Reactions of Aralkyl and Unsaturated Chloramines: The Nitrenium Ion Question[1]

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Received December 5, 1973

O. E. EDWARDS, G. BERNATH, J. DIXON, J. M. PATON, and D. VOCELLE. Can. J. Chem. **52**, 2123 (1974).

Evidence for intermolecular electrophilic halogenation of aromatic rings and olefinic double bonds by aliphatic chloramines at low p*H*, and for homolytic cyclization of unsaturated chloramines in neutral medium is presented. Independent proof of structure and stereochemistry of derivatives of 6-azabicyclo[3.2.1]octane and 2-azabicyclo[2.2.2]octane was provided. No evidence for involvement of nitrenium ions in the chloramine reactions was observed.

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L'évidence, d'un processus d'halogénation électrophile intermoléculaire par les chloramines aliphatiques en milieu acide, est démontrée pour les composés contenant des cycles aromatiques ou des doubles liaisons à caraitire oléfinique. Nous démontrons aussi que la cyclisation thermique des chloramines non saturées, en milieu neutre, procède de façon homolitique. Des preuves de la structure et de la stéréochimie des dérivés de l'aza-6 bicyclo[3.2.1]octane et de l'aza-2 bicyclo[2.2.2]octane sont présentées.

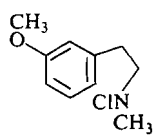
Aucune évidence de l'implication d'un ion nitrénium dans ces réactions de chloramines ne fut observée. [Traduit par le journal]

Some time ago we concluded that nitrenium ions (R_2N^+) could be generated from aliphatic chloramines using silver ions in polar solvents (1). However, subsequent work showed that the reactions were mainly homolytic (2) and that near room temperature simple aliphatic chloramines do not react at an appreciable rate with silver ions. It occurred to us that if there were any tendency for silver-promoted ionization of the N—Cl bond as in eq. 1, the presence of a nucleophilic aromatic ring might assist in the ionization and result in amination of the ring. Again, however, mixtures of silver nitrate and *N*-chloropiperidine with 2-methoxynaphthalene or anisole in methanol reacted very slowly at room temperature. A mixture of diethylchloramine and silver perchlorate in anisole was inert at room temperature, and at 65° no diethylaminoanisoles were produced.

[1] $$R_2\ddot{N}Cl\cdots Ag^+ \rightarrow R_2\ddot{N}^+ + AgCl$$

In order to enhance the chance of electrophilic attack on the aromatic nucleus by developing nitrenium ions, we next examined the reactions of *N*-chloro-2′-methylamino-3-methoxyphenylethane (**1**) and *N*-chloro-3′-methylamino-3-methoxyphenylpropane (**2**). These proved inert at room temperature to silver perchlorate in benzene, and silver nitrate in methanol or acetonitrile, provided the p*H* was above 5. Reaction of **1** and **2** with silver perchlorate in benzene was slow (*ca.* 20% per hour) even at reflux temperature and only traces of tertiary amines were formed.

At low p*H* electrophilic chlorination of the aromatic nuclei became rapid. Anisole and *N*-chloropiperidine in methanol containing *p*-toluenesulfonic acid gave *O*- and *p*-chloroanisoles in the ratio 1:2. This is the ratio for attack on the nucleus by cationic chlorine as distinct from homolytic chlorination (3). 2-Methoxynaphthalene gave 1-chloro-2-methoxynaphthalene in high yield under similar conditions and chloramines **1** and **2** gave mixtures of nuclear chlorinated products.



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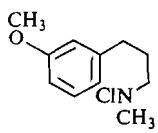

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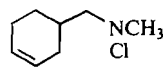

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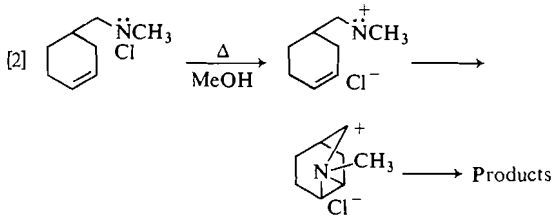
Thus we had again failed to demonstrate any tendency of aliphatic N—Cl bonds to ionize toward nitrenium ions even with silver ion assistance and the proximity of nucleophilic aromatic nuclei. However, Gassman and co-workers have claimed that nitrenium ions are important in a variety of chloramine solvolyses in hot polar solvents (4, 5*a*). Among these cases were reports of a π route to azabicyclic compounds (*e.g.* eq.

[1]Issued as NRCC No. 13880. Presented in part at the Symposium on Heterocyclic Chemistry, Poznan, July 24–26, 1972.

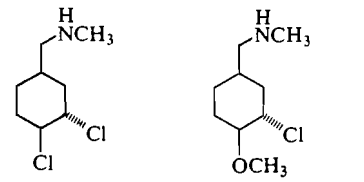
[2]NRCC Postdoctorate Fellows.



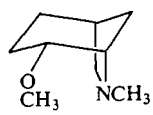
2). Since such cyclic products could have arisen by (*a*) electrophilic chlorination followed by cyclization or (*b*) by homolytic fission of the N—Cl bonds followed by cyclization, we decided to reexamine these reactions.

At room temperature in methanol *N*-chloro-4-methylaminomethylcyclohexene (**3**) was inert in the presence of silver salts provided the p*H* was above 5. At reflux temperature the initial reaction was slow and the major product (70%) was parent amine.

When chloramine **3** was treated at 5 °C with *p*-toluenesulfonic acid in methanol a rapid reaction ensued. Unless more than 1 molar equiv. of acid was present the reaction ended when the acid was neutralized by products. With excess acid, the chloramine reacted completely in 2 h at room temperature. The mixture of salts of the initial products was converted to the free bases, then a methanol solution of these refluxed. The bases **4** (if present) and **5** cyclized to give *N*-methyl-4-



4 **5** **6**



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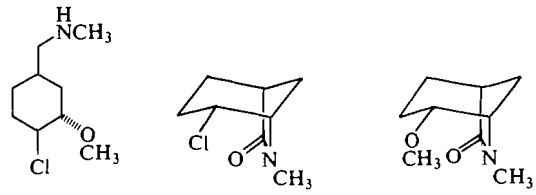
endo-chloro-6-azabicyclo[3.2.1]octane (**6**) and *N*-methyl-4-*endo*-methoxy-6-azabicyclo[3.2.1]octane (**7**). The remaining base, which did not cyclize, was separated and characterized as its *N*-acetyl derivative. It was assigned the structure *N*-methyl-*cis*-4-chloro-*trans*-3-methoxy-1-aminomethylcyclohexane (**8**) on the basis of analysis, spectra, and the failure to cyclize. The location of the substituents is surmised on mechanistic grounds (see Discussion).

The best yield of **6** was 7%. Its structure and stereochemistry were deduced from its failure to

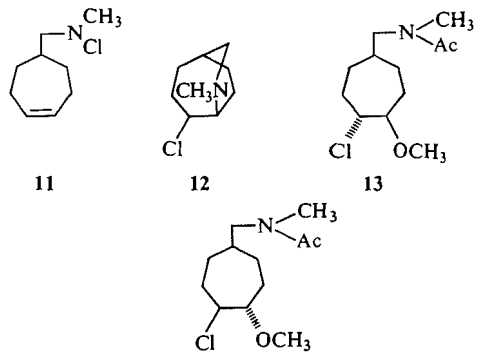


8 **9** **10**

cyclize, and its oxidation to the γ-lactam **9** (ν_{max} ($CHCl_3$) 1690 cm^{-1}). The best yield of **7** was 32%. Its nonidentity with the *trans* isomer (see below) and its oxidation to a γ-lactam (**10**) proved its structure and stereochemistry.

If the total base from the acid-catalyzed reaction of **3** in methanol was isolated under mild conditions, then acetylated, the only tertiary base found was **6** (7.5%). It was shown that the *N*-acetyl fraction contained derivatives of **5** and **8**.

When *N*-chloro-*N*-methyl-5-aminomethylcycloheptene (**11**) was decomposed by *p*-toluenesulfonic acid in methanol and the basic products refluxed in methanol very little bicyclic material formed. A 0.02% yield of the chlorobicyclic base **12** (*N*-methyl-*cis*-4-chloro-6-azabicyclo[3.2.2]-nonane) was isolated as its perchlorate but the small amount of methoxybicyclic base was not obtained pure. The main products were secondary bases, isolated as their *N*-acetyl derivatives. The mixture analyzed approximately correctly for **13** (and/or **14**) and its n.m.r. spectrum was consistent with these structures.



