corrected in this fashion, are

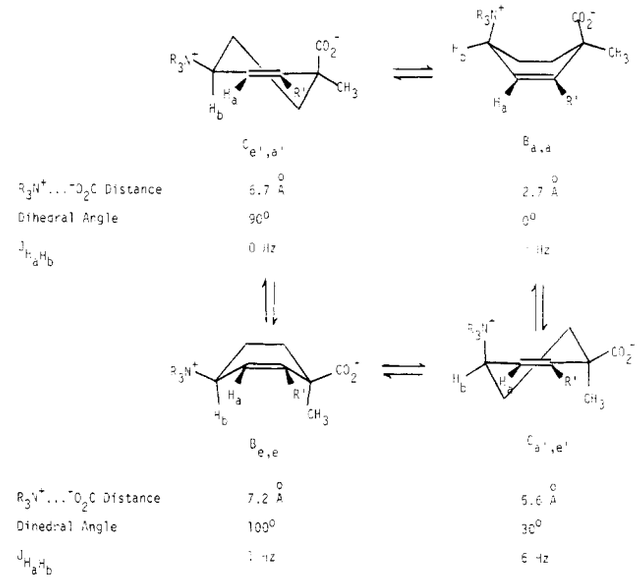


Figure 3. The four limiting conformations of the 4-amino-2-cyclohexene-1-carboxylic acids.

greater for the zwitterionic form than for either the anionic or cationic form for the cis isomers of the NCH_3 compounds (i.e., **7** and **17a**). Since this is not true for any of the other compounds shown in Figure 4, it suggests that the cis compounds **7** and **17a** may, at least to some small extent, exist in a boat conformation. A similar circumstance is observed when the "corrected" widths at half-height for the H_b hydrogens are considered; here, also, the widths for the cis isomers of the NCH_3 compounds are greater for the zwitterions than for the anionic and cationic species, although the uncertainties in the measurements are even more apparent in these cases.

The widths at half-height for H_b hydrogens are somewhat greater for the cis isomers of the $N(CH_3)_3^+$ compounds (14.0–18.5 Hz) than for the cis isomers of the NCH_3 compounds (9.5–12.5 Hz), suggesting that the two series assume different conformations. It is known that hydrogens in the axial alignment on a cyclohexane ring have broader resonances than those in the equatorial alignment,[7] and Garbisch[8] has shown this to be true for the allylic hydrogens in 1-methylcyclohexene as well. Thus, the greater width of the H_b resonances in the trimethylammonium compounds **8** and **18a** as compared with the methylamino compounds **7** and **17a** suggests that the former are in the $C_{e'a'}$ conformation and the latter in the $C_{a'e'}$ conformation (or, possibly, the B_{aa} conformation). That the larger trimethylammonium group should show a greater preference than the smaller methylamino group for a pseudoequatorial alignment is reasonable.

The relative energies of the half-chair and boat conformations for the compounds represented in Figure 3 depend, among other things, on the size of the R′ group. In the half-chair conformations $C_{e'a'}$ and $C_{a'e}$, the R′ group is approximately staggered with the CH_3 and CO_2H groups at C-1, whereas in the boat conformations B_{aa} and B_{ee} it is eclipsed with the CH_3 or the CO_2H group at C-1. Thus, the energy difference between the half-chair and boat forms might be expected to be lower when R′ is hydrogen than when it is methyl (as in **17a–20**) or methylene (as in **7–10**). However, the compounds in which R′ is hydrogen (i.e., **17b** and **18b**) give no clearer ^1H NMR evidence for conformational differences between the neutral zwitterion species and the charged anionic or cationic species than do the members of the other two series of compounds. They do, though, show well-resolved ^1H NMR envelopes for the vinyl hydrogens at C-3 (i.e., H_b) and C-2, from which the following coupling constants were measured:

Table I. ^{1}H NMR Data for 4-Amino-2-cyclohexene-1-carboxylic Acids

registry no.	compd	nitrogen function	config-uration	charge species	widths at half height, Hz: vinyl proton (H_a) a	b	diff	allyl proton (H_b) a	c	diff
67394-09-6	**9**	$NHCH_3$	trans	0,+	7.0	3.0	4.0	10.5	9.5	1.0
				−,+	6.5	3.0	3.5	9.0	7.5	1.5
				−,0	6.0	3.0	3.0	10.0	7.0	3.0
67394-10-9	**10**	$^+N(CH_3)_3$	trans	0,+	5.5	4.0	1.5	12.5	13.0	0.5
				−,+	6.0	4.5	1.5	13.0	12.0	1.0
67394-11-0	**7**	$NHCH_3$	cis	0,+	4.5	4.0	0.5	12.0	11.0	1.0
				−,+	4.0	2.5	1.5	13.0	9.5	3.5
				−,0	3.5	3.0	0.5	12.5	10.0	2.5
67394-12-1	**8**	$^+N(CH_3)_3$	cis	0,+	5.0	4.5	0.5	18.5	17.5	1.0
				−,+	5.0	4.5	0.5	17.5	17.0	0.5
67394-13-2	**19a**	$NHCH_3$	trans	0,+	6.0	4.0	2.0	13.0	14.0	−1.0
				−,+	6.0	4.0	2.0	14.0	15.5	−1.5
				−,0	5.5	4.0	1.5	14.0	17.0	−3.0
67394-14-3	**20a**	$^+N(CH_3)_3$	trans	0,+	5.5	5.0	0.5	15.5	15.5	0
				−,+	5.5	4.5	1.0	14.0	15.0	−1.0
67394-15-4	**17a**	$NHCH_3$	cis	0,+	5.5	4.0	1.5	13.0	12.0	1.0
				−,+	6.0	4.0	2.0	13.5	11.0	2.5
				−,0	5.5	4.5	1.0	13.0	12.5	0.5
67394-16-5	**18a**	$^+N(CH_3)_3$	cis	0,+	5.5	5.0	0.5	16.0	17.0	−1.0
				−,+	6.0	5.0	1.0	17.0	17.0	0

