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Bicyclic Enamines. VIII. Mechanistic Studies of Rearrangements in a Quinuclidine System[1]

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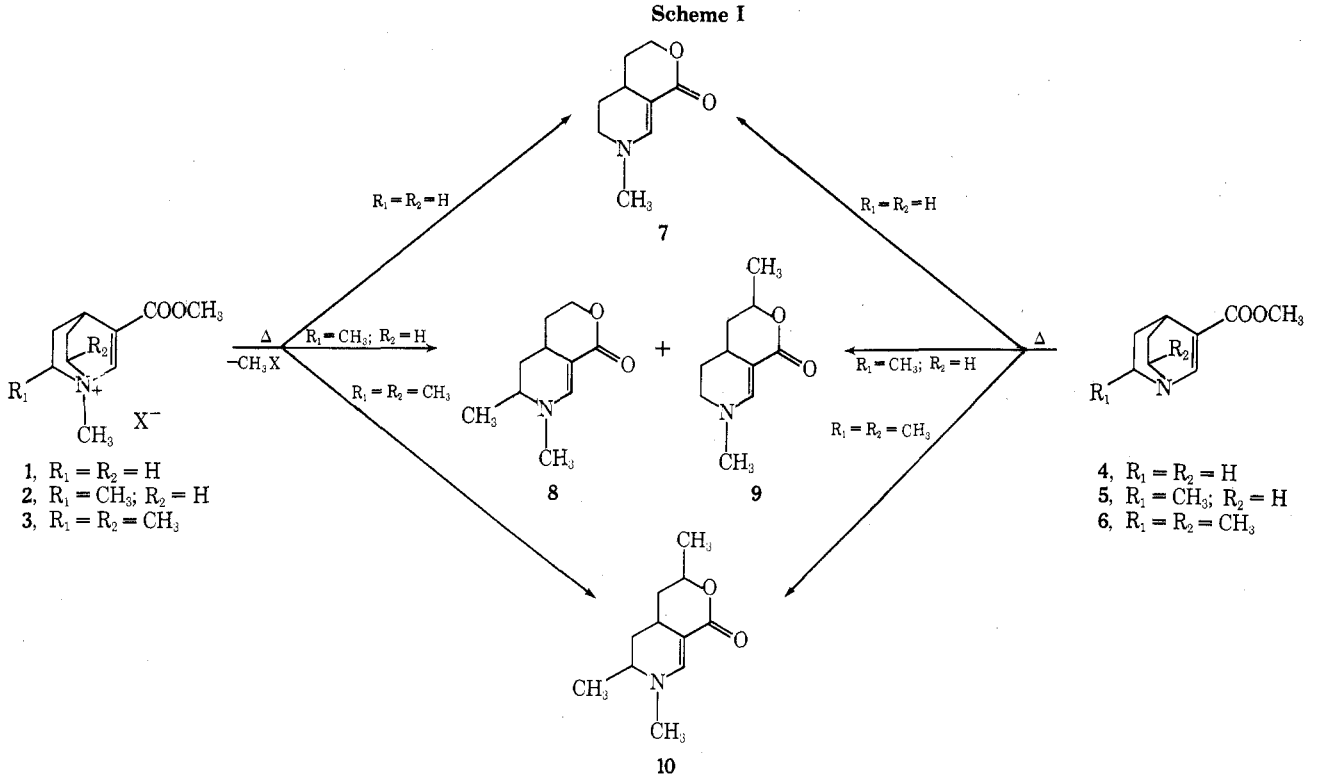
When an unsaturated quaternary quinuclidine-3-carboxylic acid ester of type **1** (X = I^-) is heated to about 150° for 1 min or less, it rearranges in very good yield to a lactone of type **7**. The same lactone is formed from the corresponding base **4**, although prolonged heating at higher temperature is required (200° for 30 min). We have shown that these conversions are multistep reactions initiated by the attack of a nucleophile, which can either be the counterion of the quaternary salts **1–3** or another base molecule in the rearrangement of the bases **4–6**.

Recently we reported[3,4] that the unsaturated quinuclidine-3-carboxylic acid esters **1** and **2**, when heated, were converted into tetrahydronicotinic acid lactones. We have now extended this work to all the esters **1–6** and studied the mechanism for their conversion into lactones **7–10**.

