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THE SYNTHESES AND POLYMERIZATION OF BICYCLIC UREA DERIVATIVES CONTAINING BRIDGEHEAD NITROGEN

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THE SYNTHESES AND POLYMERIZATION OF BICYCLIC UREA DERIVATIVES CONTAINING BRIDGEHEAD NITROGEN

by

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GRADUATE COLLEGE

As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Oluchukwu Ebenezer Ekechukwu

entitled The Syntheses and Polymerization of Bicyclic Urea Derivatives Containing Bridgehead Nitrogen

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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SIGNED: 

To my wife, Myriette, and children, Ijeoma, Obioma, and Chioma, whose patience and understanding helped to make this work possible.

ACKNOWLEDGMENTS

The author wishes to thank Dr. H. K. Hall, Jr. for his guidance during the course of this work and the preparation of this dissertation.

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ABSTRACT

In the present study, a new "anti-Bredt" bicyclic urea, 1,3-diazabicyclo[3·3·1]nonan-2-one, and an isomeric bond-bridged reference compound 1,8-diazabicyclo[4·3·0]nonan-9-one, were synthesized.

The [3·3·1] urea was prepared in two ways. 3-Aminomethylpiperidine was reacted with phosgene. Deprotonation of the precipitated ammonium salt with triethylamine gave the urea. In another method, thermal depolymerization (in vacuo) of a glassy product arising from the reaction of 3-aminomethylpiperidine with diphenyl carbonate afforded the urea.

The [4·3·0] urea was obtained through the reaction of diphenyl carbonate with 2-aminomethylpiperidine. No glassy intermediate was observed.

The [4·3·0] and [3·3·1] ureas resisted hydrolysis. The former would not polymerize either in bulk or in solution at any temperature with or without initiator catalysts. At 120° and above the [3·3·1] urea bulk polymerized within 30 minutes with or without catalysts. The uncatalysed thermal polymerization gave lower molecular weight polymers in lower yield than the catalysed one. Cationic initiator, phenylphosphonic acid, and anionic potassium tertiary butoxide catalysts gave highest molecular weight polymers. Comparatively, the anionic initiator generated a higher molecular weight polymer than the cationic one. Dibutyltin oxide which is a coordination metal catalyst was also

effective in generating high polymer but the yield compared favorably only with the uncatalysed thermal polymerization.

The bulk polymerization of the [3·3·1] urea is one of the rare cases of polymerization of a bicyclo [3·3·1] nonan derivative.

The mechanism proposed for the thermal polymerization of [3·3·1] urea involved the dissociation of the urea to an aminoisocyanate which then propagated the polymerization.

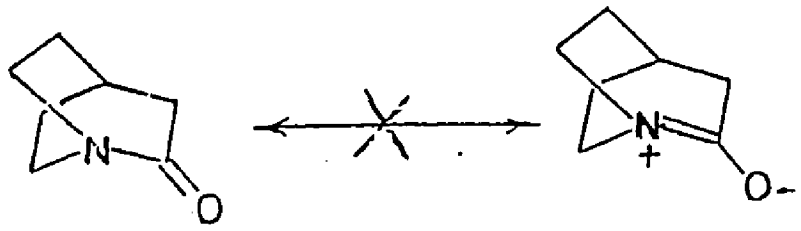
The reaction of 3-aminopiperidine with diphenyl carbonate afforded a urea which was proposed to be a dimer of the desired urea, 1,6-diazabicyclo[3·2·1]octan-7-one.

The unsuccessful syntheses of two ureas possessing two nitrogen bridgehead atoms, 1,5-diazabicyclo[3·2·1]octan-8-one, and 1,5-diazabicyclo[3·3·1]nonan-9-one, and another which was seven-membered, 1,3-diazabicyclo[3·2·2]nonan-2-one, were explained in terms of their canonical forms violating Wiseman's rule. However, a nuclear magnetic resonance (NMR) spectrum evidence of the formation of 1,5-diazabicyclo-[3·2·1]octan-8-one in the NMR tube was presented.

INTRODUCTION

Anti-Bredt Lactams

According to Lukes (1938), bicyclic lactams such as 1-azabicyclo[2·2·2]octan-2-one (i.e., 2-quinuclidone) 1[1] should not be capable of existence. This is because its canonical form 1b violates Bredt's rule (Bredt, 1924; Bredt, Houben, and Levy, 1902) which forbids a bridgehead double bond in a multi-cyclic system. According to



1a 1 1b

Wiseman (1967) and Wiseman and Pletcher (1970), the practical limit for isolable strained bridgehead bicycloalkenes is trans cyclooctene. Anti-Bredt trans bicycloheptenes could exist only briefly (Wiseman, 1967). Bridgehead small ring cis cycloalkenes would not exist at all. An application of Wiseman's (1967) and Wiseman and Pletcher's (1970) restatement of Bredt's rule would therefore preclude the accessibility of 1 since 1b incorporates a "trans cyclohexene" structure which is undetectable even as a transient intermediate. However, despite the reservations arising from the foregoing considerations about the stability and the existence of 1, Pracejus (1969, 1965) prepared the

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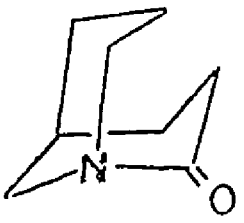
1. Compound numbers and their structures are listed in Appendix D.

6,6-dimethyl and 6,6,7-trimethyl derivatives of 1. In 1957, Yakhontov and Rubsitov reported the synthesis of 1. While the present work was in progress, Shaw (1979) prepared 1-azabicyclo[3·3·1]nonan-2-one 2 in 7% yield. It was found to polymerize with 85% phosphoric acid. The lactam 3 was recently prepared by McKee (1978) and by Weinreb, Khatri, and Shringarpure (1979) in low yields. However, in this bond-bridged system, overlap is allowed.



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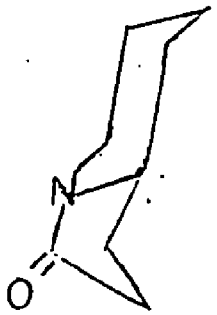

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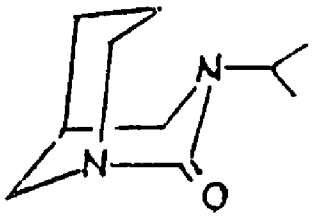
Anti-Bredt Urethanes

Hall and Johnson (1972) postulated that the N-C=O resonance strain in "anti-Bredt" lactams could be alleviated by an adjacent electron donating atom such as oxygen or nitrogen. The resulting urethane or urea would thus suffer less "anti-Bredt" strain and become more readily isolable. To test the postulate, Hall and Johnson (1972) prepared the urea 4 in 50% yield and found it to be stable and un-polymerizable. While the present work was in progress, El-Shekeil (1980) synthesized in high yields, the urethanes 1-aza-3-oxa-bicyclo-[3·3·3]nonan-2-one 5 and 1-aza-6-oxabicyclo[3·2·1octan-7-one 6 (as well



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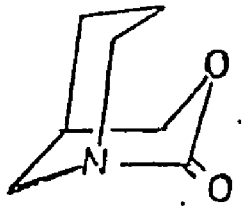

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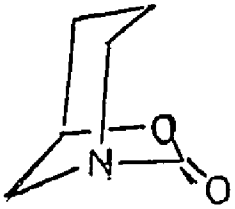


6

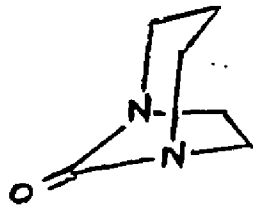
7

as 1-aza-8-oxabicyclo[4·3·0]nonan-9-one 7). In these instances, oxygen was the electron donating atom placed adjacent to the carbonyl. These urethanes except 7 were found to be polymerizable and so till now, Hall and Johnson (1972) have been proved partly right. It now remained to show the effect of placing unsubstituted nitrogen as an electron-donating atom adjacent to the N-C=O moiety. The result would be the formation of "anti-Bredt" ureas. This is one of the objectives of the present investigation.