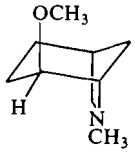
11 **12** **13**

14

We next studied the thermolysis of **3** and **11** in pure methanol under nitrogen. In each case the reactions at reflux temperature showed a marked induction period (1–3 h before reaction began) followed by fairly rapid decomposition of the chloramine (Fig. 1). This is characteristic of homolytic reactions. In accord with this, the presence of around 1 mol% of benzoyl peroxide eliminated the induction period (Fig. 1). In the

case of **3** the product composition was identical with or without the peroxide. However, in the case of **11** the product ratios changed moderately when the initiator was present. If the thermolysis was conducted under oxygen the reaction was markedly slowed (Fig. 1) and the major product became parent secondary amine.

The main products from **3** were the same as described by Gassman and Dygos (5), *N*-methyl-4-*endo*-chloro-6-azabicyclo[3.2.1]octane (**6**) (13%), *N*-methyl-4-*exo*-methoxy-6-azabicyclo[3.2.1]octane (**15**) (18%), *N*-methyl-*trans*-6-methoxy-2-azabicyclo[2.2.2]octane (**16**) (27%), and parent amine (14%). In addition traces of two volatile tertiary bases, probably **17** and **18**, and 15% of higher boiling bases were produced.



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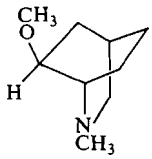

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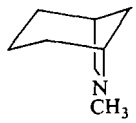

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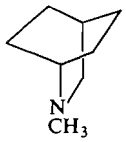

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The structure and stereochemistry that had been assigned to **15** and **16** (5) was confirmed by independent synthesis from cyclohex-1-ene-3-carboxylic acid using acyl nitrene cyclization (6) (Scheme 1).

The ring system in **17** and **20** was deduced on the basis of the carbonyl stretching frequency (γ- and δ-lactam, respectively) (7).

The cycloheptene analogue **11** similarly gave parent amine (3.5%), the bicyclic chloro base **12** (4.5%), and a methoxy bicyclic base (25%). By

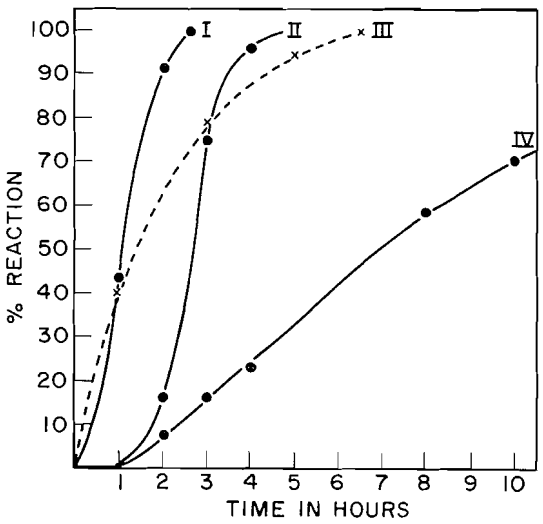
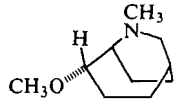


FIG. 1. Reaction of **3** in methanol: (I) reflux, 1 mol % perbenzoic acid, N_2; (II) reflux, N_2; (III) Ag^0, 25 °C, N_2; (IV) reflux, O_2.

analogy to the cyclohexene case this was assigned the structure *N*-methyl-*trans*-4-methoxy-6-azabicyclo[3.2.2]nonane (**21**).



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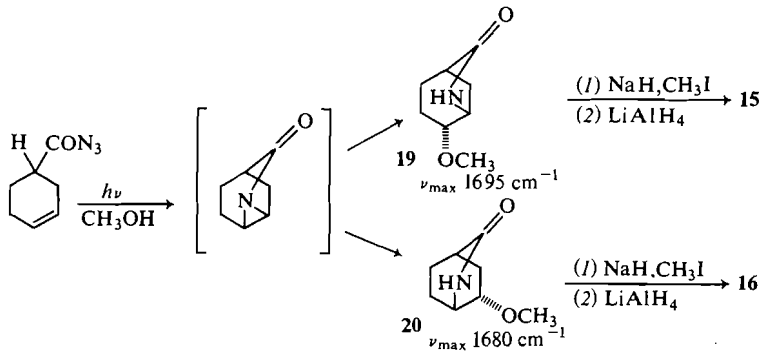
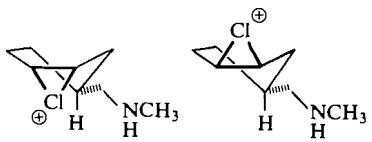
In view of the relatively efficient production of amine radicals from medium ring chloramines by Tollens' silver reported earlier, the action of this reagent on a number of the above-mentioned chloramines was studied. In all cases the major product was the parent amine.

Discussion

The electrophilic chlorinations are mainly understandable in terms of transfer of positive chlo-

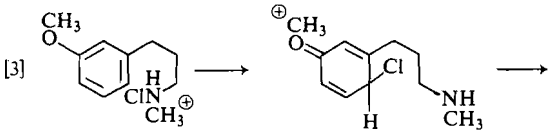


SCHEME 1

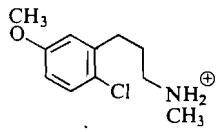


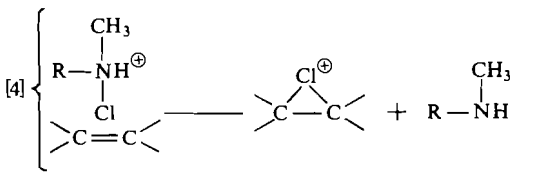
22 23

rine from protonated chloramine to aromatic rings or double bonds (eqs. 3 and 4).



[3]



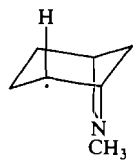


[4]

Diaxial opening by methanol of the two chloronium ions **22** and **23** from **3** would give the two methoxy–chloro bases **5** and **8**, respectively. The fact that both are formed in similar yields shows that intermolecular reaction is dominant.

We cannot exclude the possibility that some chlorine was produced as the reactions progressed, formed by the action of chloramines on small amounts of chloride ion produced in cyclization reactions. Indeed, the hydrochloride of *N*-methyl-4-aminomethylcyclohexene in methanol containing *p*-toluenesulfonic acid reacted rapidly with chlorine, giving after work-up the three main products found in the acid-catalyzed reaction of the chloramine. However, the minor amounts, if any, of **7** and **8** in the thermal and benzoyl peroxide-initiated reactions show that free chlorine plays no significant role in these reactions.

The chlorobicyclic base **6** could arise in the acid-catalyzed reactions by cyclization of **4**, which could arise by chloride ion attack on chloronium ions **22** or **23**. Since, however, **6** is the only bicyclic product formed unless the basic products are heated in methanol, this would demand that **4** would cyclize very much faster than **5**. An alternate possibility is that a small homolytic



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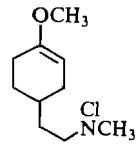

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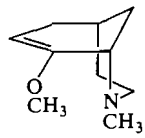

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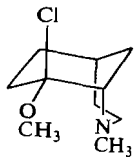