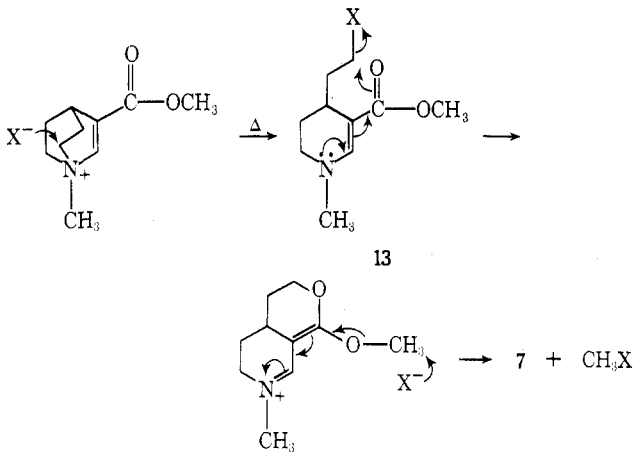
In a preliminary report[3] several mechanisms were considered for the thermal conversions of Scheme I, and it was concluded that the intermediate **11** (Scheme II) was formed by successive sigmatropic rearrangements. Further studies have shown that this proposal was in error, and evidence now indicates that, contrary to the preliminary report, the rearrangements probably occur by attack of the counterion of the quaternary salt. Rearrangement of the tertiary bases probably occurs *via* a related mechanism.

In our early studies on this problem we observed that bases **4** and **5** gave lactones in a manner similar to that of quaternary salts **1** and **2** (Scheme I). This indicated to us that the bases and the quaternary salts were converted *via* the same mechanism, and in a preliminary report[3] we proposed that the lactone **7** was formed *via* sigmatropic rearrangements. However, we later found that the nitrogen substituent of compounds of type **1** influenced the ease of rearrangement to lactones. We could thus demonstrate that *N*-allyl- and *N*-propargylquinuclidine-3-carboxylic acid esters gave the corresponding lactones when

Scheme I



Scheme II



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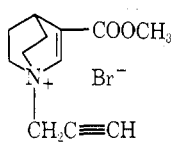
11

the compounds were stored at room temperature for a few weeks, while the *N*-methyl derivative 1 rearranged only when heated above 100°. This prompted us to investigate the mechanism further.

Results and Discussion

To study the effect of various negative ions on the rearrangement, salts with counterions of different nucleophilicity were prepared and heated to 150° for 10 min. We found that 1 with X = I^- as well as 12 with X = Br^-, the



12

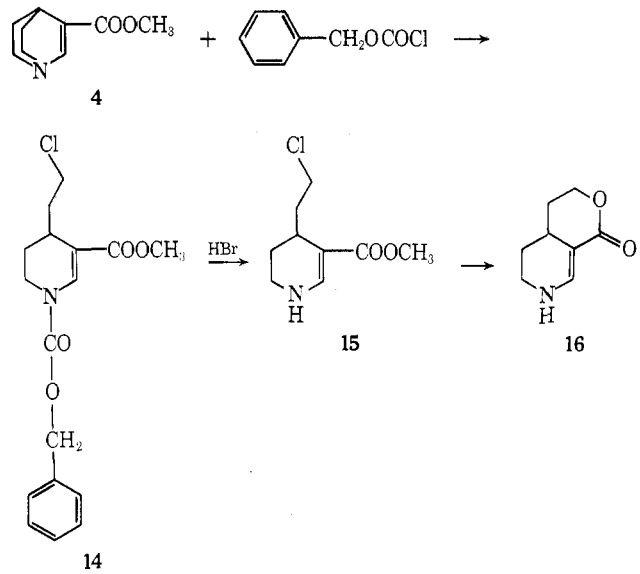
hydrochloride of 4[5] and the hydriodide of 5 smoothly rearranged to the corresponding lactones. However, the quaternary salt 1 with X = NO_3^- or ClO_4^- as well as the hydrotosylate of 4 and the hydroperchlorate of 5 did not rearrange. This indicates that the counterion is involved in the mechanism and that it must have a certain nucleophilicity either to react with 1 and form the intermediate 13 or with the hypothetical intermediate 11 in the terminating step of the reaction sequence.

The occurrence of 11 as an intermediate is supported by the observation that the alkyl halide formed is derived from the ester function of 1, since ethyl iodide could be isolated during the rearrangement of the corresponding ethyl ester.

To get further mechanistic evidence, it was necessary to determine if an ester of type 13 in Scheme II can undergo the proposed ring closure to a lactone. We therefore carried out the reaction sequence depicted in Scheme III. The unsaturated quinuclidine ester 4 was treated with benzyloxycarbonyl chloride which opened the bicyclic structure[6] and gave the carbamate 14. This was then treated with anhydrous HBr in acetic acid to remove the benzyloxycarbonyl group affording the ester 15, which at room temperature spontaneously underwent ring closure to the lactone 16. This shows that conversion of 13 into 11 is a highly favored reaction and that the intermediate 11 is unstable and spontaneously converted into the lactone at room temperature.