[a] Without decoupling. [b] With decoupling with H_b. [c] With decoupling with H_a.

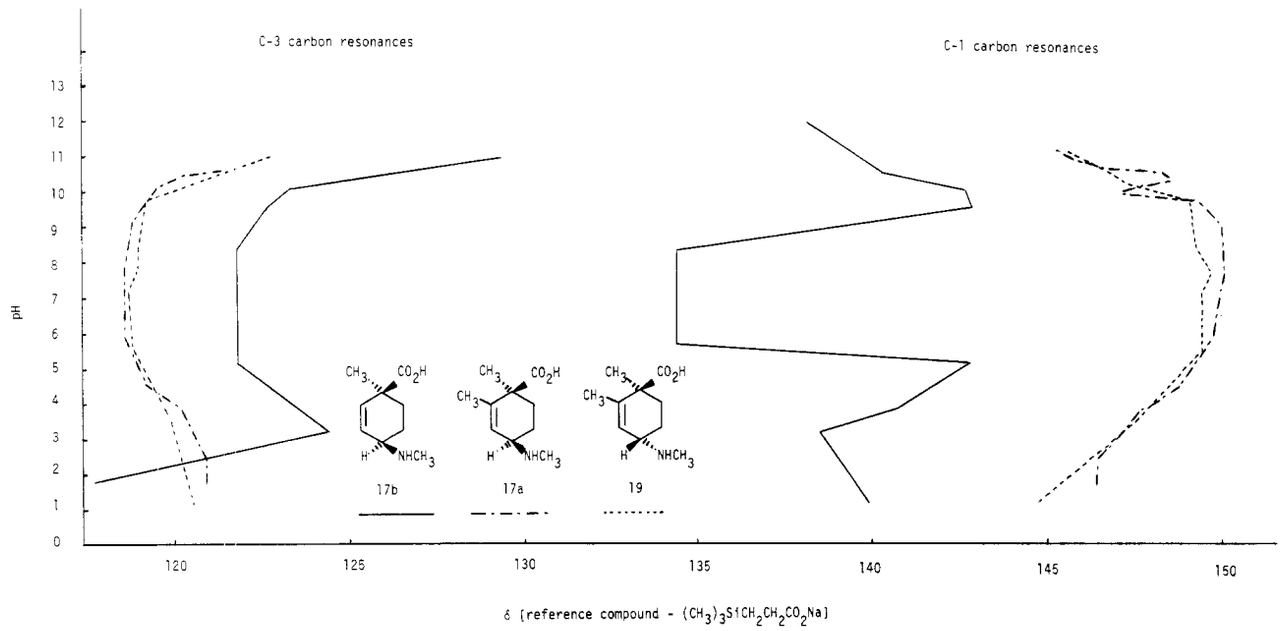


Figure 4. ^{13}C NMR–pH profiles for 4-amino-2-cyclohexene-1-carboxylic acids.

J_{ab} for **17b**, (0,+) form = 2.0 Hz, (−,+) form = 2.0 Hz, (−,0) form = 1.5 Hz; J_{ab} for **18b**, (0,+) form = 1.0 Hz, (−, +) form = 1.0 Hz. The ^{13}C NMR spectra, on the other hand, provide a modicum of evidence for special behavior of the zwitterion of **17b**. As shown in Figure 4, the chemical shift pH profile for **17b** is different from that of **17a** and **19a**, particularly in the pH region 5–8 where the zwitterion is present as the major species.

The difference in energy between the boat and half-chair conformations of cyclohexene is estimated, both on the basis of experiment[9a] and theory,[9b] to be approximately 5 kcal/mol. Substitution of a pair of geminal allylic hydrogens by a methyl or methylene group and a carboxyl group (the common feature at C-1 in all of the cyclohexenes in the present study) should probably not change this value significantly because of the similarity in size of these two groups (e.g., ΔG value of CH_3 is 1.70 and that of CO_2^- is 1.92[10]). On the basis of ΔG values for substituents in cyclohexane systems,[10] however, the substituent at C-4 is estimated to increase the nonbonded interaction by 1–2 kcal/mol for the $NHCH_3$ and $NH_2CH_3^+$ groups and 4 kcal/mol for the $N(CH_3)_3^+$ group; the nonbonded interaction between the groups at C-1 and the substituent at C-2 will also increase the relative stability of the half-chair form. Thus, the difference in energy between the boat and half-chair conformations for **7**, **9**, **17a**, and **19a** is predicted to be at least 7 kcal/mol, that for **8**, **10**, **18a**, and **20** to be at least 10 kcal/mol, that for **17b** to be ~6 kcal/mol, and that for **18b** to be ~9 kcal/mol.