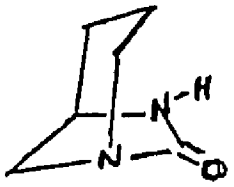
Anti-Bredt Ureas

The work reported here aimed at synthesizing some of the "anti-Bredt" ureas. It complements the investigations of Hall (1958a, 1958b), Hall and Schneider (1958), Hall and Johnson (1972), Shaw (1979), and

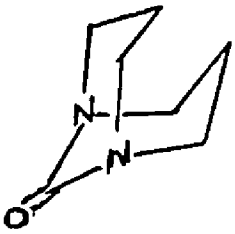
El-Shekeil (1980). In the present investigation, nitrogen was the electron-donating atom placed adjacent to the carbonyl. Thus, two types are possible--one comprising two bridgehead nitrogens as in 8 and the other, one bridgehead nitrogen atom, as in 9. Accordingly, efforts were made to synthesize and polymerize the following unknown ureas, 8-13:



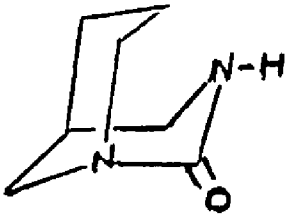
1,5-diazabicyclo[3·2·1]octan-8-one, 8



1,6-diazabicyclo[3·2·1]octan-7-one, 9



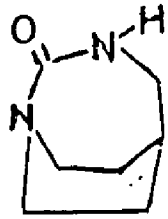
1,5-diazabicyclo[3·3·1]nonan-9-one, 10



1,3-diazabicyclo[3·3·1]nonan-2-one, 11

12

1,8-diazabicyclo[4·3·0]nonan-9-one, 12



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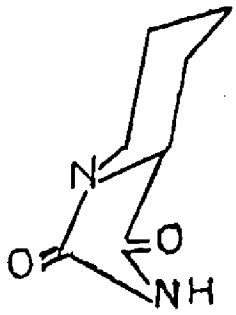
1,3-diazabicyclo[3·2·2]nonan-2-one, 13



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Since the hydantoin 14 (Freed and Day, 1960) and the lactams 1 (Yakhontov and Rubsitov, 1957) and 2 (Shaw, 1979) exist, it seemed reasonable to anticipate that the ureas 8-13 might be prepared. It was reasonable to expect that 9, 11, 12, and 13 might be made without too much difficulty. Ureas 8 and 10, however, possess severe internal

strain because their canonical forms seriously violate Bredt's and Wiseman's rules. Therefore, their syntheses were viewed as a serious challenge.

Purpose of Research

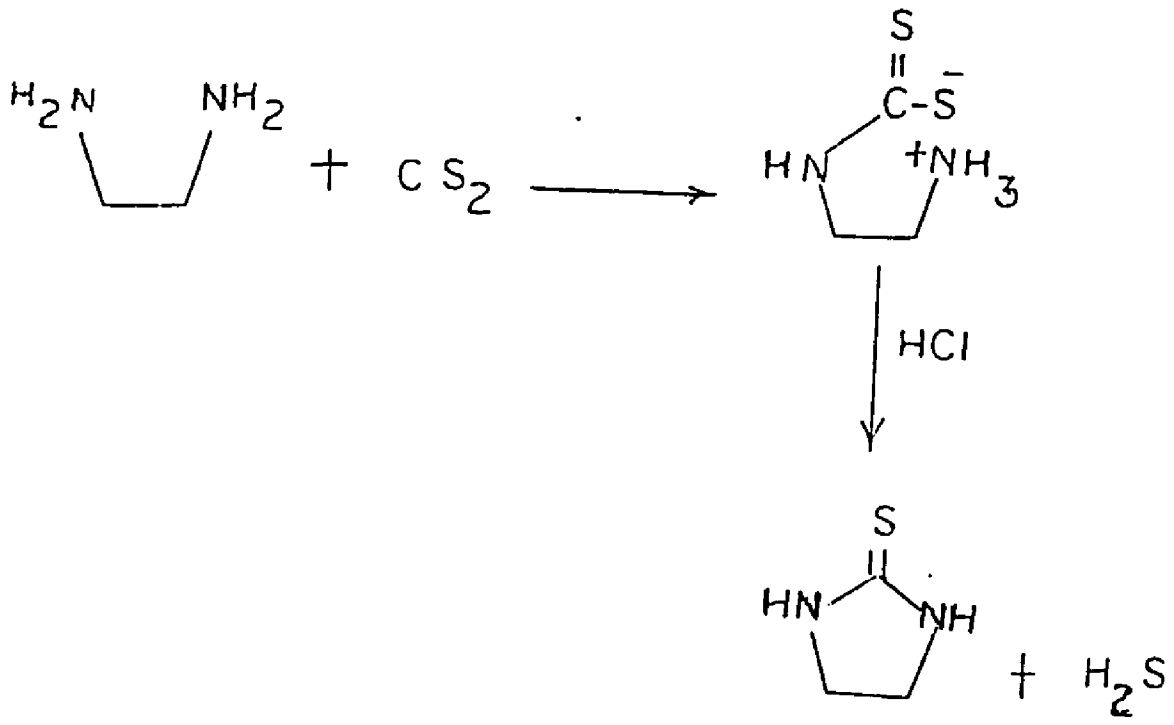
The present work attempts to synthesize the ureas 8-13 and to compare their polymerizability with the polymerizability of:

1. Their non N-bridgehead isomers described by Hall (1958b).
2. The substituted N-bridgehead urea 4 prepared by Hall and Johnson (1972).
3. Their oxygen homomorphs (urethanes, 5-7) prepared by El-Shekeil (1980), their carbon homomorphs (lactam 2) prepared by Shaw (1979), and a few other lactams prepared by Hall (1960).