The experiments with counterions of different nucleophilicity as well as the reactions outlined in Scheme III support a mechanism involving an attack by the counterion as a primary step. We therefore propose, contrary to our previous report,[3] that the quaternary salts 1–3 form lactones 7–10 according to this mechanism.

Scheme III



4

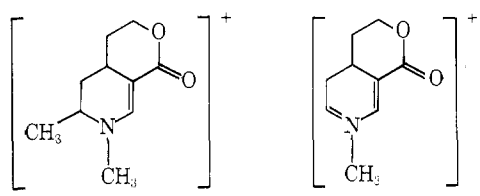
14

15

16

To determine if other parallel mechanisms were operating, several additional experiments were carried out. Rearrangements *via* mechanisms involving formation of a radical or a carbonium ion intermediate[3] should be facilitated by alkyl substituents at the migrating carbon. We therefore decided to study the rearrangement of the C_6-methyl substituted ester 2. If the conversion of 2 occurred *via* these mechanisms, compound 9 would probably be the main product since an unpaired electron[7,8] or a positive charge[7] reside preferably on a secondary carbon. Rearrangement of 2 yielded a mixture of two products present in a ratio of 4:1.

Crystallization gave the pure main product. The ir and uv spectra indicate that the compound is an enamino lactone.[9] The nmr spectrum is consistent with the lactone 8. It shows, among other signals, a multiplet at 4.4–4.1 ppm (2 H) due to the $-CH_2O-$ protons of the lactone ring and a doublet at 1.29 ppm (3 H) corresponding to the C_6-methyl protons. Structure 8 was also confirmed by the mass spectrum which shows a molecular ion at *m/e* 181 (rel intensity 100%) and a diagnostically valuable peak at *m/e* 166 (53%) due to an α cleavage[10] to fragment 8a. Other fragments are presented in the Experimental Section.

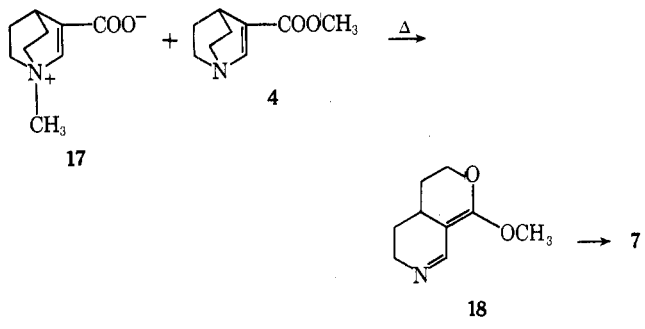


8. *m/e* 181 8a, *m/e* 166

The mass spectrum of the minor component is very similar to that of 8. It shows the ion at *m/e* 181 (79%) but the peak at *m/e* 166 has only an intensity of 8%, indicating that the 6 position of the molecule is unsubstituted. The mass spectrum is therefore consistent with structure 9. This structure is also supported by the observation that the mass spectra of 7, 8 and 16, all with the structure $-CH_2OCO-$ in the lactone ring, have a peak at M − 31, whereas this fragment is not formed from the lactones 9 and 10 which have a methyl-substituted lactone ring. The appearance of compound 9 as a minor conversion product from 2, as well as from 5, indicates that a radical or a carbonium ion mechanism is not involved to a major extent in the rearrangements depicted in Scheme I.

As indicated in Scheme I, bases 4–6 are rearranged to lactones. Thus, we observed that the base 4 was converted

Scheme IV



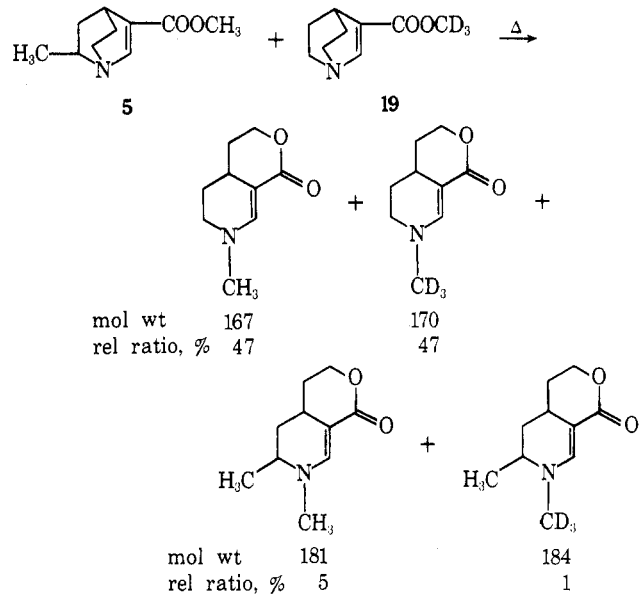
into **7** in 75% yield when heated for 30 min at 200° (Scheme IV). Similar to the rearrangement of the quaternary compound **2**, the C_6-methyl substituted base **5**, upon heating gave a mixture of the lactones **8** and **9** in a ratio of 4:1. Under the conditions used for the rearrangement of the quaternary compounds **1** and **2** no reaction occurred. It is also of interest to note here that the hydrotosylate of **4** (above) gave lactone **7** when heated at 200° for 30 min. The same lactone was also formed from betaine **17** under these conditions. In these cases, no reaction occurred at 150° for 10 min.