By means of the Kirkwood–Westheimer method for estimating the magnitude of electrostatic interactions[11] it was calculated that the stabilization from the coulombic interaction between the carboxylate and ammonium centers should be 3–5 kcal/mol in the boat conformation. Thus, it is not surprising that most of the compounds tested failed to show

significant conformational responses to changes in pH, although it might have been expected that **17b** should show more dramatic behavior than was observed.

Experimental Section[12]

Synthesis of *cis*- and *trans*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Iodide (8 and 10). Ethyl 3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylate (4a). A 222-g (1.0 mol) sample of ethyl 3-ketobicyclo[4.4.0]dec-1-ene-6-carboxylate (**1a**)[13,14] was reduced to **2a** by treatment at 0 °C for 2 h with 18.9 g (0.50 mol) of sodium borohydride in 1 L of absolute ethanol. A 203-g sample of the crude product, obtained in 96% yield, was dissolved in 200 mL of dry benzene, cooled to 0 °C and treated with a solution of 77 mL (1.07 mol) of purified[15] thionyl chloride in 200 mL of benzene, added over a period of 1.5 h. The reaction mixture was stirred an additional 5 h at 0 °C, and the solvent and excess reagent were removed under reduced pressure at 35–45 °C to leave 234 g (100%) of a brown oil consisting of a mixture of *cis*- and *trans*-ethyl 3-chlorobicyclo[4.4.0]dec-1-ene-6-carboxylate (**3a**): IR (neat) ν 1735 (C=O), 1675 (C=C), 680 cm^{-1} (CCl); NMR (CCl_4) δ 5.59 (m, 1, CCH), 4.54 (m, 1, HCCl), 4.15 (2 q, 2, J = 7.5 and 7.0 Hz, ester CH_2), 2.54–0.83 (m, 12, ring CH_2), 1.25 (2 t, 3, J = 7.5 and 7.0 Hz, ester CH_3). Attempted purification of **3a** at 80 °C resulted in dehydrochlorination, yielding **ethyl bicyclo[4.4.0]deca-1,9-diene-6-carboxylate:** bp 63–65 °C (0.26 mm); IR (neat) ν 1725 (C=O), 1600 (C=C), 690 cm^{-1} (=CH); NMR (CCl_4) δ 6.14–5.33 (m, 3, =CH), 4.06 (q, 1, J = 7 Hz, ester CH_2), 2.95–1.00 (m, 10, ring CH_2), 1.2. (t, 3, J = 7 Hz, ester CH_3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.84; H, 9.01.

A 216-g sample of **3a** was dissolved in 430 mL of dry benzene, and gaseous methylamine was bubbled through the solution until it was saturated. The flask was tightly stoppered, and the reaction mixture was stirred at room temperature for 10 days. The crude product was distilled through a 12-in. Vigreux column to give 144 g (65%) of a mixture of *cis*- and *trans*-**4a**: bp 93–94 °C (0.10 mm); IR (neat) ν 3400 (NH), 1740 cm^{-1} (C=O); NMR (CCl_4) δ 5.45 (m, 1, =CH), 4.10 (q, 2, J = 7 Hz, ester CH_2), 2.94 (m, 1, HCN), 2.33 (s, 3, NCH_3), 2.23–1.00 (m, 12, ring CH_2), 1.24 (t, 3, J = 7 Hz, ester CH_3), 0.87 (s, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.96; H, 9.71; N, 5.95.

From the acid-insoluble fraction, 42 g (19%) of **3a** was recovered; no trace of the diene was discerned. An alternative procedure involving a 12-h reaction at 45 °C in a high-pressure bomb resulted in a 51% yield of **4a** and the production of a significant amount of diene.

10-Methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-2-en-9-one (6). Using a procedure analogous to that of Bassett and Thomas,[16] a 26.5-g (0.167 mol) sample of a mixture of *cis*- and *trans*-**4a** in 150 mL of ether was added over a period of 1 h to a solution containing 26 g (0.182 mol) of methyl iodide in 225 mL of ether. The mixture was refluxed for 12 h, cooled, treated with 100 mL of water followed by 100 mL of 2 N hydrochloric acid added slowly, and stirred until all of the solid had dissolved. The solution was then extracted with ether and the ether was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate, and saturated sodium chloride solution, dried over magnesium sulfate, and removed under vacuum to yield 23 g (63%) of **6** as a colorless oil: bp 95 °C (0.13 mm); IR (neat) ν 1665 cm^{-1} (C=O); NMR (CCl_4) δ 6.00 (t of d, 1, J = 5.5 and 1.5 Hz, =CH), 4.02 (m, 1, HCN), 2.78 (s, 3, NCH_3), 2.48–1.11 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.23; H, 8.82; N, 7.52.

10-Methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-3-en-9-one, a double bond position isomer of **6**, was produced by the action of anhydrous hydrogen chloride on **6** and was obtained as a colorless oil: IR (neat) ν 1690 cm^{-1} (C=O); NMR (CCl_4) δ 5.49 (m, 1, =CH), 3.56 (m, 1, HCN), 3.11 (s, 3, NCH_3), 2.54–0.88 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.20; H, 9.05; N, 7.28.