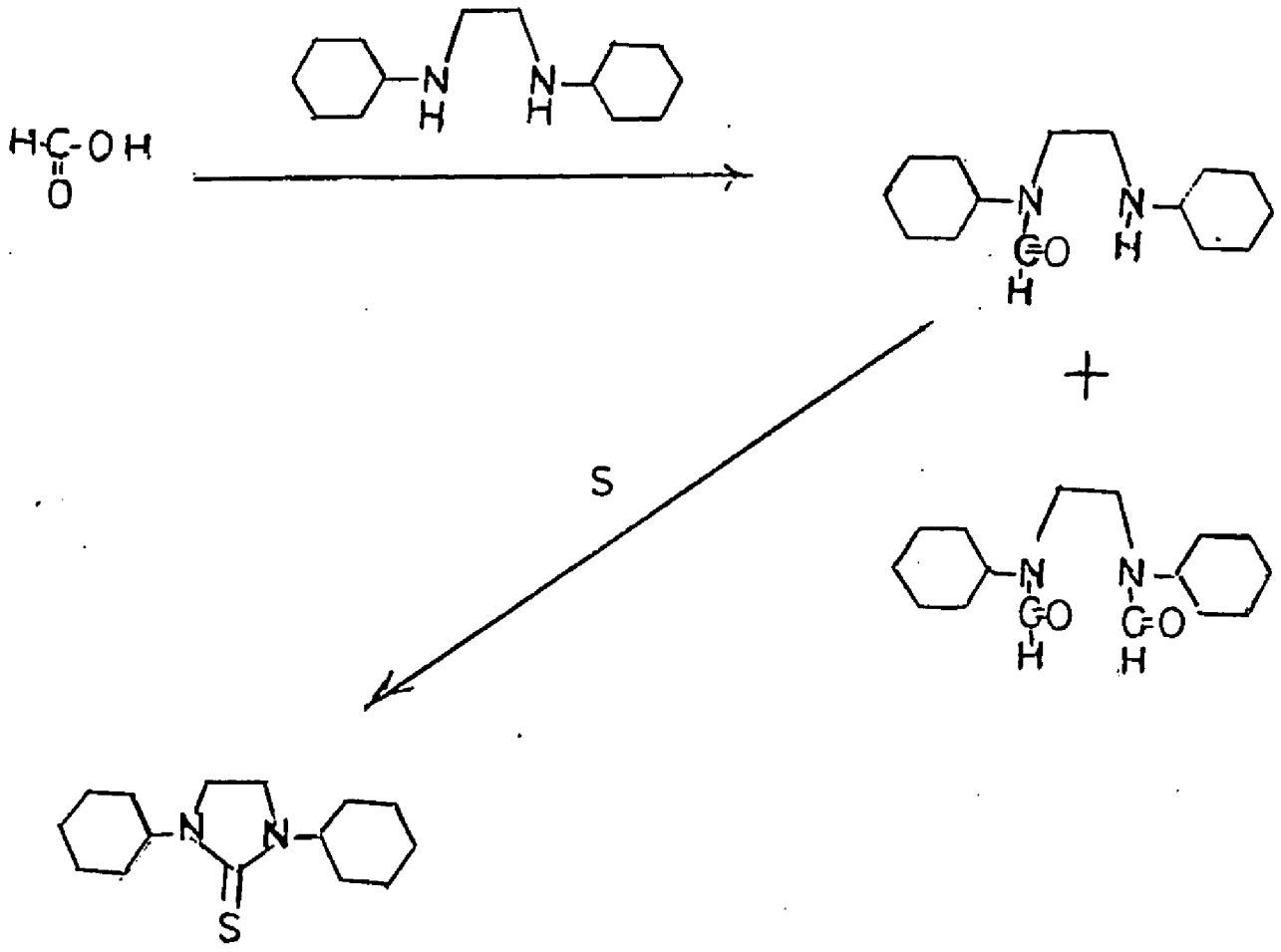
RESULTS AND DISCUSSION

Various methods of transforming diamines to cyclic ureas have been reported in the literature. These include:

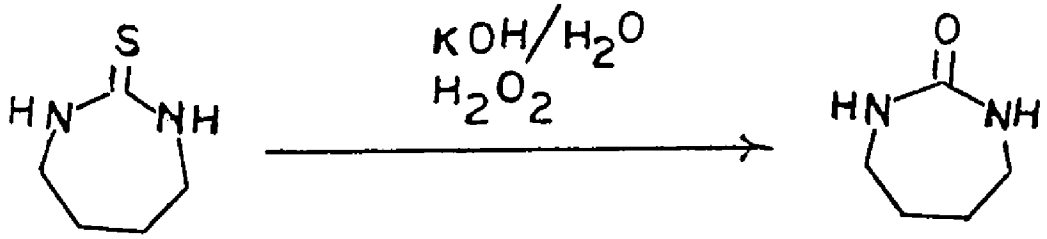
1. The action of the diamine upon carbon disulfide in aqueous alcohol to afford a thiocarbamic acid which on acidification generated thiourea (Allen, Edens, and Van Allen, 1955).



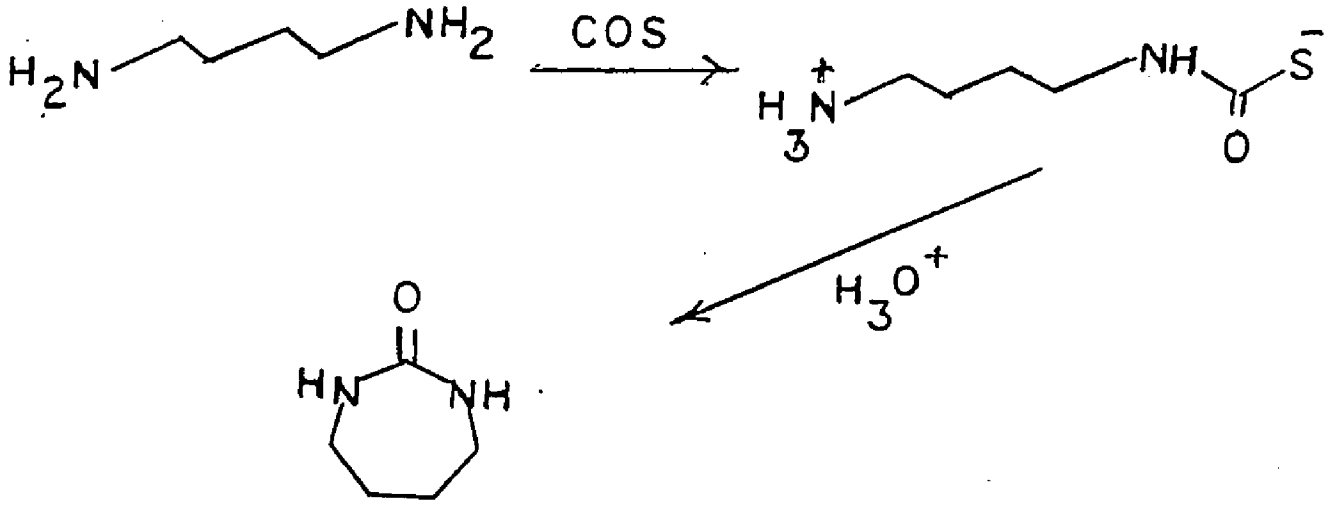
2. The reaction of the diamine with formic acid and the subsequent heating of the resulting N-formyl diamine with sulfur to give thiourea (Zienty and Thielke, 1945; Zienty, 1946).



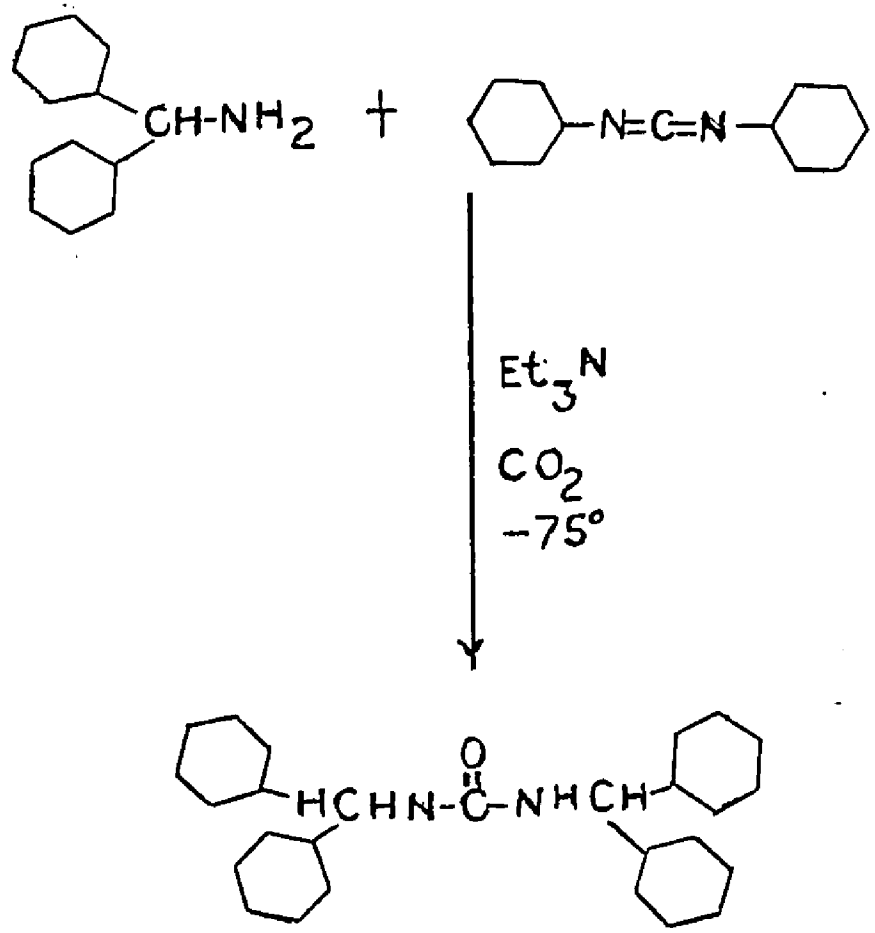
3. The desulfurization of thiourea with alkaline hydrogen peroxide (Mecke, 1956; Hall and Schneider, 1958).