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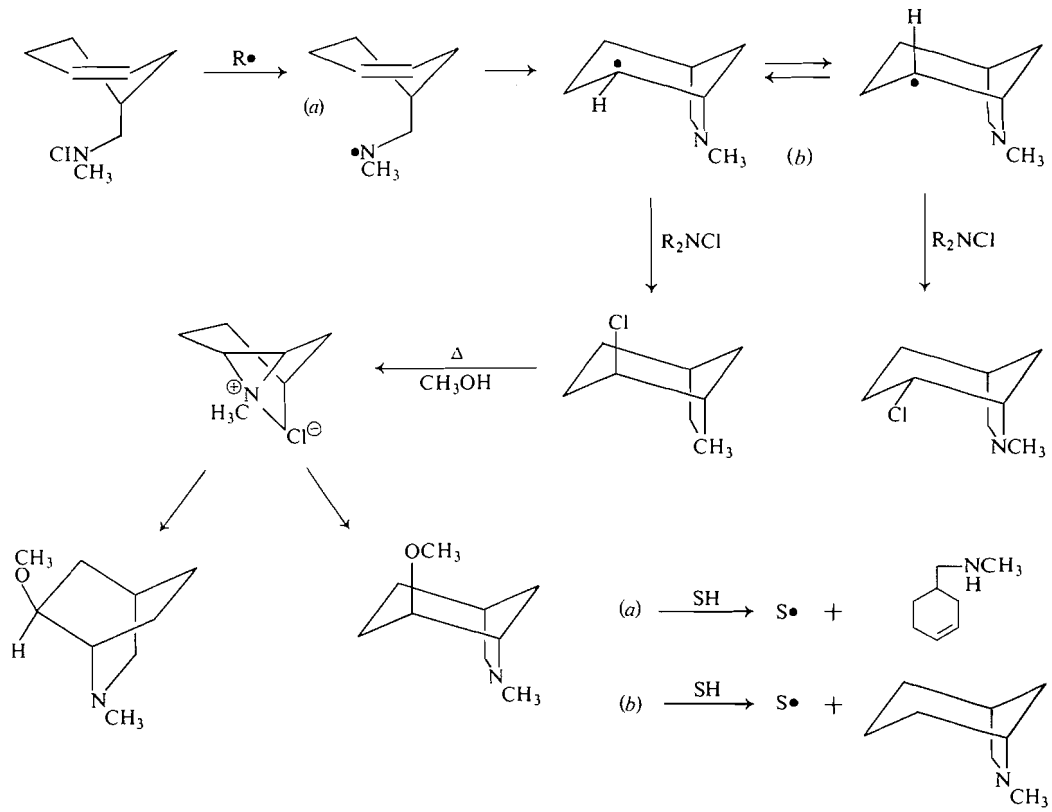
component of reaction leads to the bicyclic radical **24**, which gives both the *cis*- and *trans*-chloro compounds. The latter could be lost during work-up (via aziridinium ion to water-soluble hydroxy base).[3]

While our studies of the acid-catalyzed reactions of **3** were in progress, Gassman and Dygos (*5b*) published an account of similar reactions of **3** in aqueous acid. However, they interpreted the reactions as involving discrete Cl^+ ions. The recent observations of Waegell and co-workers on chloramines containing enol ether functions (8) parallel nicely the above electrophilic chlorination of **3**. Surprisingly, however, they encountered predominant electrophilic chlorination in the thermal reaction of **25** in methanol without added acid. This is probably a consequence of the high nucleophilic potential of the enol ether. Contrary to their conclusions, however, we consider the origin of the bicyclic enol ether **26** formed during the initial reaction to be the chloromethoxy compound **27** produced in a radical process.

Neale and Marcus described acid catalyzed intermolecular electrophilic chlorination of olefins by chloramines but interpret these as Cl^+ ion reactions rather than direct transfer of chlorine from protonated chloramine to olefin (9). However, Hickinbottom and co-workers (10) have presented evidence that chlorination of aromatic nuclei by protonated *N*-chloroacetanilides in the absence of chloride ion is direct electrophilic chlorination. Chloroaminations of double bonds catalyzed by aluminum chloride have been described by Kovacic and Lowery (11) and Waegell and co-workers (12). Whereas these reactions could be interpreted as involving initial

[3]Prof. J. D. Hobson (personal communication) and co-workers have observed this selective loss in related work.



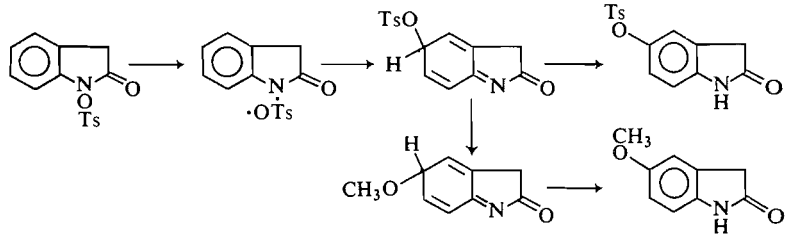
SCHEME 2

attack by Cl^+ ions (13), addition as nitrenium ion – $AlCl_4^-$ pairs is also possible in view of the molecular rearrangements observed under the influence of the same catalyst (14–20).

It is clear from the complete difference in the methoxybicyclic products between the acid-catalyzed and thermal reactions of **2** and **11** that a different mechanism is operative in the latter. The observed induction period, the retardation by oxygen, and the acceleration of reaction by radical sources such as benzoyl peroxide demonstrate that the thermal reactions are homolytic. The mechanism in Scheme 2 accounts for all the observed products and their stereochemistry. Hobson and co-workers have reached the same conclusion in their work on cyclooctene derivatives (21). They also showed that oxygen or *N,N*-diphenylpicrylhydrazyl markedly slowed the thermal decomposition. Parallel cyclizations of **3** and its close relatives have been described by Surzur and co-workers (22) using redox systems or photolysis to generate the nitrogen-centered radical, and by Chow and Perry (23) using photolysis of the related *N*-chloro- and *N*-nitrosoamides.

We conclude that nitrenium ions are not formed from simple aliphatic chloramines near room temperature, even when double bonds or aromatic rings are available to provide anchimeric assistance, and silver ions are present to assist ionization. In addition, no heterolytic fission takes place at 60–80 °C, decomposition at these temperatures only being initiated by traces of adventitious radicals. Possible homolytic mechanisms can be written for other reactions considered to involve nitrenium ions. For example, arenesulfonyloxy radicals have been shown to be good electrophilic reagents (24), hence the *N*-tosyloxyoxindole reactions (25) may be formulated as in eq. 5. However, the molecular rearrangements observed by Gassman (26), Kovacic and co-workers (19), Wasserman and co-workers (20), and by Rautenstrauch (27) seem best explained as involving assisted ionizations in the $>N^+\cdots Cl^-$ sense.

We had hoped that silver metal would provide

[5] 

us with a room temperature preparation of the various nitrogen radicals, as in the reactions with medium ring chloramines (2). However, the major products were the parent secondary amines. This could have been rationalized if the initial nitrogen-centered radicals were reduced by excess silver to the anion (eq. 6).[4] This is in ac-

$$[6]\quad >N\cdots Cl + Ag^0 \rightarrow >N\cdot + AgCl \xrightarrow{Ag^0} >N^- + Ag^+$$

cord with our observation of reduction of succinamidyl radical to the anion by silver (28). However, nearly 1 equiv. of silver chloride was produced (few chain reactions) and no other Ag(I) products were formed. Hence we must conclude that most of the nitrogen-centered radicals produced in this way are unable to cyclize before abstracting hydrogen from solvent and that the reduction shown in eq. 6 does not take place.

Mass Spectra

We had hoped that electron impact mass spectra would distinguish between the bicyclo[3.2.1] and bicyclo[2.2.2] structures, and possibly between the epimers **7** and **15**. In actuality, the spectra of all three components (**7**, **15**, and **16**) were very similar down to *m/e* 82 (Table 1). Since

TABLE 1. Relative abundance of ions

	Base		
m/e	**7**	**15**	**16**
155	15	14	29
140	25	33	81
97	6	9	40
96	21	26	49
94	12	14	27
82	100	100	100
72	140	165	23
57	175	159	35

[4]We thank Prof. J. D. Hobson who independently suggested this possibility.

this ion most probably has the structure **28** (see also refs. 29 and 30), we were unable to convincingly account for its formation from **16**, hence we proved the structure of **16** as described above. The probable origin of the more abundant ions with higher masses is outlined in Scheme 3. It now

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appears that the ions at *m/e* 72 and 57 are the most characteristic features from the two bicyclo[3.2.1] bases. These ions are unimportant for the parent heterocycle (29) and of low abundance in the spectrum of **16**. We account for them as shown in Scheme 4. The stereochemistry of the methoxyl group in **7** and **15** only makes a small difference in the fragmentation (see also ref. 29). As anticipated on the basis of more advantageous stereoelectronic factors, the ratio of *m/e* 140 to the parent ion was higher for the *trans* isomer (2.3) than for the *cis* (1.7).