For the tertiary base **4**, successive sigmatropic rearrangements to the intermediate **18** was considered as a possibility. To form the lactone **7**, the methyl group of **18** would migrate from the oxygen to the nitrogen. To test this possibility of intramolecular methyl migration we heated an equimolecular mixture of the two bases **5** and **19** at 200° for 30 min (Scheme V). The reaction mixture was analyzed by mass spectrometry and this revealed the presence of all the four possible lactones (Scheme V) showing that an intermolecular reaction had taken place.

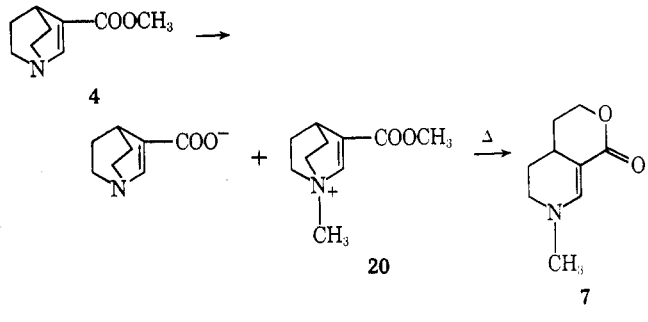
We have previously shown[3] that the lactones **9** (from **2** or **5**) and **10** (from **3** or **6**) cannot be formed *via* sigmatropic rearrangements. It therefore seems reasonable to exclude the sigmatropic rearrangements from the discussion.

An alternative mechanism for the lactone formation from the ester **4** is outlined in Scheme VI. The basic nitrogen in one molecule is attacking the ester methyl group of another molecule forming the quaternary salt **20**. The cation of this ion pair is then rearranged to the lactone according to Scheme II, and the nucleophilic species involved in the reaction is probably the carboxylate ion of **20**. This is supported by the observation given above, that the betaine **17** is rearranged to **7** at 200° for 30 min. The carboxylate ion can thus function as a nculeophile in this reaction. Similarly, we could also show that the perchlorate of **1** (X = ClO_4^-) is rearranged at 150° for 10 min if small amounts of the base **4** are added. Under these conditions neither the pure base nor the pure perchlorate is rearranged to the lactone. We therefore propose that the bases **4–6** are converted into the lactones **7–10** by the reaction presented in Scheme VI, a sequence closely related to the mechanism proposed in Scheme II for the rearrangement of the quaternary salts **1–3**.

Scheme V



Scheme VI



Experimental Section

General Comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Ir spectra were run on a Perkin-Elmer 457 spectrophotometer. Uv spectra were measured on a Perkin-Elmer 402 spectrophotometer and a Zeiss PMQ II Spectralphotometer. Nmr spectra were measured with a Varian Associates A-60 instrument using $CDCl_3$ solutions. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded using an LKB 9000 apparatus at 70 eV. Microanalysis were performed in the laboratories of Dr. A. Bernhardt Mülheim, Germany. Methyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (**1**) and methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (**4**) were prepared as previously described.[4]

3-Ethoxycarbonyl-3-hydroxyquinuclidine. 3-Cyano-3-hydroxyquinuclidine[5] was hydrolyzed, and the acid was esterified with ethanol by the methods used in the preparation of 3-methoxycarbonyl-3-hydroxyquinuclidine.[5] This yielded the title compound in 77% yield; mp 117–119° (from chloroform–pentane). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.60; N, 7.03. Found: C, 60.2; H, 8.63; N, 7.20.

Ethyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate hydrochloride was prepared by $SOCl_2$ treatment[5] of the above hydroxy ester; yield 69%, mp 149–151° dec (from acetone). *Anal.* Calcd for $C_{10}H_{15}NO_2 \cdot HCl$: C, 55.2; H, 7.41; N, 6.44. Found: C, 54.8; H, 7.69; N, 6.32.

Ethyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide was prepared from the above ester as described for **1**,[4] mp 128–129° dec. *Anal.* Calcd for $C_{11}H_{18}INO_2$: C, 40.9; H, 5.57; N, 4.33 Found: C, 40.8; H, 5.59; N, 4.45. Rearrangement of this compound gave the lactone **7** with concomitant evolution of ethyl iodide.

Methyl 1,6-dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (2) was prepared from methyl 6-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate **5**[11] as described for **1**;[4] yield 77%; mp 134–135° dec (from acetone); ir (KBr) 1730 (C=O) and 1660 cm^{-1} (C=C); uv (EtOH) 221 nm (ϵ 16,400); nmr δ 7.75 (s, 1 H, vinylic), 3.90 and 3.80 (s, 3 H each, NCH_3 and $-COOCH_3$), 1.77 (d, J = 6.5 Hz, 3 H, CCH_3). *Anal.* Calcd for $C_{11}H_{18}INO_2$: C, 40.9; H, 5.60; N, 4.35. Found: C, 40.7; H, 5.58; N, 4.33.

Methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide was prepared as described for **1**,[4] mp 95–96° dec. *Anal.* Calcd for $C_{12}H_{18}INO_2$: C, 43.0; H, 5.41; N, 4.18. Found: C, 43.0; H, 5.25; N, 4.31.

Methyl 1-propynyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate bromide (12) was also prepared as described for **1**,[4] mp 123–124° dec. *Anal.* Calcd for $C_{12}H_{16}BrNO_2$: C, 50.4; H, 5.64; N, 4.90. Found: C, 50.8; H, 5.55; N, 4.71.

Methyl 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (1) as Nitrate or Perchlorate. The iodide **1** was dissolved in

methanol and stirred with 1 equiv of silver nitrate or silver perchlorate over night at room temperature. Filtration and evaporation of the solvent yielded the crystalline salts, mp 102–103° (nitrate) (from methanol) and 138–139° (perchlorate) (from methanol–ether). The nitrate was very hygroscopic, but the perchlorate could be subjected to elementary analysis. *Anal.* Calcd for $C_{10}H_{16}ClNO_6$: C, 42.7; H, 5.74; N, 4.97. Found: C, 42.8; H, 5.75; N, 4.88.

Methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (1) hydrotosylate was obtained by precipitating the salt from an ether solution of **4**, mp 118–120° (from ethanol–ether). *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.7; H, 6.24; N, 4.13. Found: C, 56.6; H, 6.26; N, 4.09.

Methyl 1-Benzyloxycarbonyl-4-(2-chloroethyl)-1,4,5,6-tetrahydronicotinate (14). Compound **4** was treated with benzyloxycarbonyl chloride using the procedure described for quinuclidine and phenyl chloroformate by Hobson and McCluskey.[6] This yielded the title compound in 78% yield as an oil which could not be distilled: ir (film) 1720, 1690, 1630 cm^{-1} (C=O and C=C); nmr ($CDCl_3$) δ 7.96 (s, 1 H, vinylic), 7.20 (s, 5 H, ArH), 5.20 (s, 2 H, $ArCH_2O$–), and 3.58 ppm (s, 3 H, OCH_3). The peaks due to other protons were not well resolved. *Anal.* Calcd for $C_{17}H_{20}NO_4Cl$: 60.5; H, 5.97; N, 4.15. Found: C, 60.3; H, 5.95; N, 4.02.

Methyl 4-(2-Chloroethyl)-1,4,5,6-tetrahydronicotinate (15). Compound **14** was dissolved in glacial acetic acid containing 30% anhydrous HBr, and this was left at room temperature for 4 hr. The hydrobromide was then precipitated as an oil by addition of anhydrous ether. The compound was very hydroscopic and could not be obtained in solid form; ir (film) 1730 cm^{-1} (C=O). *Anal.* Calcd for $C_9H_{14}ClNO_2 \cdot HBr \cdot H_2O$: C, 35.7; H, 5.66; N, 4.60. Found: C, 35.4; H, 5.61; N, 4.30. Attempts to convert the hydrobromide into the free base yielded the lactone **16** within a few hours at room temperature. Compound **16** was identified by melting point and spectroscopic comparisons with an authentic sample.[12]

1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate 17. A solution of methyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide[3] (0.7 g) in water (2 ml) was applied to a hydroxyl saturated ion-exchange column (Dowex 1-X8, 50–100 mesh) (10 g). The column was eluted with water and the fraction containing **12** as indicated by a Uvicord II uv absorptiometer was collected and evaporated to yield the carboxylate **12** in 91% yield as a crystalline material, mp 260° dec (from ethanol). *Anal.* Calcd for $C_9H_{13}NO_2 \cdot H_2O$: C, 58.4; H, 8.16; N, 7.56. Found: C, 58.5; H, 7.82; N, 7.47.