***cis*-3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic Acid (7).** A mixture of 31 g (0.162 mol) of **6** in 180 mL of ethanol and 180 mL of 4 N sodium hydroxide was refluxed for 156 h in an atmosphere of nitrogen. Most of the ethanol was then removed by evaporation, the aqueous solution was filtered, and the filtrate was washed four times with ether and made acidic with concentrated hydrochloric acid. The gelatinous substance that formed was removed by dissolving the acidified filtrate in hot ethanol, filtering the cooled solution, and concentrating the filtrate. The thick oil that remained after the fourth of these treatments solidified and was recrystallized from ethanol–acetone to give 9.8 g of the hydrochloride salt of **7**: mp 245 °C dec; IR (KBr) ν 2490 (N^+H), 1730 (C=O), 1680 (C=C), 718 cm^{-1} (CN^+); NMR (D_2O) δ 5.88 (s, 1, =CH), 4.12 (m, 1, HCN), 2.91 (s, 3, NCH_3), 2.66–1.00 (m, 12, ring CH_2). A solution containing 9.8 g of the hydrochloride salt of **7** in 35 mL of water was adjusted to pH 8 with 8 N sodium hydroxide solution and cooled in an ice bath for 1 h. The precipitate was removed by filtration, washed with ice water and cold ethanol, and dried to yield 8.89 g (99%) of the monohydrate of **7**: mp 214 °C dec; IR (KBr) ν 1670 (C=C), 1630 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.46 (s, 1, =CH), 3.83 (m, 1, HCN), 2.70 (s, 3, NCH_3), 2.40–0.90 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{19}NO_2 \cdot H_2O$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.27; H, 9.38; N, 6.06.

The combined ether extracts of the basic solution yielded 22 g (71% recovery) of unchanged **6.**

***trans*-3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic Acid (9).** The combined acid extract from the preparation of 10-methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-2-en-9-one (see above) was made basic (pH 11) with 5 N sodium hydroxide solution, and most of the magnesium hydroxide was removed by centrifugation. The supernatant solution was extracted with four 50-mL portions of ether, and the ether extract was then dried and saturated with anhydrous hydrogen chloride. The hydrochloride salt of **5a** precipitated and was removed by filtration. This material was treated with 25 mL of 5 N sodium hydroxide solution and extracted with ether, and the ether was dried and evaporated to give 7.8 g (19%) of **5a**: bp 87–89 °C (0.15 mm); IR (neat) ν 3400 (NH), 1735 (C=O), 1680 cm^{-1} (C=C); NMR (CCl_4) δ 5.52 (d, 1, J = 3.8 Hz, =CH), 4.13 (q, 2, J = 7 Hz, ester CH_2), 2.89 (m, 1, HCN), 2.35 (s, 3, NCH_3), 2.23–1.03 (m, 12, ring CH_2), 1.22 (t, 3, J = 7 Hz, ester CH_2), 0.68 (s, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.91; H, 9.65; N, 5.97.

A solution of 10.4 g of **5a** in 104 mL of 2 N hydrochloric acid was refluxed for 120 h in an atmosphere of nitrogen. The acidic solution was made basic (to pH 11) with 5 N sodium hydroxide, extracted four times with ether, made acidic (to pH 2) with concentrated hydrochloric acid, and extracted four more times with ether. The water was evaporated under reduced pressure, and the sodium chloride was removed by dissolving the slurry in hot absolute ethanol, filtering the chilled solution, and concentrating the filtrate, this process being repeated several times. The remaining oil solidified upon contact with acetone to give 7.27 g (69%) of the hydrochloride of the desired acid, mp 225 °C dec. Treatment of a solution of this material with 5.07 g of silver oxide for 5 h at room temperature yielded 6.02 g (98%) of **9** as colorless needles after recrystallization from ethanol–acetone–water: mp 168 °C dec; IR (KBr) ν 1680 (C=C), 1640 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.73 (d, 1, J = 4 Hz, =CH), 3.82 (m, 1, HCN), 2.87 (s, 3, NCH_3), 2.62–1.08 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.75; H, 9.14; N, 6.53.

***cis*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Chloride (8).** Using a procedure modeled after that of Patchett and Witkop,[17] a slurry of 0.84 g (4 mmol) of **7** and 1.11 g (5 mmol) of silver oxide in 20 mL of water was stirred at room temperature for 3 h. A solution of 0.51 mL (12 mmol) of methyl iodide in 100 mL of methanol was then added, the mixture was stirred for 3 h, a second solution of 0.34 mL of methanol was added, and stirring was continued another 4 h. The methanol and excess methyl iodide were removed by evaporation, the remaining aqueous solution was treated with 1.11 g (5 mmol) of silver oxide, and the mixture was stirred for 0.5 h. Filtration, acidification with concentrated hydrochloric acid followed by another filtration, and concentration of the filtrate produced a thick oil which, after trituration with acetone, yielded 0.74 g (67%) of **8**. Recrystallization from ethanol–acetone yielded a colorless solid: mp 226 °C dec; IR (KBr) ν 1700 (C=O), 720 cm^{-1} (CN^+); NMR (D_2O) δ 5.95 (m, 1, =CH), 4.30 (m, 1, HCN), 3.24 (s, 9, NCH_3), 2.64–1.16 (m, 12, ring CH_2).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.43; H, 8.84; N, 5.12. Found: C, 61.26; H, 9.01; N, 4.99.