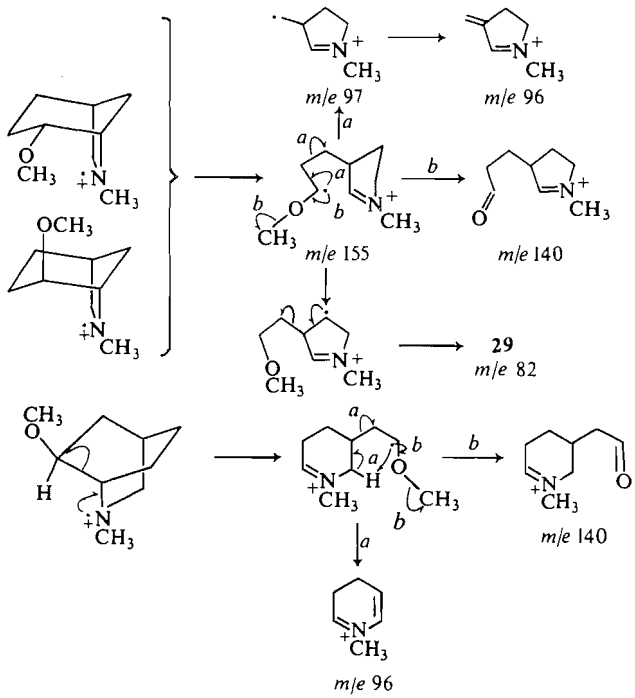
Experimental

The i.r. spectra were obtained using a Perkin-Elmer model 257 grating spectrometer, and n.m.r. spectra on a Varian A60A spectrometer. Mass spectra were obtained using a Perkin Elmer-Hitachi single-focussing instrument. The g.l.c. analyses of amines were done using a 6 ft × ¼ in. column of OS-138 (polyphenyl ether, 20%) on Chromosorb and preparative separations using a 6 ft × 3/8 in. column with the same packing. The yields were calculated on the assumption that peak areas using a thermal conductivity detector were proportional to the mol fraction of the very similar molecules being separated.

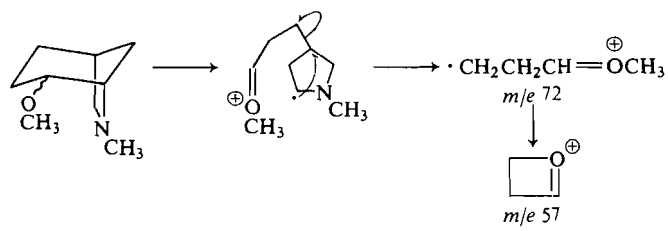
Anisole Reactions

(*i*) Two grams of diethylchloramine was added to a solution of 4 g of anhydrous silver perchlorate in 30 ml of anisole. Only a trace of silver perchlorate precipitated in 17 h at room temperature in the dark. In 3 h at 65° a heavy precipitate formed which consisted of 1.9 g of silver chloride and 3.3 g of amine perchlorate. The latter was converted to the base which was extracted into ether. On evaporation no base higher boiling than diethylamine was found.

(*ii*) A solution of 1.08 g of anisole (10 mmol) and 3.8 mg of *p*-toluenesulfonic acid (20 mmol) in 40 ml of methanol



SCHEME 3



SCHEME 4

and 5 ml of water was prepared. To this was added 1.18 g of *N*-chloropiperidine (10 mmol) in 5 ml of methanol and the mixture stirred under nitrogen in the dark. After 1 h 25% and after 5 h, 70% of the chloramine had reacted. The mixture was left overnight at room temperature, the bulk of the methanol removed under reduced pressure, and the product extracted into ether. The ether was washed with water, then with sodium carbonate solution, dried, and evaporated. The 600 mg of product recovered were demonstrated by n.m.r. spectroscopy to consist of *O*-chloroanisole (δ OCH_3 3.87) and *p*-chloroanisole (δ OCH_3 3.79) in the ratio 1:2.

2-Methoxynaphthalene and N-Chloropiperidine

(*i*) With $AgNO_3$ in methanol: to a solution of 1.58 g (10 mmol) of 2-methoxynaphthalene and 1.185 g (10 mmol) of *N*-chloropiperidine in 40 ml of methanol and 5 ml of water was added 1.7 g (10 mmol) of silver nitrate. A very slow reaction ensued (*ca.* 25% per day at first). After 1 week only a trace of chloramine was identified among the less-volatile product.

(*ii*) A solution of 1.58 g (10 mmol) of 2-methoxynaphthalene and 1.185 g of *N*-chloropiperidine in 45 ml of methanol and 5 ml of water was stirred under nitrogen for 5 h. No reaction occurred. Addition of 20 mmol of *p*-toluenesulfonic acid in 10 ml of methanol induced rapid reaction. In 10 min at room temperature only 5% of the *N*-chloropiperidine remained. After 1 h the bulk of the solvent was removed under reduced pressure, the product extracted into ether. the ether washed with sodium carbonate solution, then water, dried, and distilled. The 1.85 g of crude product was shown by t.l.c. separation of an aliquot to contain 1.64 g (85%) of 1-chloro-2-methoxynaphthalene, m.p. 68–69° (lit. (31, 32) m.p. 69°).

2′-Methylamino-3-methoxyphenylethane

This was prepared by reduction of the corresponding amide by lithium aluminum hydride in refluxing tetrahydrofuran. It gave a hydrochloride which crystallized as fine needles from ethanol – ethyl acetate, m.p. 119–120°.

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.70; H, 7.96; N, 6.96. Found: C, 59.82; H, 7.87; N, 6.97.

3'-Methylamino-3-methoxy-1'-phenylpropane

This was prepared as described for the lower homologue. Its hydrochloride had m.p. 106–107°.

Anal. Calcd. for $C_{11}H_{18}ClNO$: C, 61.25; H, 8.35; N, 6.50. Found: C, 61.43; H, 8.29; N, 6.43.

Reactions of N-Chloro-2'-methylamino-3-methoxyphenylethane (1)

(a) With Silver Nitrate in Methanol

A solution of 1.45 g of silver nitrate in 30 ml of methanol (heating) was stirred with powdered calcium carbonate to give a p*H* of near 6, then filtered. A portion (20 ml) of this was added to 431 mg (2.16×10^{-3} mol) of the chloramine (**1**). No reaction took place in 1 h at room temperature. The solution was then placed in a bath at 64° under nitrogen. The extent of reaction was: 1 h, 18%; 2 h, 43%; 3 h, 59%; 4¾ h, 78%. The heating was continued for a further 6 h to ensure complete reaction. The product isolated consisted of 259 mg of silver chloride (1 equiv. = 280 mg), 66 mg of neutral oil (aldehyde and amides), and bases which after acetylation gave 20 mg of tertiary base and 270 mg of *N*-acetyl derivative. The latter was shown by n.m.r. to be essentially pure *N*-acetyl derivative of the parent amine.

Comparable results were obtained when the reaction was done in air.

(b) With Silver Perchlorate in Benzene

A solution of 500 mg of anhydrous silver perchlorate and 329 mg (1.65×10^{-3} mol) of the chloramine in 12 ml of dry benzene gave a clear solution. No silver chloride formed in 2 h at room temperature. After 3 h at 65°, 45% of the chloramine had reacted. Reaction was nearly complete after a further 6 h heating. Silver chloride and a brown methanol-soluble solid had separated. The products isolated were 139 mg of silver chloride (1 *M*equiv. is 220 mg), 67 mg of ether-soluble neutral oil, and bases which on acetylation gave 104 mg of *N*-acetyl derivative of the parent base and 33 mg of tertiary base. In each case the neutral and tertiary base products were mixtures and because of the low yields the components were not identified.

(c) With Silver Perchlorate in Acetonitrile

One gram of anhydrous silver perchlorate was dissolved in 5 ml of acetonitrile (freshly filtered through Activity 1 alumina). The solution was added to 10 ml of dry acetonitrile containing 309 mg (1.55×10^{-3} mol) of chloramine **1**. No reaction was detected in 2 h at room temperature but after 17 h in the dark, 32% of the chloramine had reacted. Subsequent heating at 50 °C for 4 h completed decomposition of the chloramine. The products isolated were 172 mg of silver chloride (70 mol %), 81 mg of ether-soluble neutral product (amides), 14 mg of "tertiary base", and 84 mg of parent amine.

Reactions of N-Chloro-3'-methylamino-3-methoxy-1'-phenylpropane (2)

(a) With Silver Nitrate in Methanol

A solution of 888 mg of silver nitrate in 30 ml of methanol containing 1 g of powdered calcium carbonate was stirred for 20 min, then filtered. The solution was added to 0.581 g (2.73×10^{-3} mol) of the chloramine (**2**). No silver chloride separated and iodimetry showed that the chloramine was unchanged after 5 h at room temperature in diffuse light. After a further 15 h at room temperature, 4.5% of the chloramine had reacted. The mixture was then heated in a bath at 60° in semidarkness. The extent of reaction was: 1.5 h, 37%; 3 h, 58%; 6 h, 76%. It was then left for 63 h at room temperature, when only a trace of oxidizing material was left. The suspension was filtered, giving 282 mg of silver chloride (1 equiv. = 353 mg). Dilute hydrochloric acid was added to the filtrate to precipitate the excess silver ions. After filtration, the solution was adjusted to p*H* 3 and the bulk of the methanol removed under reduced pressure below room temperature. The product was separated into 101 mg of aldehyde (ν_{max} 1740 cm^{-1}, C*H*O signal a doublet at δ 9.4), 347 mg of parent amine and 28 mg of tertiary base.