3-Cyano-3-hydroxy-6,8-dimethylquinuclidine. This compound was prepared from 6,8-dimethyl-3-quinuclidinone[13] according to Grob and Renk;[5] yield 89%, mp 152–154° (from ethyl acetate). The compound showed a tendency to lose HCN, and it was therefore identified by its ir, and mass spectra: ir (KBr) 2230 cm^{-1} (C≡N); mass spectrum *m/e* (rel intensity) 180 (3, $M\cdot^+$), 165 (3), 153 (2), 125 (50), 110 (63), 83 (22), 70 (25), 68 (24), 57 (20), 56 (100), 55 (25).

3-Methoxycarbonyl-3-hydroxy-6,8-dimethylquinuclidine was prepared from the above hydroxynitrile as described for 3-methoxycarbonyl-3-hydroxyquinuclidine;[5] yield 87%, mp 136–137° (from carbon tetrachloride). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 8.98; N, 6.57. Found: C, 61.7; H, 8.78; N, 6.45.

Methyl 6,8-dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (6) was prepared from the above hydroxy ester using $SOCl_2$;[5] yield 70%, mp 36–38°. *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.78; N, 7.18. Found: C, 67.4; H, 8.65; N, 7.03.

Methyl 1,6,8-Trimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (3) was prepared from the above ester as described for **1**;[4] yield 88%; mp 153–154° dec (from acetone–ether); ir (KBr) 1730 (C=O) and 1655 cm^{-1} (C=C); uv (EtOH) 221 nm (ϵ 17,300). *Anal.* Calcd for $C_{12}H_{20}INO_2$: C, 42.7; H, 5.98; N, 4.15. Found: C, 42.6; H, 5.60; N, 3.81.

Azabicyclo[2.2.2]oct-2-ene-3-carboxylic Acid Hydrochloride. An aqueous solution of **4** hydrochloride (250 mg; 1.2 mol) was converted into its acid, using a basic ion-exchange Dowex-1 column (2 × 100 cm), and the acid was eluted with 2 *N* HCl (100 ml). Evaporation gave colorless crystals: mp 193–194° dec (from methanol); 250 mg (98% yield); ir (KBr) at 3380 ($^+$NH), 3050 (C=CH), 1700 (C=O), and 1600 cm^{-1} (C=C). *Anal.* Calcd for $C_8H_{11}NO_2 \cdot HCl$: C, 50.7; H, 6.38; N, 7.46. Found: C, 50.9; H, 6.61; N, 7.41.

Methyl-d_3 1-Azabicyclo[2.2.2]oct-2-ene-3-carboxylate (19). A solution of the above acid (190 mg, 1 mmol) was dissolved in CD_3OD (1 ml), and dry HCl gas was passed through for a few minutes. The reaction mixture was then kept at room temperature for 60 hr. The excess CD_3OD was evaporated under vacuum yielding a white solid residue (189 mg, 99%): mp 178–179° (from MeOH); ir (KBr) at 3380 ($^+$NH), 3020 (C=CH), 2160 and 2060 (CD), 1710 (C=O), 1300 and 1290 ($COCD_3$), and 740 cm^{-1} (C=CH). The free base was obtained as an oil, purified by a thick layer chromatography on silica gel G [ether–methanol, (8:2)]: ir (film) at 3030 (C=CH), 2240, 2180, and 2070 (C—D), 1710 (C=O), 1605 (C=C), 1290 and 1270 cm^{-1} ($COCD_3$). Mass spectrum showed a molecular ion peak at *m/e* 170.

General Procedure for the Rearrangements. The quaternary compounds were rearranged to the lactones when heated without solvent to 150° for 1 min.[3] To ensure complete reaction some compounds were heated for 10 min. Under these conditions, tertiary bases **4–6** were unchanged. These compounds could be rearranged by prolonged heating at higher temperature, usually 30 min at 200°, and purified by column chromatography as previously described.[4] The lactones formed were crystallized from ethyl acetate and were obtained in 70–90% yield. The lactones were identified by elementary analysis and ir and uv spectra. An extensive investigation of the spectral properties of lactones of type **7** and related compounds have been described in a previous paper.[9] The rearrangement of a few special compounds will be discussed below in detail.