***trans*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Chloride (10).** Using the procedure described above, **10** was obtained as a colorless solid: mp 211 °C dec; IR (KBr) ν 1720 (C=O), 1680 (C=C), 720 cm^{-1} (CN^+); NMR (D_2O) δ 6.03 (m, 1, =CH), 4.20 (m, 1, HCN), 3.28 (s, 9, NCH_3), 2.62–1.20 (m, 12, ring CH_2).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.43; H, 8.84; N, 5.12. Found: C, 61.28; H, 8.79; N, 4.98.

Benzyl 3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylate (4b). Benzyl 2-ketocyclohexanecarboxylate, prepared by ester interchange from the ethyl 2-ketocyclohexanecarboxylate and benzyl alcohol, was subjected to the Robinson annelation procedure[18] to yield **benzyl 3-ketobicyclo[4.4.0]dec-1-ene-6-carboxylate (1b)**

as a colorless oil: bp 170 °C (0.43 mm); IR (neat) ν 1740 (ester C=O), 1680 (ketone C=O), 1500 (Ar), 788, 756, 699 cm^{-1} (Ar); NMR (CCl_4) δ 7.25 (s, 5, ArH), 5.78 (s, 1, =CH), 5.13 (s, 2, ester CH_2), 2.74–0.94 (m, 12, ring CH_2).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 7.22.

Reduction of a 33.4-g (0.12 mol) sample of this material with lithium tri-*tert*-butoxyaluminum hydride, prepared from 5.2 g (0.13 mol) of lithium aluminum hydride, yielded 32.2 g (96%) of the alcohol **2b**. Treatment of 10 g (35 mmole) of crude **2b** with 2.78 mL (38 mmole) of thionyl chloride in 30 mL of dry pyridine at 0 °C yielded 7.81 g (74%) of the chloro compound **3b**. A 10.3-g (34 mmole) sample of **3b** was allowed to react with an equal volume of methylamine in a pressure bomb for 18 h at 60 °C. The crude hydrochloride of **4b** was recrystallized from ethanol–ether to give 3.9 g of material, mp 172–174 °C, which was converted to 2.9 g (29%) of **4b** by treatment with sodium hydroxide: bp 142 °C (0.09 mm); IR (neat) ν 3450 (NH), 1740 (C=O), 1640 (C=C), 1620 (Ar); 752, 736, 698 cm^{-1} (Ar); NMR (CCl_4) δ 7.25 (s, 5, ArH), 5.50 (d, 1, J = 4 Hz, =CH), 5.06 (s, 2, ester CH_2), 2.89 (m, 1, HCN), 2.30 (s, 3, NCH_3), 2.27–0.98 (m, 12, ring CH_2), 0.82 (s, 1, NH).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.09; H, 8.61; N, 4.57.

When a 6.95-g (23 mmol) sample of **4b** was refluxed for 24 h with 100 mL of 20% hydrochloric acid, 4.7 g (82%) of *trans*-3-(methylamino)-6-carboxybicyclo[4.4.0]dec-1-ene chloride, mp 225 °C dec, was obtained that had spectral properties identical with those of the product obtained from the ethyl ester, **4a**, as described above.

Synthesis of *cis*- and *trans*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexane Chloride (18a and 20a). Ethyl 2,3-Dimethyl-6-(methylamino)cyclohexene-3-carboxylate (14a). Ethyl 2,3-dimethyl-6-ketocyclohexene-3-carboxylate (**11a**) was prepared by condensation of ethyl methylacetoacetate with methyl vinyl ketone to ethyl 2-acetyl-2-methyl-5-ketohexanoate followed by piperidine acetate catalyzed cyclization.[19] Following the procedure of Plieninger, Arnold, and Hoffmann,[20] a 42-g (0.215 mol) sample of this material was converted in 100% yield to the alcohol **12a** by treatment with 4.1 g (0.107 mol) of sodium borohydride in 300 mL of absolute ethanol at 0 °C. By the action of thionyl chloride in benzene **12a** was converted in 100% yield to the chloride **13a**, obtained as a pale yellow oil which was used without purification. Treatment of **13a** in benzene solution with methylamine for 12 days at room temperature yielded, after distillation of the crude product through a 12-in. Vigreux column, 79 g (79%) of **14a** as a colorless oil: bp 80–81 °C (0.35 mm); IR (neat) ν 3380 (NH), 1735 (C=O), 1675 cm^{-1} (C=C); NMR (CCl_4) δ 5.47 (q, 1, J = 1.5 Hz, =CH), 4.10 (q, 2, J = 7 Hz, ester CH_2), 2.98 (m, 1, HCN), 2.36 (s, 1, NCH_3), 2.24–1.41 (m, 7, ring CH_2, $=CCH_3$), 1.26 (s, 3, CCH_3), 1.22 (t, 3, J = 7 Hz, ester CH_3), 1.02 (s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.38; H, 9.98; N, 6.79.