(b) With Silver Perchlorate in Benzene

A solution of 1.5 g of anhydrous silver perchlorate in 20 ml of hot benzene was filtered to remove a trace of brown solid. The filtrate was added to 0.555 g (2.6×10^{-3} mol) of chloramine **2**. No silver halide formed at room temperature. In a bath at 70°, 48% of the chloramine reacted in 1.25 h, 60% in 2.25 h, and 97% in 6 h. A brown solid deposited on the walls. The products isolated from the solid and solution were silver chloride contaminated with a methanol-insoluble brown solid, 68 mg of methanol soluble ether insoluble solid and 396 mg of bases. The latter were shown by acetylation to contain 19 mg of tertiary bases and 377 mg of parent base.

(d) With Acid in Methanol

A solution of 1.11 g (5.2 mmol) of **2** and 1.9 g (10 mmol) of *p*-toluenesulfonic acid hydrate in 30 ml of methanol was left at room temperature. In 15 min, 85% of the chloramine had decomposed. After complete reaction (1 h) the products were separated by acetylation into tertiary base (*ca.* 50 mg) and *N*-acetyl secondary bases (950 mg). The latter was analyzed for chlorine.

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl, 13.86. Found: Cl, 14.06%.

Acid Catalyzed Reactions of Chloramine (3)

(*a*) A methanol solution (53 ml) containing 1.99 g (1.25×10^{-2} mol) of chloramine **3** was cooled in an ice bath. Over a period of 5 min 5 g of *p*-toluenesulfonic acid hydrate was added to the stirred chloramine solution. After a further 15 min the reaction mixture was removed from the ice bath and allowed to come to room temperature. After a total time of 1.3 h only a trace of chloramine remained (iodimetry). The remaining solution (1 ml removed for titrations) was evaporated to a syrup on a rotating evaporator. The residue was diluted with water, neutralized with sodium carbonate, made strongly alkaline with sodium hydroxide solution, then thoroughly extracted with ether. The 2.02 g of faintly yellow base was dissolved in 100 ml of methanol then the solution refluxed under nitrogen for 16.5 h during which time 3.54×10^{-3} g-atom of chloride ion was formed (29% of theory). The solution was acidified with hydrochloric acid, the methanol removed under reduced pressure and the base recovered as before. The 1.61 g of base and 2 ml of acetic anhydride was heated on the steam bath for 30 min. The excess anhydride was destroyed using methanol, then the methanol and methyl acetate removed *in vacuo*. The residue was separated into 702 mg of tertiary base and 1.05 g of *N*-acetyl derivative. The base contained three

components by g.l.c. on OS-138, corresponding to a trace of parent amine and the *cis*-methoxy base **7** and *cis*-chloro base **6** in the ratios 4.4:1. The yield of **7** was 30% and that of **6**, 7% based on chloramine used. The perchlorate of the tertiary base crystallized from ethyl acetate containing a trace of alcohol giving 761 mg of moderately pure salt of **7** (24%).

(*b*) In a run comparable to *a* using 8.7 mmol of chloramine **3** the total basic product was distilled over a short path up to 140° under 12 mm pressure. The residue weighed 263 mg. The distillate (975 mg) was acetylated, giving 509 mg (2.18 mmol, 25%) of the *N*-acetyl derivative of **8** and tertiary bases. The latter was estimated by g.l.c. to contain 92 mg (0.58 mmol, 7%) of **6** and 430 mg (2.8 mmol, 32%) of **7**. To prepare analytic specimens of the tertiary bases they were separated using an OS-138 column at 180°. The fractions were further purified as their perchlorates.

(*c*) The acid-catalyzed reaction of **3** was carried out as in *a* (97% reaction in 1.3 h). The basic products were then isolated and acetylated with acetic anhydride. The tertiary base was separated from the *N*-acetyl derivatives. It proved to be nearly pure chlorobicyclic base **6** (7.5% yield) by g.l.c. on OS-138 (picrate m.p. 215°, perchlorate m.p. 223°).

The *N*-acetyl derivative gave one main peak on g.l.c. analysis (SE-30 column) but contained a small amount of compound with longer retention time. It was distilled *in vacuo*. When 919 mg of the *N*-acetyl derivative was refluxed for 44 h in 3 ml of 6 *N* sulfuric acid the hydrolysis was incomplete. Ether extraction of the acid solution gave 109 mg of *N*-acetyl derivative. The acid layers gave 459 mg of base. The base was refluxed in methanol for 8 h, then separated into secondary and tertiary bases by acetylation (376 mg of *N*-acetyl derivative, 115 mg of fairly pure methoxybicyclic base **7**).

*cis-4-Methoxy-6-methyl-6-azabicyclo[3.2.1]octane (**7**)*

The main tertiary base from the acid catalyzed reactions gave a perchlorate which crystallized as blades from methanol – ethyl acetate, m.p. 121–122°.

Anal. Calcd. for $C_9H_{18}ClNO_5$: C, 42.28; H, 7.10; N, 5.48. Found: C, 42.26; H, 7.21; N, 5.40.

*cis-4-Chloro-6-methyl-6-azabicyclo[3.2.1]octane (**6**)*

The minor tertiary base from the acid-catalyzed reactions gave a perchlorate which crystallized from methanol – ethyl acetate, m.p. 224°.

Anal. Calcd. for $C_8H_{15}Cl_2NO_4$: C, 36.92; H, 5.81; N, 5.39; Cl, 27.31. Found: C, 36.82; H, 5.87; N, 5.31; Cl, 26.94.

The base gave n.m.r. signals at δ 3.79 (t, J = 8 Hz, with small secondary coupling), 3.05 (s, 1H), 2.93 (s, 1H), and 2.50 (s, 3H). The spectrum coincided with that of a sample of the same base, provided by Prof. Y. L. Chow.

N-Acetyl-cis-4-chloro-trans-3-methoxy(methylaminomethyl)cyclohexane

The derivative from run *a* distilled over a short path at a bath temperature of 120° under 0.01 mm as a colorless oil. It gave p.m.r. signals at δ 2.12 ($NCOCH_3$), 2.97 and 3.05 ($N—CH_3$), 3.43 (OCH_3), and 4.32 br ($CHOCH_3$). In pyridine at 60 °C the $N—CH_3$ pair of signals collapsed to a sharp singlet.

Anal. Calcd. for $C_{11}H_{20}ClNO_2$: C, 56.53; H, 8.56; N, 5.99, Cl, 15.19. Found: C, 56.37; H, 8.70; N, 5.89; Cl, 15.32.

*cis-4-Methoxy-6-methyl-7-oxo-6-azabicyclo[3.2.1]octane (**10**)*

A portion (200 mg) of the perchlorate of **7**, m.p. 120°, was dissolved in 8 ml of acetone, 0.2 ml of acetic acid, and 0.4 ml of water. After addition of 100 mg of anhydrous sodium acetate the mixture was heated to give a clear solution. This was cooled to room temperature, then 348 mg of powdered potassium permanganate added over 1.5 h with stirring. The small excess was destroyed with sodium sulfite solution and the manganese dioxide removed by filtration. The acetone was removed under reduced pressure, the residual liquid diluted with 1 ml of water then basified using sodium carbonate. The product was extracted into methylene chloride giving 127 mg of oil. This was separated using preparative t.l.c. (10% methanol in chloroform, silica gel) into 68 mg of nearly pure γ-lactam **10** and 51 mg of nearly pure *N*-formyl derivative. A third amide, probably the de(*N*-methyl)lactam was present as a minor component. The lactam from several runs was purified further by preparative t.l.c. then distillation over a short path at 75° under 0.01 mm.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.63; H, 8.79; N, 8.11.

It had ν_{max} ($CHCl_3$) 1685 cm^{-1} and gave n.m.r. signals at δ 3.07 (NCH_3) and 3.45 (OCH_3). The *N*-formyl derivative had ν_{max} ($CHCl_3$) 1660 cm^{-1} and gave an n.m.r. signal at δ 3.45 (OCH_3).