4. The reaction of the diamine with carbonyl sulfide to form an inner salt which, upon treatment with concentrated hydrochloric acid gave the urea (Ulrich, Tucker, and Richter, 1978).



5. The direct synthesis of ureas from carbon dioxide and amines in the presence of a tertiary amine and dicyclohexylcarbodiimide as a condensing agent (Ogura et al., 1978).



Since homopiperazine 20 was readily available, it was used as a model diamine and the various methods listed above were explored in the attempts to prepare 8. The successful method of synthesis would then be applied in the conversion of 32 to 10. Unfortunately, 8 could not be obtained by any of the above methods. Polymeric substances having broad infrared (IR) absorption at 1620 cm^{-1} were obtained. Therefore, alternative routes to 8 and 10 were sought.

The reaction of homopiperazine 20 with N,N'-carbonyldiimidazole again largely gave polymers and a lesser amount of imidazole homopiperazine urea.

Attempted Synthesis of 1,5-Diazabicyclo[3·2·1]octan-8-one 8 via Demethanolation (Figure 1)

Next, N-methoxycarbonyl homopiperazine 15a was prepared (Figure 1). The method employed was a variant of the procedure developed by Jacobi (1933) and utilized by Hall (1956) in synthesizing monoacylpiperazines. In the present study, the pH was monitored with a pH meter as homopiperazine was reacted first with concentrated hydrochloric acid at pH 2-3 and in the next step by methyl chloroformate. Attempts to prepare 8 by demethanolating the urethane 15a at various temperatures and in the presence of different types of catalysts such as barium oxide, titanium(IV)tertiary butoxide, $Ti(OtBu)_4$, and potassium carbonate mixed with crown ether failed (Figure 1). Although at 260° and in the presence of catalytic amount of $Ti(OtBu)_4$ methanol distilled out, the mixture obtained absorbed sharply in the infrared (IR) at 3325 cm^{-1} (NH), and at 1660 cm^{-1} (urea C=O). The products could not be separated

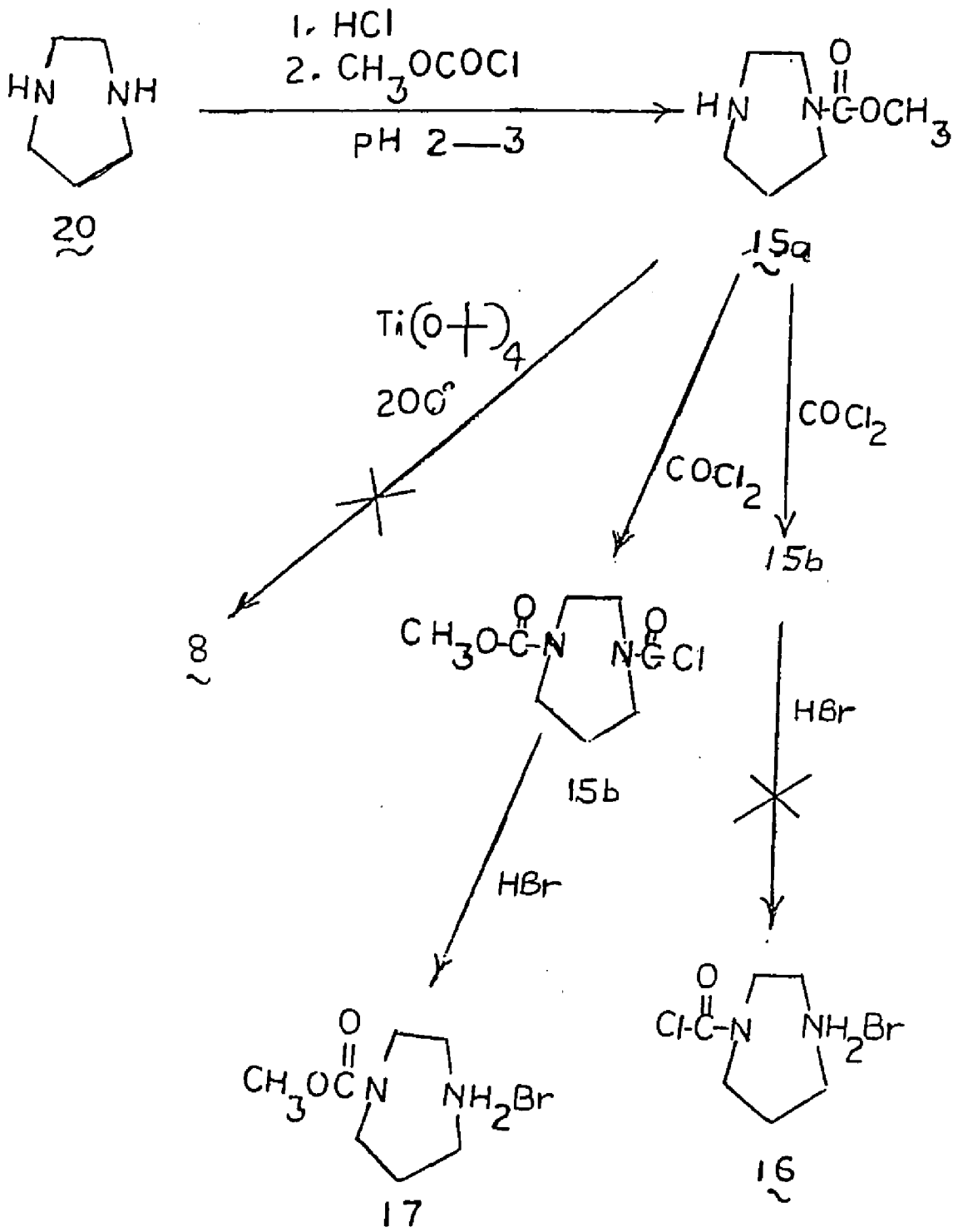


Figure 1. The First Attempted Synthesis of 8 and 16 via Demethanolation of 15

on silica gel thin layer chromatography (TLC) using various solvents. It was conceivable that the dimer 73 was present.

Attempted Synthesis of 1,5-Diazabicyclo[3·2·1]octan-8-one 8 and 1,5-Diazabicyclo[3·3·1]nonan-9-one 10 via Phosgene Route (Figures 3, 4, 5, 9a, and 9b)

Hall and Johnson (1972) prepared 3-isopropyl-1,3-diazabicyclo-[3·3·1]nonan-2-one 4 via the sequence of reactions shown in Figure 2. Under similar conditions, equimolar quantities of commercially available 1,4-diazacycloheptane (i.e., homopiperazine) 20 and phosgene in ether reacted to give 1,4-diazacycloheptan-1,4-dichlorocarbonyl[1] (i.e., the biscarbamoyl chloride of homopiperazine 21) in 70% yield, mp 106-107°, ν_{CO} = 1720 cm^{-1} (Figure 3).

Treatment of 21 with silver carbonate and with potassium carbonate in various solvents in the manner of Hall and Johnson (1972) did not afford 8 (Figure 3). When 21 was strongly heated in the presence of powdered CsF, a mixture of biscarbamoyl fluorides and chlorides were obtained, identified by a complex carbonyl absorption in the IR (Figure 4).