1,6,8-Trimethyl-8-azabicyclo[2.2.2]oct-5-en-7-one (16a). Employing the procedure described above for the conversion of **4a** to **6**, 79 g (0.37 mol) of **14a** was treated with methylmagnesium iodide to yield, after distillation of the crude product through a 6-in. Vigreux column, 19 g (31%) of **16a**, obtained as a colorless oil: bp 69–70 °C (0.20 mm); IR (neat) ν 1675 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 6.08 (t of t, 1, J = 1.5 and 5.5 Hz, =CH), 4.02 (m, 1, HCN), 2.75 (s, 3, NCH_3), 2.21–1.11 (m, 4, ring CH_2), 1.72 (d, 3, J = 1.5 Hz, $=CCH_3$), 1.27 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.54; H, 8.97; N, 8.61.

***cis*-2,3-Dimethyl-6-(methylamino)cyclohexenecarboxylic Acid (17a).** A two-phase system containing 27 g of **16a** and 270 mL of 2 N sodium hydroxide was refluxed for 42 h in an atmosphere of nitrogen. The cooled solution was filtered, and the filtrate was washed three times with ether and acidified to pH 2 with concentrated hydrochloric acid. The acidified solution was filtered, washed with three portions of ether, and evaporated under reduced pressure. The residue was triturated three times with ethanol to leave 22 g (61%) of the chloride of **17a**, mp 211 °C dec. A slurry of 7.2 g (33 mmol) of the chloride was stirred for 5 h at room temperature with 5.1 g (22 mmol) of silver oxide in 150 mL of water to yield 6.0 g (100%) of a solid which was recrystallized from acetone–ethanol to give **17a** as colorless rhombs: mp 220 °C dec; IR (KBr) ν 1635 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.66 (m, 1, =CH), 3.87 (m, 1 HCN), 2.86 (s, 3, NCH_3), 2.42–1.50 (m, 7, ring CH_2 and $=CCH_3$), 1.33 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.42; H, 9.40; N, 7.50.

***trans*-2,3-Dimethyl-6-(methylamino)cyclohexenecarboxylic Acid (19a).** The combined acid extract from the preparation of 1,6,8-trimethyl-8-azabicyclo[2.2.2]oct-5-en-7-one (**16a**) was treated as described above for the corresponding tricyclic lactam **6** to yield 19% of **ethyl *trans*-2,3-dimethyl-6-(methylamino)cyclohexenecarboxylate (15a)** as a colorless oil: bp 78 °C (0.20 mm); IR (neat) ν 3380 (NH), 1735 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 5.44 (q, 1, J = 1.4 Hz, =CH), 4.09 (q, 2, J = 7.5 Hz, ester CH_2), 2.99 (m, 1, HCN), 2.35 (s, 3, NCH_3), 2.22–1.42 (m, 7, ring CH_2 and $=CCH_3$), 1.24 (s, 3, CCH_3), 1.22 (t, 3, J = 7.5 Hz, ester CH_3), 0.72 (s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.05; H, 10.13; N, 6.67.

A 15-g sample of **15a** was refluxed for 24 h with 150 mL of 2 N hydrochloric acid in an atmosphere of nitrogen to yield 13 g (87%) of the chloride of **19a**, obtained as colorless rhombs after recrystallization from ethanol–acetone, mp 178 °C dec. Treatment of this material with silver oxide in the manner described above for the cis isomer yielded **19a** as colorless rhombs after recrystallization from ethanol–acetone: mp 239 °C dec; IR (KBr) ν 1635 cm^{-1} (CO_2^-); NMR (CCl_4) δ 5.64 (m, 1, =CH), 3.92 (m, 1, HCN), 2.85 (s, 3, NCH_3), 2.50–1.60 (m, 7, ring CH_2 and $=CCH_3$), 1.39 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.63; H, 9.36; N, 7.54.

***cis*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene Chloride (18a).** A slurry of 4.5 g (25 mmol) of **17a** and 6.9 g (29 mmol) of silver oxide in 90 mL of water was treated with an excess of methyl iodide in the manner described above for the bicyclic analogue **7** to yield 4.6 (77%) of crude product which was recrystallized from ethanol–acetone to yield **18a** as colorless rhombs: mp 229 °C dec; IR (KBr) ν 1730 (C=O), 1670 (C=C), 730 cm^{-1} (CN^+); NMR (D_2O) δ 5.94 (m, 1, HCN), 3.32 (s, 9, NCH_3), 2.56–1.67 (m, 7, ring CH_2 and $=CCH_3$), 1.45 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 58.15; H, 8.90; N, 5.65. Found: C, 58.01; H, 8.98; N, 5.58.

***trans*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (20)** was obtained in a comparable fashion as colorless rhombs after recrystallization from ethanol–acetone: mp 225 °C dec; IR (KBr) ν 1725 (C=O), 1665 (C=C), 720 cm^{-1} (CN^+); NMR (D_2O) δ 5.83 (m, 1, =CH), 4.25 (m, 1, HCN), 3.25 (s, 9, NCH_3), 2.60–1.72 (m, 7, ring CH_2 and $=CCH_3$), 1.49 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 58.15; H, 8.90; N, 5.65. Found: C, 58.02; H, 9.06; N, 5.48.