*cis-4-Chloro-6-methyl-7-oxo-6-azabicyclo[3.2.1]octane (**9**)*

The base was liberated from 169 mg of the perchlorate of the chlorobicyclic base **6**. It was dissolved in a mixture of 4 ml of acetone, 0.1 ml of acetic acid, and 0.2 ml of water. A total of 322 mg of powdered potassium permanganate was added to the stirred solution during 0.75 h. After an extra 0.5 h of reaction time the mixture was worked up as for lactam **10**. The 98 mg of product was estimated by t.l.c. separation to contain 15 mg of γ-lactam **9**, 58 mg of *N*-formyl derivative and 17 mg of other amides.

The γ-lactam from several runs was combined, purified from *N*-formyl derivative by 1.5 h hydrolysis in 6 *N* sulfuric acid, and then distilled over a short path at 70° under 0.1 mm. It had ν_{max} ($CHCl_3$) 1690 cm^{-1} and gave an n.m.r. signal at δ 3.18 ($N—CH_3$). Its n.m.r. spectrum was nearly identical to that of a chlorolactam from which had been assigned the same structure by Chow and Perry (23). We thank Prof. Chow for a copy of the spectrum.

Action of Chlorine in Methanol on 4-Methylaminomethylcyclohexene Hydrochloride

Chlorine was bubbled into a solution of 3 g of *p*-toluenesulfonic acid hydrate in 50 ml of methanol at 0–5 °C until it contained 3.5×10^{-2} mol of available chlorine (iodimetry). To the stirred solution was added 1.1 g of 4-methylaminomethylcyclohexene hydrochloride. The reaction mixture was removed from the cooling bath, then left for a total time of 3 h at room temperature. After removal of methanol under reduced pressure, the base (1.05 g) was recovered (aqueous NaOH, ether), dissolved in 55

ml of methanol, and the solution refluxed for 22 h. In this time 75 mg of chloride ion (38% of 1 equiv.) was produced. The base was recovered, acetylated, and the tertiary bases (164 mg) analyzed by g.l.c. on an OS-138 column. The ratio of the areas of the two peaks corresponding to *cis*-chlorobicyclic base **6** and *cis*-methoxybicyclic base **7** was 1:1.1.

Action of Chlorine in Water on 4-Methylaminomethylcyclohexene Hydrochloride

Chlorine was bubbled into a cooled solution of 1.24 g of the base hydrochloride, 1 ml of concentrated hydrochloric acid, and 1 g of sodium chloride in 20 ml of water until the weight had increased by 564 mg. The mixture was left for 2 h at room temperature, at which time no free chlorine was left (KI–starch). The solution was reduced to 10 ml under reduced pressure and the base isolated (NaOH, ether). The 1.15 g of base was dissolved in 40 ml of pure dioxane and 10 ml of water. The solution was heated at 80 °C under nitrogen for 16.5 h, cooled, acidified with hydrochloric acid, then taken to small volume under reduced pressure. The 964 mg of bases were isolated (NaOH, ether), then adsorbed from 1:1 ether–hexane onto 20 g of neutral alumina (activity I); 60 ml of 1:1 ether–hexane eluted 102 mg of pure chlorobicyclic base **6**, characterized as its perchlorate (overall yield 7%). The mixture of more strongly adsorbed hydroxy bases was not characterized.

N-Acetyl-4-methylaminomethylcyclohexene

This was prepared by acetylation of 4-methylaminomethylcyclohexene, followed by distillation at 120°, 0.01 mm. It gave n.m.r. signals at δ 2.12 ($NCOCH_3$), 2.98, and 3.08 ($N—CH_3$), 3.25, 3.33, 3.43 (2H multiplet, $CH_2—N$), and 5.8 (narrow 2H multiplet, vinyl hydrogens). In pyridine at 60° the *N*-methyl signals collapsed to a sharp singlet but the CH_2N signals remained complex even at 100°.

Thermolysis of N-Chloro-4-methylaminomethylcyclohexene (3)

The chloramine was prepared by addition of a solution of 644 mg of 4-methylaminomethylcyclohexene hydrochloride (m.p. 202°) to excess aqueous alkaline sodium hypochlorite solution below 20 °C, 1 h stirring followed by extraction into pentane. The pentane solution was washed with water, a small volume of 0.1 *N* sulfuric acid, then with sodium carbonate solution. The solvent was removed on a rotating evaporator below room temperature. The colorless oil was dissolved in 20 ml of methanol (freshly purified by double distillation over sodium hydroxide then over *p*-toluenesulfonic acid). The p*H* of the solution, which contained 3.8×10^{-3} mol of the chloramine (iodimetry) was 6.8 (glass electrode). The solution was split in two parts.

(*a*) The methanol solution (6.5 ml) was refluxed under pure nitrogen while shielded from light. After 2 h no reaction had taken place but after 4.7 h 96.5% of the chloramine had reacted (iodimetry). (In other runs the induction period varied between 1 and 3 h.) After a further 45 min reflux the mixture was left overnight at room temperature. The p*H* was now 5.7. After being acidified with hydrochloric acid the solution was reduced to a syrup *in vacuo* below room temperature. The residue was separated into a small amount of sweet smelling neutral oil and a mixture of bases. Gas–liquid chromatography analysis on an OS-138 column at 180° showed the base composition to be nearly identical to that from *b*.

(*b*) Benzoyl peroxide (7 mg, 2.9×10^{-5} mol) was added to 13 ml of the methanol solution of the chloramine (2.5×10^{-3} mol). The mixture was refluxed under pure nitrogen. In 2 h 68.5% of the chloramine had reacted. After 4.5 h reaction was complete. After standing at room temperature overnight the reaction mixture had p*H* 5.8. It was worked up as in *a*. The neutral product gave a nearly identical g.l.c. pattern (SE-30 column) to that from *a* and the g.l.c. of the bases (OS-138 at 180°) was nearly identical to that from *a*.

The neutral products had ν_{max} 1732 cm^{-1}. The bases were distilled over a short path up to 140° under 12 mm pressure. The viscous residue weighed 75 mg. The 278 mg of distillate was analyzed using an OS-138 column at 180°. The bases were, in order of emergence: two tertiary bases (3%) (probably 6-methyl-6-azabicyclo[3.2.1]octane and 2-methyl-2-azabicyclo[2.2.2]octane); parent amine (14%); *trans*-4-methoxy-6-methyl-6-azabicyclo[3.2.1]octane (**15**) (18%); *trans*-6-methoxy-2-methyl-2-azabicyclo[2.2.2]octane (**16**) (27%); and *cis*-4-chloro-6-methyl-6-azabicyclo[3.2.1]octane (**6**) (13%). In several runs the total base was acetylated and the *N*-acetyl derivative identified as *N*-acetyl-4-methylaminomethylcyclohexene (15% recovery).

The bases were separated by preparative g.l.c. on an OS-138 column or by chromatography on a t.l.c. silica gel column (ratio 100:1) using 10% diethylamine in benzene as developing solvent, and the abundant ones characterized as salts.

trans-4-Methoxy-6-methyl-6-azabicyclo[3.2.1]octane (15)

This gave a crystalline perchlorate separating from ethyl acetate as thin plates, m.p. 130°. It proved identical with the salt of the *N*-methyl base prepared from *trans*-4-methoxy-6-azabicyclo[3.2.1]octane-7-one.

Anal. Calcd. for $C_9H_{18}ClNO_5$: C, 42.28; H, 7.10; N, 5.48. Found: C, 42.42; H, 7.33; N, 5.32.

trans-6-Methoxy-2-methyl-2-azabicyclo[2.2.2]octane (16)

The perchlorate of this base did not crystallize readily from ethyl acetate hence the picrate was prepared. This crystallized as stout needles from methanol, m.p. 176–178°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 46.73; H, 5.29; N, 14.55.