Rearrangement of 1,6-Dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Iodide (2). The rearrangement was carried out as described above. Gas chromatography (Aerograph 1700 with a 6 ft × ⅛ in. i.d. glass column filled with 5% SE-30 on Gas-Chrom P, 100–120 mesh. Flow rate (25 ml of N_2/min, temp 160°) of the crystalline material obtained indicated the presence of two compounds in a ratio of 4:1. Recrystallization from ether gave the pure main product (73% yield), mp 82–84°. The structure elucidation was based on the data presented: ir (KBr) 1670 and 1590 cm^{-1} (C=O and C=C);[9] uv (EtOH) 305 nm (ϵ 21,400); nmr δ 7.55 (1 H, d, J = 2 Hz, C=CH), 4.4–4.1 (2 H, m, CH_2O–), 2.96 ppm (3 H, s, NCH_3), and 1.29 ppm (3 H, d, J = 6.5 Hz, CCH_3); mass spectrum *m/e* (rel intensity %) 181 (100 $M\cdot^+$), 166 (53), 150 (11), 137 (27), 122 (33), 109 (30), 108 (45), 94 (24), 44 (34), 42 (54). These data are consistent with structure **8**. Using combined glc–mass spectrometry, a mass spectrum was obtained on the minor product. This shows *m/e* (rel intensity %) 181 (79 $M\cdot^+$), 166 (8), 137 (20), 136 (18), 122 (35), 109 (28), 108 (19), 94 (35), 44 (100). This is consistent with structure **9**. The same compounds (**8** and **9**) were obtained in the same ratio (4:1) when **5** was heated at 200° for 30 min.

4-(2-Hydroxyethyl)-1,4,5,6-tetrahydro-1-propynylnicotinic Acid Lactone. This compound was obtained in 82% yield by rearrangement of methyl 1-propynyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate bromide: mp 121–122°; uv (EtOH) 300 nm (ϵ 22,500); ir (KBr) 3210 (C=CH), 2110 (C=C), 1660 and 1580 cm^{-1} (C=O and C=C). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.1, H, 6.85; N, 7.33. Found: C, 69.3; H, 6.55; N, 7.09.

1-Allyl-4-(2-hydroxyethyl)-1,4,5,6-tetrahydronicotinic Acid Lactone. This compound was obtained in 80% yield by rearrangement of methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide: mp 95–97°; uv (EtOH) 304 nm (ϵ 24,800); ir (KBr) 1670, 1640, and 1575 cm^{-1} (C=O and C=C). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.82; N, 7.25. Found: C, 68.6; H, 7.58; N, 7.33.

Rearrangement of 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate 17. This compound was heated in a sealed ampoule at 200° for 30 min. The dark product was purified by column chromatography as previously described.[4] The compound thus obtained (75% yield) had identical spectral properties and melting point as an authentic sample[4] of **7**.

Rearrangement of Methyl 1,6,8-Trimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Iodide (3). The reaction was carried out as described above. The product was obtained in 64% yield; mp 124–126° (from ether); ir (KBr) 1670 and 1595 cm^{-1} (C=O and C=C);[9] uv (EtOH) 308 nm (ϵ 24,100); nmr δ 7.62 (s, 1 H, vinylic) 4.8–4.1 (m, 1 H, =CHO–), 3.9–3.2 (m, 1 H, =CHN=), 2.97 (s, 3 H, NCH_3), 2.3–1.7 (m, 2 H, aliphatic ring protons), 1.38 and 1.27 ppm (d, 3 H each, J = 4 Hz, $>NCHCH_3$ and $-OCHCH_3$); mass spectrum (prominent peaks) *m/e* (rel intensity %) 196 (16), 195 (100 $M\cdot^+$), 180 (41), 151 (35), 150 (25), 138 (24), 136 (100), 108 (63), 94 (26), 42 (54). *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.6; H, 8.78; N, 7.18. Found: C, 67.5; H, 8.54; N, 7.17. These data are consistent with the lactone **10**. The same compound was obtained from **6** when this was heated at 200° for 30 min.

Rearrangement of a Mixture of 5 and 19 (Scheme V). A mix-

ture of equimolecular amounts (10 mg) of **5** and **19** was heated in a sealed tube under N_2 at 200° for 30 min. The lactone fraction was separated from unreacted starting material by tlc and analyzed by mass spectrometry. The mass spectrum showed four molecular ion peaks at *m/e* 167, 170, 181, and 184 (relative ratio: 47:47:4.7:1.3) indicating the presence of the four lactones presented in Scheme V.