Synthesis of *cis*-3-Carboxy-3-methyl-6-(trimethylammonio)cyclohexene Chloride (18b). Ethyl 3-Methyl-6-(methylamino)cyclohexene-3-carboxylate (14b). Following the general procedures described above for the preparation of **14a**, ethyl 2-formylpropanoate[21] was condensed with methyl vinyl ketone[22] to yield ethyl 2-formyl-2-methyl-5-ketohexanoate, which was cyclized in the presence of piperidine acetate to ethyl 3-methyl-6-(methylamino)cyclohexene-3-carboxylate (**11b**), obtained as a colorless oil, bp 87–88 °C (2 mm). Reduction of 239 g (1.31 mol) of **11b** in 650 mL of absolute ethanol by treatment at −5 °C with a solution of 24.8 g (0.66 mol) of sodium borohydride in 1500 mL of absolute ethanol yielded 240 g (100%) of the alcohol **12b** as a slightly greenish oil which was converted, without purification, to the chloride **13b** by treatment with thionyl chloride in benzene at 0–5 °C. This product, isolated in 100% yield, was also used without purification for conversion to the methylamino compound **14b** by treatment with methylamine in the manner described above for the analogues **3a** and **13a**. The product **14b** was obtained in 37% yield as a colorless oil: bp 65–68 °C (0.36–0.27 mm); IR (neat) ν 3400 (NH), 1740 (C=O), 1660 cm^{-1} (C=C); NMR (CCl_4) δ 5.68 (s, 3, NCH_3), 2.27–1.10 (m, 4, ring CH_2), 1.23 (s, 3, CCH_3), 1.20 (t, 3, J = 7 Hz, ester CH_3), 0.82 (s, 1, NH).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.01; H, 9.67; N, 7.09.

6,8-Dimethyl-8-azabicyclo[2.2.2]oct-2-en-7-one (16b). A 20-g sample of **14b** was heated for 20 h at 170 °C in an atmosphere of nitrogen. The reaction mixture was dissolved in 100 mL of ether, and the ether solution was saturated with anhydrous hydrogen chloride. The precipitate that formed was removed by filtration, the filtrate was again saturated with hydrogen chloride, and a second crop of crystals was collected. The filtrate was concentrated, and the residue was distilled through a 6-in. Vigreux column to yield 3.1 g (31%) of **16b** as a colorless oil: bp 60 °C (0.21 mm); IR (neat) ν 1675 (C=O), 1635 cm^{-1} (C=C); NMR (CCl_4) δ 6.41 (d of d, 1, J = 7.5 and 6 Hz, =CHCN), 6.00 (d of d, J = 7.5 and 1 Hz, HC=CCN), 4.24–4.00 (m, 1, HCN), 2.80 (s, 3, NCH_3), 2.20–1.00 (m, 4, ring CH_2), 1.32 (s, 3, CCH_3).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.36; H, 8.70; N, 9.63.

The precipitate described above consisted of the hydrochloride of the starting material **14b**, from which **14b** could be recovered by basification.

***cis*-3-Methyl-6-(methylamino)cyclohexenecarboxylic Acid**

Table II. pK Values of Compounds 7–10 and 17–20

compd	pK_1	pK_2
7	3.79 ± 0.04	11.10 ± 0.03
8	3.97 ± 0.02	
9	3.75 ± 0.02	10.92 ± 0.02
10	3.79 ± 0.04	
17a	3.82 ± 0.04	11.08 ± 0.04
18a	3.95 ± 0.03	
19a	3.79 ± 0.02	10.81 ± 0.01
20	3.83 ± 0.02	

(17b). A mixture of 9.37 g of **16b** in 93 mL of 2 N sodium hydroxide was refluxed for 24 h in an atmosphere of nitrogen. The product was worked up as described above for **17a** to give the chloride of **17b** as colorless rhombs, mp 182 °C dec. A slurry of 3 g of the chloride and 2.55 g of silver oxide in 60 mL of water was stirred at room temperature for 4 h to yield 2.24 g (91%) of material from which pure **17b** was obtained as colorless rhombs by recrystallization from absolute ethanol: mp 256 °C dec; IR (KBr) ν 2500 (N^+H), 1640 cm^{-1} (CO_2^-); NMR (D_2O) δ 6.11 (d of d, 1, J = 10 and 1 Hz, HC=CCN), 5.65 (d of d, J = 10 and 3 Hz, =CHCH), 3.91–3.58 (m, 1, HCN), 2.67 (s, 3, NCH_3), 2.30–1.04 (m, 4, ring CH_2), 1.18 (s, 1, CCH_3).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.56; H, 9.04; N, 8.12.

***cis*-3-Carboxy-3-methyl-6-(trimethylammonio)cyclohexene Chloride (18b).** A slurry of 4 g (19.4 mmol) of **17b** and 7.86 g (34 mmol) of silver oxide in 80 mL of water was treated with an excess of methyl iodide in the manner described above for the bicyclic analogue **7** to yield 3.18 g (70%) of crude product which was recrystallized from ethanol–acetone to yield **18b** as colorless rhombs: mp 250 °C dec; IR (KBr) ν 1730 (C=O), 1670 (C=C), 740 cm^{-1} (CN^+); NMR (D_2O) δ 6.29 (d of d, 1, J = 10 and 1 Hz, =CHCH), 6.00 (br d, 1, J = 10 Hz, HC=CCN), 4.39–4.03 (m, 1, HCCN), 3.11 (s, 9, NCH_3), 2.55–1.50 (m, 4, ring CH_2), 1.30 (s, 3, CCH_3).

Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.46; H, 5.55; N, 5.99. Found: C, 56.02; H, 5.49; N, 6.08.