Thermolysis of Chloramine 3 in Acetonitrile

A solution of 4.8 mmol of chloramine **3** in 20 ml of acetonitrile (dried over molecular sieve, distilled) was flushed with nitrogen, then refluxed under nitrogen. In 1 h the chloramine had completely reacted. Methanol (5 ml) was added and the mixture refluxed under nitrogen for 1.5 h. The weakly basic solution was acidified using hydrochloric acid and evaporated to near dryness. The residue yielded 176 mg of neutral product (ν_{max} 3030, 2720, 1733, and 1660 cm^{-1}) and 453 mg of base. Gas–liquid chromatography on an OS-138 column showed this to be mainly parent amine, but also to contain some of the bicyclic amines **6**, **15**, and **16**. The bases were acetylated, and the product separated into neutral *N*-acetyl derivative (237 mg) and 130 mg of tertiary bases. Gas–liquid chromatog-

raphy on the OS-138 column confirmed the presence of the bicyclic amines **6**, **15**, and **16** and two minor tertiary amines with short retention time, probably the bicyclic bases **17** and **18**.

Thermolysis in an Oxygen Atmosphere

Simultaneous refluxing of aliquots of a 0.15 *M* solution of chloramine **3** in methanol under pure nitrogen and pure oxygen are compared in Fig. 1. The reaction under oxygen was 89% complete after 16.5 h refluxing. The basic products were acetylated, giving a 49% yield of the *N*-acetyl derivative of the parent amine and 16% of a mixture of the same tertiary amines produced in the reactions under nitrogen.

Action of Silver on Chloramine 3 in Methanol

(*a*) A solution of 1.65×10^{-3} mol of the chloramine in 15 ml of purified methanol was prepared and flushed with nitrogen. Water and methanol-washed Tollens' silver from 626 mg of silver nitrate was added, and the suspension again flushed with nitrogen. The mixture was heated under reflux in an oil bath. A rapid reaction ensued. After 1 h 93% of the chloramine had reacted. Refluxing was continued for 1 h more to complete reaction. The solids were removed by filtration, the basic filtrate was acidified using hydrochloric acid, and then evaporated to small volume. The bases were liberated and extracted into ether. Gas–liquid chromatography on an OS-138 column at 180° showed the major product to be parent secondary amine. Acetylation, followed by base–neutral separation, gave 122 mg of *N*-acetyl derivative and 57 mg of tertiary base. The latter gave five peaks on the OS-138 column, corresponding to the three bicyclic bases **6**, **15**, and **16** and two readily eluted minor bases (probably **17** and **18**). The solids contained 195 mg (1.36 mmol) of silver chloride.

(*b*) Chloramine **3** (2.2 mmol) and Tollens' silver from 1.02 g of silver nitrate (washed with water and methanol) in 15 ml of pure methanol were stirred under nitrogen. The extent of reaction was: 1.3 h, 67%; 3 h, 87%; 5.5 h, 99%. The base recovered from the reaction was shown by g.l.c. to be mainly parent amine. The solids contained 255 mg of silver chloride (1.78 mmol).

Action of Silver Perchlorate in Methanol on Chloramine (3)

A solution of 1.29 of silver perchlorate in 15 ml of methanol (p*H* approximately 1) was adjusted to p*H* 6 (by cautious addition of sodium methoxide). After removal of 47 mg of silver oxide by filtration the volume was readjusted to 15 ml and the solution added to the chloramine prepared from 0.30 g of the hydrochloride of 4-methylaminomethylcyclohexene. After 3 h in the dark at room temperature no reaction had taken place. The reaction mixture was then heated under nitrogen in a bath at 65°. The extent of reaction was: 1 h, 22%; 2 h, 65%. The mixture was left overnight at room temperature, then reaction completed by 2 h reflux. The p*H* of the solution was now 3, and 178 mg of silver chloride had precipitated (AgCl/chloramine = 0.95). The rest of the silver was precipitated using hydrochloric acid, the suspension filtered, the bulk of the solvent removed, then the base recovered. Gas–liquid chromatography on the OS-138 column showed it to consist of at least nine products, with parent amine being the dominant one (70%). Three peaks corresponding to the bases **6**, **15**, and **16** were present.

Photolysis of 3-Cyclohexenecarbonyl Azide

A solution of 3.4 g of the azide in 125 ml of methanol at 5 °C was irradiated through a Vycor glass sleeve using a 100 W Hanovia high pressure immersion lamp in a central well. The azide was completely decomposed in 3 h. The methanol and some volatile products were evaporated on a rotating evaporator. The residue was distilled over a short path under 0.5 mm pressure. A mobile oil (965 mg) distilled at a bath temperature of 75–80°. It had an ester odor and had ν_{max} 3435, 1715, and 1511 cm^{-1}. Gas–liquid chromatography on an OS-138 column at 235° showed it to be mainly one compound, presumably the expected methyl urethane.

The bulk of the remaining product distilled at bath temperatures between 80 and 135°. It consisted mainly of amides (broad i.r. absorption centered at 1690 cm^{-1}). Gas–liquid chromatography on an OS-138 column at 190° showed it to consist of three main components, the *N*-methoxy amide of 3-cyclohexenecarboxylic acid and the γ- and δ-lactams **19** and **20**. These were separated on preparative t.l.c. plates, developing with 5% methanol in chloroform.

For larger preparative runs the lactam mixture after distillation was oxidized with potassium permanganate in acetone to remove unsaturated products, then the γ- and δ-lactams were separated on columns of t.l.c. silica gel.

N-Methoxy-3-cyclohexenecarboxamide

The yield of this product was estimated to be 17%. After distillation over a short path at 90°, 0.2 mm, then recrystallization from ethyl acetate–hexane it melted at 71–74°. It had ν_{max} 3400, 3220, 2840, and 1669 cm^{-1} and n.m.r. signals at δ 5.80 (barely resolved doublet, 2H) and 3.83 (3H).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.94; H, 8.56; N, 8.97.

trans-4-Methoxy-6-azabicyclo[3.2.1]octan-7-one (19)

The γ-lactam (yield 4.6%) crystallized as thick plates from ethyl acetate – hexane mixtures. It had m.p. 83–85°, ν_{max} 3435, 3220, and 1695 cm^{-1}, and gave n.m.r. signals at δ 3.85 and 3.50 (broad 1H singlets, hydrogens on C-1 and C-7, respectively) and a 3H singlet at δ 3.41 (OCH_3).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.11; H, 8.54; N, 9.01.

trans-4-Methoxy-6-methyl-6-azabicyclo[3.2.1]octan-7-one

The γ-lactam **19** (105 mg), 205 mg of sodium hydride powder, and 480 mg of methyl iodide in 4 ml of dry dioxane was heated at 70° under nitrogen for 3 h. The solution was filtered through sintered glass. The filtrate was evaporated to small volume on a rotating evaporator at 40°. The 104 mg of crude product had no N—H absorption, ν_{max} 1690 cm^{-1}, and gave only one peak on g.l.c. on an SE-30 column at 200°. It gave n.m.r. signals at δ 2.87 (NCH_3) and 3.39 (OCH_3).

trans-4-Methoxy-6-methyl-6-azabicyclo[3.2.1]octane (15)

The above *N*-methyllactam (100 mg) was dissolved in 4 ml of dry dioxane, 365 mg of powdered lithium aluminum hydride added, the system flushed with nitrogen, then the

mixture placed in a bath at 100° for 1 h. The mixture was cooled, ether added, followed by methanol to destroy excess lithium aluminum hydride. After addition of 1 ml of saturated sodium sulfate solution, the suspension was filtered through celite. The filtrate was taken to p*H* 3 using hydrochloric acid, then evaporated to dryness. The base was liberated and converted to its perchlorate. This crystallized from ethyl acetate giving 64 mg, m.p. 125°. After recrystallization from ethyl acetate this melted at 129° and showed no mixture m.p. depression with the perchlorate m.p. 130° from the thermolysis of chloramine **3** in methanol.

The base was converted to its methiodide using methyl iodide in ether. This had m.p. 206° and did not depress the m.p. of a sample of the corresponding methiodide (m.p. 199°, mixture m.p. up to 202°) from thermolysis of chloramine **3** in methanol kindly supplied by Prof. P. Gassman (5).

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71. Found: C, 40.44; H, 6.83; N, 4.69.

*trans-6-Methoxy-2-azabicyclo[2.2.2]octan-3-one (**20**)*

The δ-lactam (yield 2.3%) crystallized from ethyl acetate – hexane as needles, m.p. 120°. It had ν_{max} 3430, 3220, and 1680 cm^{-1} and gave an n.m.r. signal at δ 3.39 (OCH_3).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.03; H, 8.61; N, 9.08.

trans-6-Methoxy-2-methyl-2-azabicyclo[2.2.2]octan-3-one

A mixture of 108 mg of δ-lactam **20**, 210 mg of sodium hydride powder and 467 mg of methyl iodide in 5 ml of dioxane was heated (under nitrogen) in a bath at 70° for 3 h. The suspension was filtered and the filtrate evaporated on a rotating evaporator. The residual oil gave one peak on g.l.c. analysis using the SE-30 column at 200°. It contained no NH, had ν_{max} 1668 cm^{-1}, and gave n.m.r. signals at δ 2.99 (NCH_3) and 3.37 (OCH_3).