Attempted Syntheses of 8-13 via N-Chlorocarbonylammonium Halides (Figures 5, 7, 8, 9, 11, 12)

It was considered that an N-chlorocarbonylammonium halides of cyclic diamines having one or two annular nitrogen atoms (e.g., 16, 24, 29, 39, and 38 or 23, 31, 34a, and 34b) would be key intermediates in the synthesis of the corresponding ureas. Ring closure would simply be

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1. Analysis: Calculated for 21 $C_7H_{10}N_2O_2Cl_2$: C, 37.30; H, 4.49; N, 12.43. Found: C, 37.32; H, 4.62; N, 12.43.

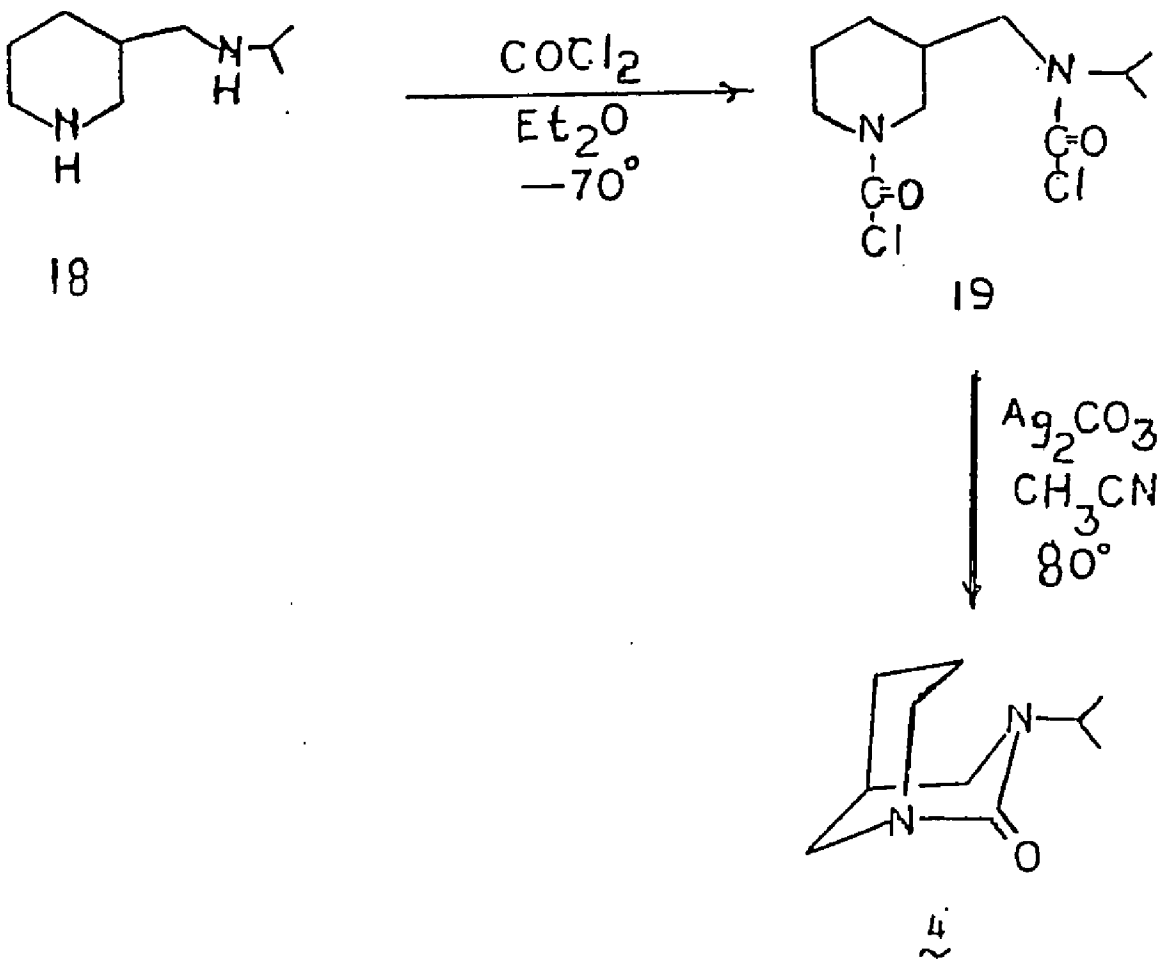


Figure 2. A Model Reaction Sequence Anticipated to be Applicable to the Synthesis of 8 and 10

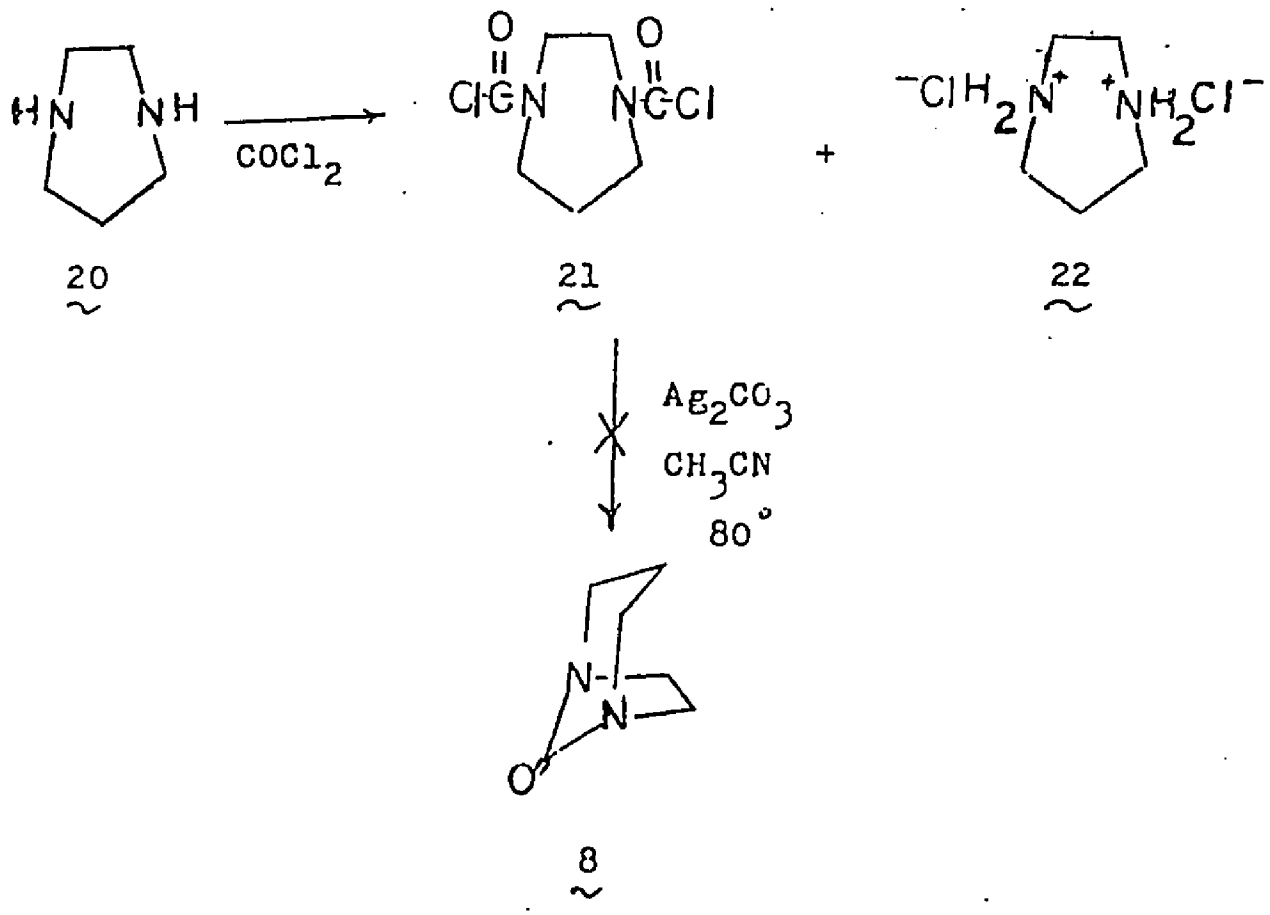


Figure 3. The Second Unsuccessful Attempt to Prepare 8 via Dechlorophosgenation of 21