Other Syntheses. Ethyl 3-oximinobicyclo[4.4.0]dec-1-ene-6-carboxylate (oxime of 1a) was obtained as colorless rhombs, mp 104–106 °C.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.79; H, 7.95; N, 6.01.

3-Methyl-2-oxo-3-azabicyclo[4.4.0]deca-1(6),4-diene (21). A 4-g sample of **6** was heated for 30 min at 265–270 °C in an atmosphere of nitrogen. The gas evolved during this treatment decolorized a solution of bromine in carbon tetrachloride. The reaction mixture was distilled, and the distillate was recrystallized from petroleum ether (bp 60–68 °C) to yield **21** as colorless rhombs: mp 81–82 °C; IR (KBr) ν 1660 (C=O), 684 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 7.12 (d, 1, J = 7 Hz, =CHCN), 5.92 (d, 1, J = 7 Hz, =CH), 3.50 (s, 3, NCH_3), 2.76–2.18 (m, 4, allylic CH_2), 1.99–1.42 (m, 4, ring CH_2); UV (95% EtOH) λ_{max} (ϵ) 295 (6760), 236 (3980) nm.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.09; N, 8.58. Found: C, 73.44; H, 8.00; N, 8.61.

1,4,5-Trimethyl-6-oxo-1-azacyclohexa-2,4-diene (22). A 6-g sample of **16a** was heated for 30 min at 265–270 °C in an atmosphere of nitrogen. The gas evolved during this treatment decolorized a solution of bromine in carbon tetrachloride. The reaction mixture, shown by NMR analysis to consist of 65% of **22** and 35% of 1,8-dimethyl-2-methylene-8-azabicyclo[2.2.0]octan-7-one (**24**), was purified by crystallization from petroleum ether (bp 28–30 °C) to yield **22** as colorless rhombs: mp 63–64 °C IR (KBr) ν 1665 (C=O), 682 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 7.20 (d, 1, J = 7 Hz, =CHCN), 6.00 (d, 1, J = 7 Hz, =CHCN), 3.51 (s, 3, NCH_3), 2.12 (s, 3, CH_3), 2.08 (s, 3, CH_3).

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.17; H, 7.92; N, 10.23.

The **lactam 24** was isolated from the reaction mixture by chromatography on alumina and was obtained, after distillation, as a colorless oil: IR (neat) ν 1665 (C=O), 890 cm^{-1} (C=C); NMR (CCl_4) δ 4.84 (m, 2, allylic CH_2), 2.08–1.47 (m, 4, ring CH_2), 1.19 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.48; H, 9.37; N, 8.20.

Physical Measurements. Ionization Constant Measurements. Using the method described by Albert and Serjeant,[23] the pK values shown in Table II were obtained. The pH measurements were made with a Beckman Model G meter equipped with a Beckman 41252 general purpose glass electrode and a Beckman 41239 fiber junction calomel reference electrode. All measurements were made under a slow stream of nitrogen at 25 ± 0.2 °C after the electrodes had been immersed in the solutions for 30 min.

^{1}H NMR Measurements. A 0.5-mL quantity of a 0.5 M deuterium oxide solution of the compound was placed in an NMR tube and treated with a measured quantity of 5 N trifluoroacetic acid-d_1 or sodium deuterioxide (0, 0.25, 0.5, 0.75, 1, and 2 molar equiv amounts used). The spectral characteristics of the H_a and H_b hydrogens are shown in Table I.

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Registry No.—**1a,** 7478-39-9; **1a** oxime, 67394-17-6; **1b,** 67394-04-1; **2a,** 67394-18-7; **2b,** 67394-19-8; *cis*-**3a,** 67394-20-1; *trans*-**3a,** 67394-21-2; **3b,** 67394-22-3; *cis*-**4a,** 67394-23-4; *trans*-**4a,** 67394-24-5; **4b,** 67394-25-6; **5a** HCl, 67394,26-7; **6,** 67394-27-8; **7** HCl, 67394-28-9; **8** chloride analogue, 67394-07-4; **10** chloride analogue, 67394-08-5; **11a,** 28790-87-6; **11b,** 1489-55-0; **12a,** 67394-29-0; **12b,** 67394-30-3; **13a,** 67393-88-8; **13b,** 67393-89-9; **14a,** 67393-90-2; **14b,** 67393-91-3; **15a,** 67393-92-4; **16a,** 67393-93-5; **16b,** 67393-94-6; **17a** HCl, 67393-95-7; **17b,** 67393-96-8; **17b** HCl, 67393-97-9; **19a** HCl, 67393-98-0; **21,** 67393-98-0; **22,** 67394-00-7; **24,** 67394-01-8; ethyl bicyclo[4.4.0]deca-1,9-diene-6-carboxylate, 67394-02-9; 10-methyl-10-azatricyclo[6.2.2.$0^{3,8}$]dodec-3-en-9-one, 67394-03-0; *trans*-3-(methylamino)-6-carboxybicyclo[4.4.0]dec-1-one hydrochloride, 67394-05-2; ethyl methylacetoacetate, 609-14-3; methyl vinyl ketone, 78-94-4; ethyl 2-acetyl-2-methyl-5-ketohexanoate, 28793-08-0; ethyl 2-formylpropanoate, 2772-62-9; ethyl 2-formyl-2-methyl-5-ketohexanoate, 1523-87-1.

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