*trans-6-Methoxy-2-methyl-2-azabicyclo[2.2.2]octane (**16**)*

The *N*-methyl δ-lactam (*ca.* 130 mg) was reduced with lithium aluminum hydride as for γ-lactam. The base gave 177 mg of picrate. After one recrystallization from methanol it formed stout needles, m.p. 175–178°. It proved identical (mixture m.p., i.r. spectra of major mulls) with the 178° picrate from thermolysis of chloramine **3** in methanol. The base was converted to its methiodide, m.p. 208°. This did not depress the m.p. of a sample of the corresponding methiodide (m.p. 200°, mixture m.p. 202°) from thermolysis of chloramine **3** in methanol (5), kindly provided by Prof. Gassman.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71. Found: C, 40.67; H, 6.86; N, 4.73.

A sample of the base assigned the above structure was kindly provided by Prof. Gassman. It was converted to its picrate which after recrystallization from methanol had m.p. 173–175.5°. It gave no mixture m.p. depression with the above picrate.

N-Methylcyclohept-4-enecarboxamide

This was prepared from cyclohept-3-enecarbonyl chloride and ice-cold saturated aqueous methyl amine. After recrystallization from acetone – ethyl acetate mixture it had m.p. 126–128°.

5-Methylaminomethylcycloheptene

Reduction of *N*-methylcyclohept-3-enecarboxamide using excess lithium aluminum hydride in refluxing dioxane for 1 h gave the base which was characterized as its hydrochloride. After recrystallization from methanol – ethyl acetate it had m.p. 204–206° (evacuated capillary).

Anal. Calcd. for $C_9H_{18}ClN$: C, 61.52; H, 10.32; Cl, 20.18. Found: C, 61.25; H, 10.51; Cl, 19.39.

*Thermolysis of N-Chloro-5-methylaminomethylcycloheptene (**11**)*

The chloramine was prepared from the secondary amine using excess sodium hypochlorite, then extracted into pentane. A solution of 1.07 g (6.09 mmol) of the chloramine was dissolved in 25 ml of methanol (distilled from sodium hydroxide, then from *p*-toluenesulfonic acid).

(*a*) After flushing with nitrogen 12.5 ml of the chloramine solution was refluxed under nitrogen while shielded from light. The decomposition rate was: 1.5 h, 0%; 3.5 h, 8.6%; 5 h, 16%; 8 h, 50%; 11 h, 86%; 15 h, 99%. The p*H* of the solution was now 5.6. It was adjusted to p*H* 2 using hydrochloric acid then evaporated to near dryness. The residue was extracted with ether, to give 4 mg of neutral product with ν_{max} 2720 and 1730 cm^{-1}. The salts gave 230 mg of base. Gas–liquid chromatography on OS-138 at 196° showed it to contain four major components with peak areas in order of emergence in the ratios 0.25:3.1:1:0.16.

(*b*) 12.5 ml of the chloramine solution containing 10 mg of perbenzoic acid was refluxed under nitrogen while shielded from light. The decomposition rate was: 1.5 h, 11%; 3.5 h, 72%; 6.5 h, 100%. The p*H* of the solution was now 5.2. Work-up as in *a* gave a small amount of neutral product identical to that in *a* and 329 mg of base. It contained the same bases as obtained from run *a* but in different ratio: (relative areas of peaks) 1.07:1.51:1:0.17. The second peak corresponded to the parent secondary base.

The bases from *a* and *b* were combined and acetylated using acetic anhydride. Base–neutral separation gave 357 mg of *N*-acetyl derivative (mainly the derivative of the parent amine) and 225 mg of tertiary base.

The tertiary bases contained at least six components but three predominated, corresponding to the first, third, and fourth peaks from the total bases with relative areas 0.08:1:0.14. Gas–liquid chromatographic separation of the product from larger runs enabled characterization of the two most abundant tertiary amines in order of emergence as *trans*-4-methoxy-6-methyl-6-azabicylco[3.2.2]-nonane (**21**) and *cis*-4-chloro-6-methyl-6-azabicyclo-[3.2.2]nonane (**12**).

*trans-4-Methoxy-6-methyl-6-azabicyclo[3.2.2]nonane (**21**)*

This base did not readily give a crystalline perchlorate but gave a picrate, m.p. 182°, which was sparingly soluble in methanol. The yield in the benzoyl peroxide catalyzed reactions averaged approximately 25%.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.09; H, 5.65; N, 13.96.

The n.m.r. spectrum of the base contained signals for the *N*-methyl and methoxyl groups at δ 2.50 and 3.39. A

doublet at δ 3.1 (J = 3 Hz) can be attributed to the N—CH_2—CH group. The hydrogens on C-1 and C-7 resonated close to δ 2.7 and 3.5, respectively.

*cis-4-Chloro-6-methyl-6-azabicyclo[3.2.2]nonane (**12**)*

This formed a perchlorate which crystallized from methanol – ethyl acetate as short needles, m.p. 246°.

Anal. Calcd. for $C_9H_{17}Cl_2NO_4$: C, 39.43; H, 6.27; N, 5.11; Cl, 25.86. Found: C, 39.54; H, 5.70; N, 4.98; Cl, 25.86.

The yield in the benzoyl peroxide catalyzed reactions approximated 4.5%.

*Acid-catalyzed Reaction of Chloramine **7** in Methanol*

p-Toluenesulfonic acid hydrate (2.5 g) was added cautiously with external cooling to a solution of 1.75 g (10.1 mmol) of chloramine 7 in 50 ml of methanol. The reaction was 94% complete in 10 min and 97% complete in 20 min. After a total reaction time of 45 min the methanol was evaporated under reduced pressure. Water was added to the residue, which was adjusted to pH 4 using sodium carbonate, then left overnight. The solution was then made strongly acid with dilute sulfuric acid, and extracted twice with ether. The ether was back-washed with acid, dried, and distilled, leaving 14 mg of neutral oil with ν_{max} 1732 cm^{-1}. The aqueous layers were basified with sodium hydroxide and thoroughly extracted with ether, yielding 1.80 g of colorless oil. This contained four bases with moderate retention times on the OS-138 column. Their peak areas in order of emergence were 0.09:0.15:1:3.5. The total base mixture was dissolved in 25 ml of methanol. The solution was refluxed for 1 h then left for 47 h at room temperature. No ionic halogen was produced. Acetic anhydride acetylated the fourth and most abundant base, giving 1.75 g of neutral *N*-acetyl derivative (77% yield, corrected for samples removed for analysis) and a small amount of tertiary base. The latter gave 54 mg of the perchlorate of *cis*-4-chloro-6-azabicyclo[3.2.2]-nonane (**12**) (see above). No pure compound was isolated from the remaining 100 mg of noncrystalline perchlorate.

The N-Acetylated Secondary Amine

The *N*-acetyl product was distilled over a short path at a bath temperature of 150–160° under 0.5 mm pressure, giving a faintly colored viscous oil. It gave n.m.r. signals at δ 3.53 (3H, OCH_3), 3.10, and 3.01 (3H, NCH_3) and 2.17 (3H, $COCH_3$).

Its n.m.r. spectrum corresponded to the expectation for *N*-acetyl-*trans*-4-chloro-*cis*-5-methoxy-1-methylaminomethylcycloheptane (δ 2.1 ($COCH_3$); 2.99, 3.09 (NCH_3); 3.52 (OCH_3); two broad 1H signals centered near 3.5 and 4.2) and it gave a single g.l.c. peak (SE-30 at 226°) superimposed on a weak broad signal. It analyzed approximately correctly.

Anal. Calcd. for $C_{12}H_{22}ClNO_2$: C, 58.18; H, 8.89; N, 5.66; Cl, 14.33. Found: C, 57.45; H, 9.12; N, 5.39; Cl, 13.81.

We thank Prof. J. D. Hobson for communicating results prior to publication, Prof. P. G. Gassman for reference samples, Prof. Y. L. Chow for reference spectra, M. Lesage and R. Kolt for technical assistance, H. Seguin for microanalyses, and B. Cougle for mass spectra.

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