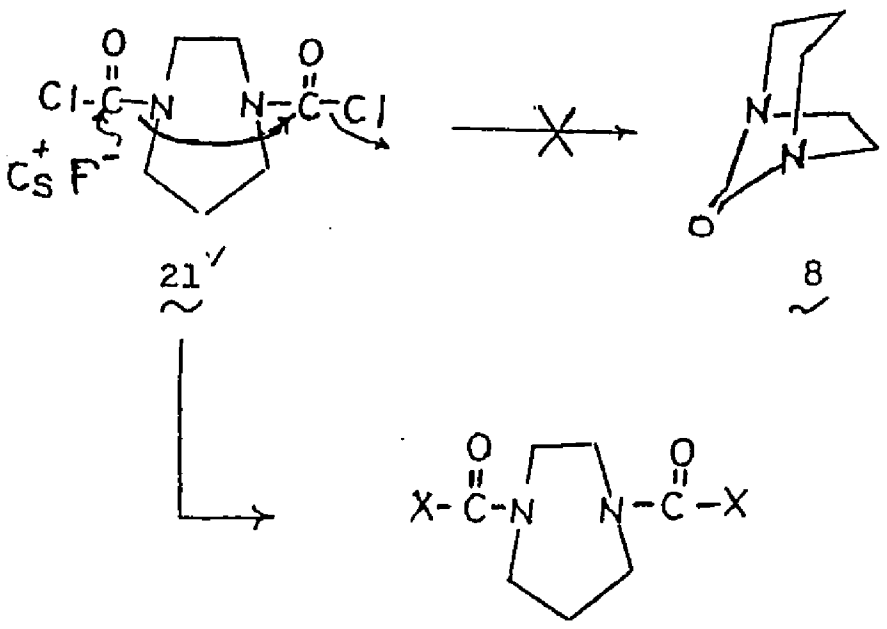
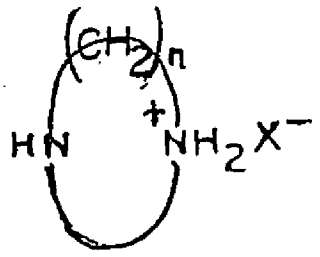
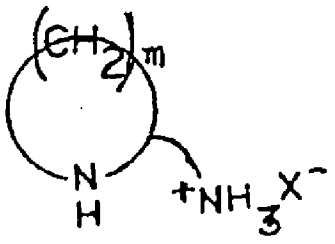


Figure 4. An Unsuccessful Attempt to Prepare 8 via Dechlorophosgenation of 21 with Cesium Fluoride

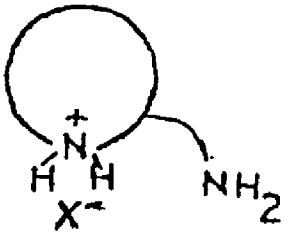
effected by deprotonation of 23 or 24 (Figure 5) by a suitable base in a high dilution medium. 3-Isopropylaminomethylpiperidine 18 available from the work of Hall and Johnson (1972) was chosen as a model cyclic one-annular-N-atom diamine. Commercially available homopiperazine 20 was the other model, an acyclic two-annular-N-atom diamine. In general, it was found that when X^- = Cl^-, Br^-, ClO_4^-, or $F_3CSO_3^-$, 23 and 24 could not be prepared by a direct method because the intermediate monoammonium salts 23a, 24b, or 24c were insoluble in most common suitable organic



23a



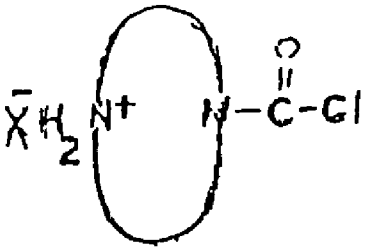
24b



24c

solvents. However, these salts were soluble in CH_2Cl_2 or $CHCl_3$ when X^- = 2,4,6-triisopropylbenzenesulphonate ion and moderately soluble when X^- = tosylate ion (Figure 5).

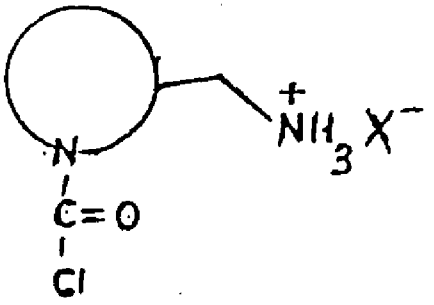
To test the above proposition concerning ring closure, an alternative route to Hall and Johnson's (1972) urea 4 was sought. The intermediate, N-chlorocarbonyl-3-N-isopropylaminomethylpiperidinium-2',4',6'-triisopropylbenzenesulfonate 29 was prepared and cyclized to 4 in 38% yield (Figure 6). Surprisingly, however, under similar conditions depicted in Figure 5, the carbamoyl chloride 37 (Figure 7) failed to cyclize to urea 11.