Rearrangement of Methyl 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Perchlorate (1, X^- = ClO_4^-) in the Presence of Methyl 1-Azabicyclo[2.2.2]oct-2-ene-3-carboxylate (4). A mixture of 136 mg of 1 (X^- = ClO_4^-) and 81 mg of 4 was heated at 150° for 10 min. It was then treated with 3 ml of ether which after evaporation afforded 28 mg of **4**. Treatment of the crystalline residue with 5 ml of ethyl acetate, evaporation of the solvent, and recrystallization from ethyl acetate afforded 20 mg of **7**. Recrystallization of the residue from methanol yielded 85 mg of 1 (X^- = ClO_4^-). Under the above conditions, separate heating of 1 (X^- = ClO_4^-) and 4 afforded only unchanged starting material.

Registry No.—**1** iodide, 33402-77-6; **1** nitrate, 50790-74-4; **1** perchlorate, 50790-75-5; **1** hydrotosylate, 50790-76-6; **2** iodide, 33816-58-9; **3** iodide, 50790-77-7; **4**, 31539-88-5; **5**, 50790-78-8; **6**, 50790-79-9; **8**, 33689-31-5; **9**, 50790-80-2; **10**, 50790-81-3; **12**, 35593-77-2; **14**, 50790-82-4; **15**, 50790-83-5; **17**, 35645-77-3; **19**, 50790-84-6; 3-ethoxycarbonyl-3-hydroxyquinuclidine, 6238-31-9; 3-cyano-3-hydroxyquinuclidine, 6238-30-8; ethyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate HCl, 50790-85-7; ethyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide, 50790-86-8; methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide, 50883-30-2; 3-cyano-3-hydroxy-6,8-dimethylquinuclidine, 50790-87-9; 6,8-dimethyl-3-quinuclidinone, 50790-88-0; 3-methoxycarbonyl-3-hydroxy-6,8-dimethylquinuclidine, 50790-89-1; azabicyclo[2.2.2]oct-2-ene-3-carboxylic acid HCl, 50790-90-4; 4-(2-hydroxyethyl)-1,4,5,6-tetrahydro-1-propynylnicotinic acid lactone, 50790-91-5; 1-allyl-4-(2-hydroxyethyl)-1,4,5,6-tetrahydronicotinic acid lactone, 50790-92-6.

References and Notes

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1-Imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole. Reactions with Electrophiles[1]

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Intramolecular cyclization of 2-thiocyanoalkylbenzimidazole yielded the novel 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (**1**). Reaction of **1** with isocyanates gave exclusively the monoureas, **4**. Treatment of **1** with strong electrophiles (acid chlorides, tosyl chloride, and halocarbonates) furnished the derivatives **8**.

In a recent communication,[2] we reported a simple synthesis of the novel 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole ring system (**1**) by the intermolecular cyclization of 2-thiocyanoalkylbenzimidazoles, **2** (Scheme I). Our interest in medicinal aspects of compounds derived from benzimidazole[3] prompted a study of the parent compound, **1a**.

Initially, we sought solely to investigate reaction of the 1-imino group of **1a** with electrophiles. Treatment of **1a** with isocyanates yielded only the ureas, **4a–c**, rather than the enureas, **5**, that would be expected based on the results obtained by Chupp[4] with imines derived from cyclohexanone. Our efforts to synthesize the thioureas corresponding to **4** failed.

The product that resulted from heating of **1a** with acetic anhydride had an nmr spectrum that showed two methyl signals at δ 2.30 and 2.65 (DMSO-d_6) and a one-proton signal at δ 6.66 that was suggestive of a vinyl grouping. To distinguish between the two possible structures **6** and **8a**, we undertook the acid hydrolysis of this product. Whereas **6** should yield the enamino ketone **7**, hydrolysis of **8a** should furnish the cyclic thiocarbamate **9**. The nmr and ir data of the product obtained on the hydrolysis were identical with those of **9**, which was derived by acid treatment of **1a**, thus establishing the enamide structure **8a**. The postulated intermediate in this reaction, monoacetate **10**, was eventually isolated in 30% yield after we had acetylated **1a** with acetic anhydride for 3 min and quenched the reaction with water. However, even under these conditions, most of the starting material had already been converted to the diacetate **8a**. In analogous fashion we prepared enamides **8b** and **8c**, encarbamates **8d** and **8e**, and ensulfonamide **8f**. The product of hydrolysis of **1a**, namely **9** when acetylated with acetic anhydride gave the enamide **11**. Finally, monourea **4a**, when treated

Scheme I