23

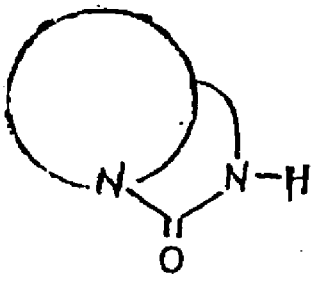
Base, high dilution

26 = 8 or 10



24

Base, high dilution



25 = 9,11,12 or 13

X^- = halide ion,

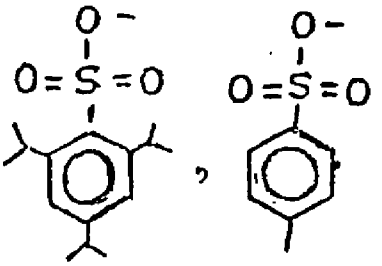


Figure 5. Generalized Intermediates Considered Likely to Lead to 8-13

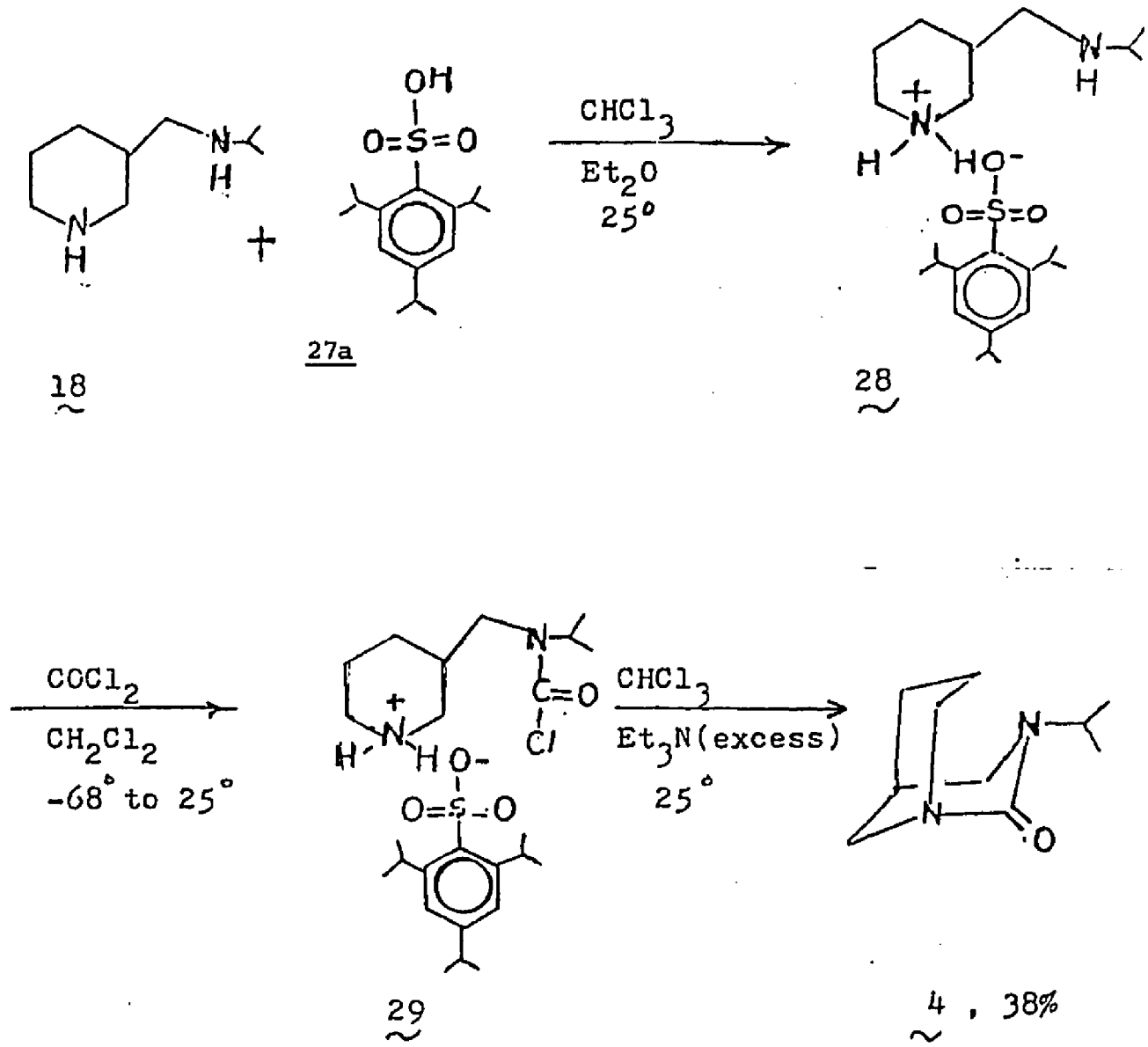


Figure 6. A Successful Alternative Route to 4 of Figure 2; a Strategem Anticipated to Lead to 8-13

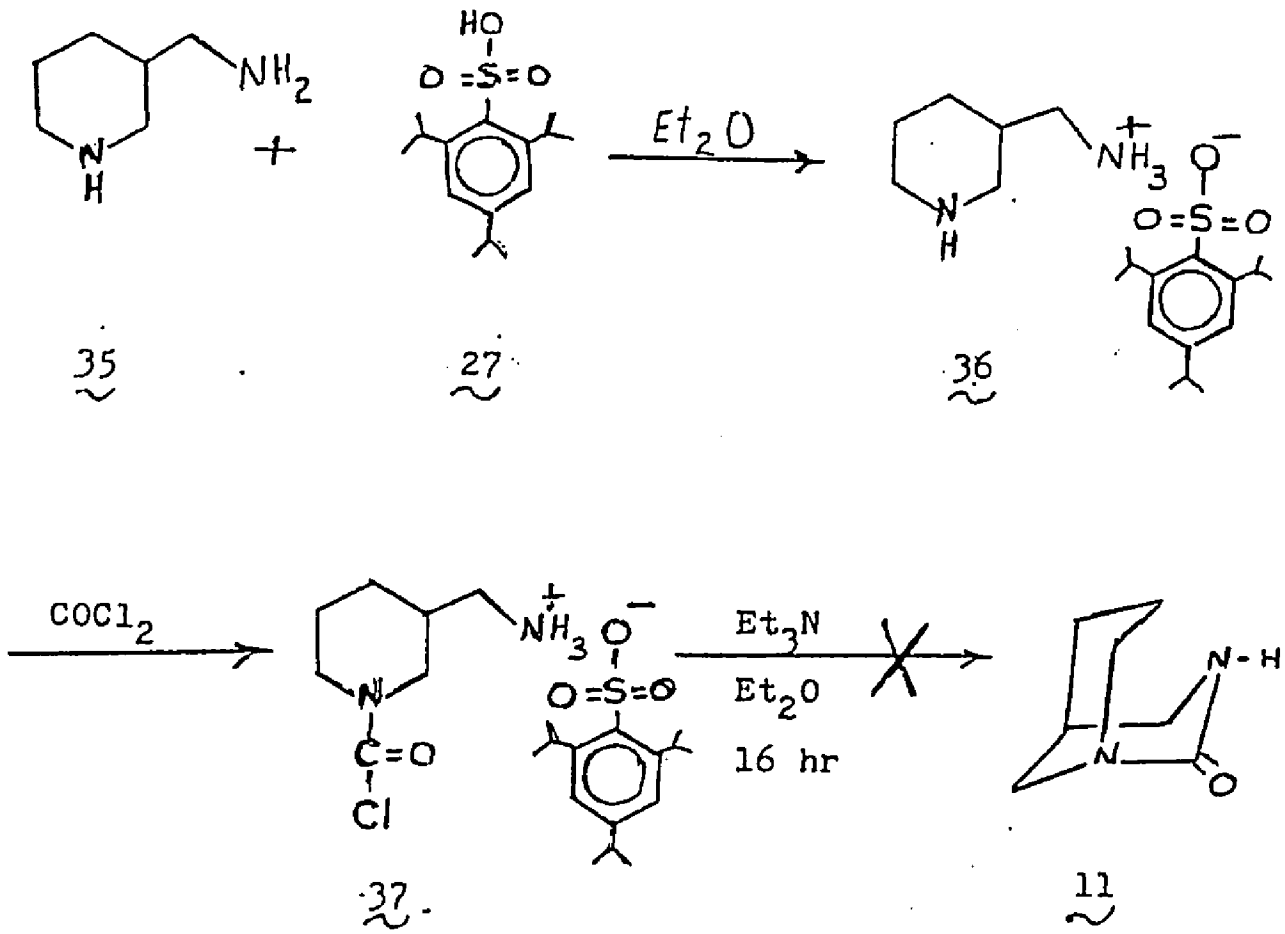


Figure 7. First Unsuccessful Attempt to Prepare 11 Using the Method of Figure 6

Similar sequences of reactions were carried out starting with homopiperazine 20 and with 1,5-diazacyclooctane 32 (Figures 8 and 9). Unfortunately, treatment of 31, 34a, and 34b with triethylamine, or 1,4-diazabicyclo[2·2·2]octane (DABCO), or 1,5-diazabicyclo[4·3·0]-5-ene (DBN), collidine, as well as with sodium hydride in various solvents (ether, CH_2Cl_2, $CHCl_3$, toluene, hexane) under various conditions did not give the expected urea 8 or 10. Rather, complex mixtures of polymers having IR absorptions at 1620 cm^{-1} and other compounds difficult to purify were obtained. An absorption in the IR region observed at 2250 cm^{-1} (-N=C=O) in both cases even suggested a ring opening of the cyclic diamine framework. In general, it was found that under the conditions of the present experiments, and where ring strain permitted, the intermediates, such as 29 (Figure 6) and 38 and 39 (Figure 10) which have only one annular nitrogen, readily cyclized to ureas on deprotonation with triethylamine. (Those which have two annular nitrogen atoms such as 31 [Figure 8] and 34(a-b) [Figure 9] failed to transform to urea). Thus, the first successful synthesis of 11 in 5% yield was achieved via this route (Figure 10).

Attempted Syntheses of 8 and 10 via Phosgene-Azolidine Route (Figures 11 and 12)

It is known that the N-C-N bridge (H on the central carbon) of some heterocyclic compounds may be opened and such groups as SO, SO_2, or CO may then substitute the central carbon atom. An aldehyde is usually eliminated in the process (Misiti and Chiavarelli, 1966 [Figure 13]; Stetter, Schafer, and Dieminger, 1958). The reaction is a consequence of the monodealkylation of tertiary amines by such reagents as phosgene, thionyl chloride,

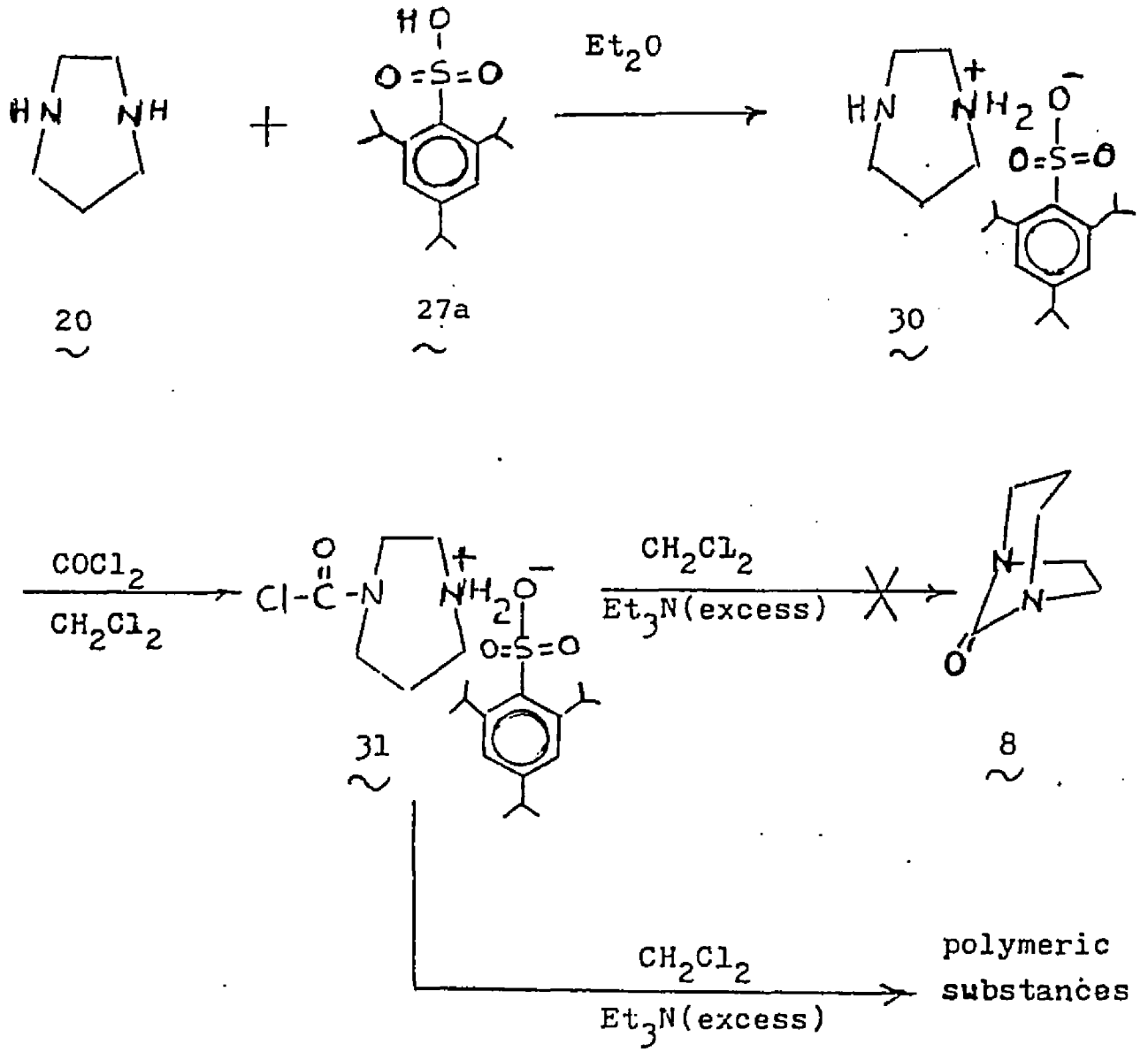
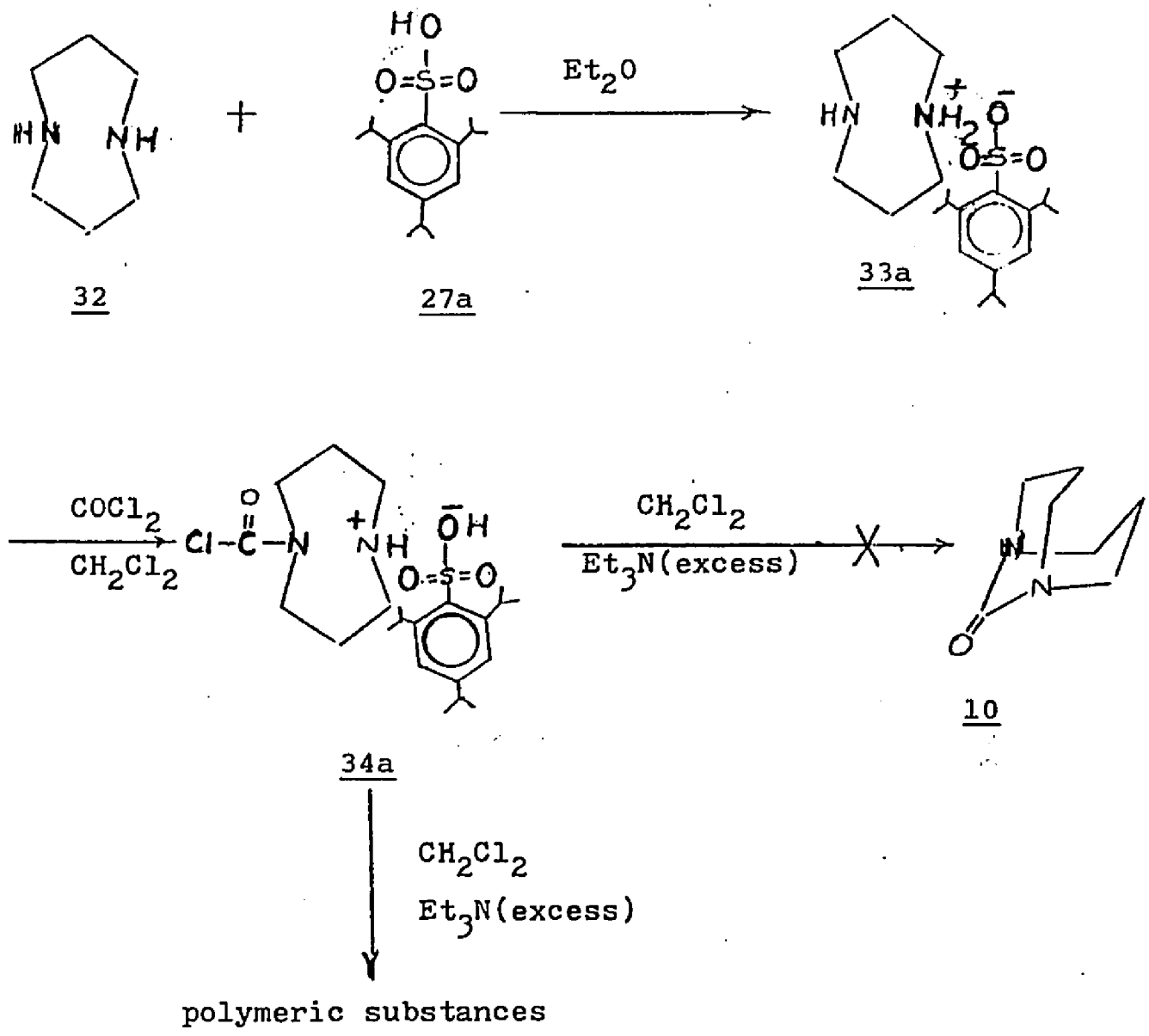
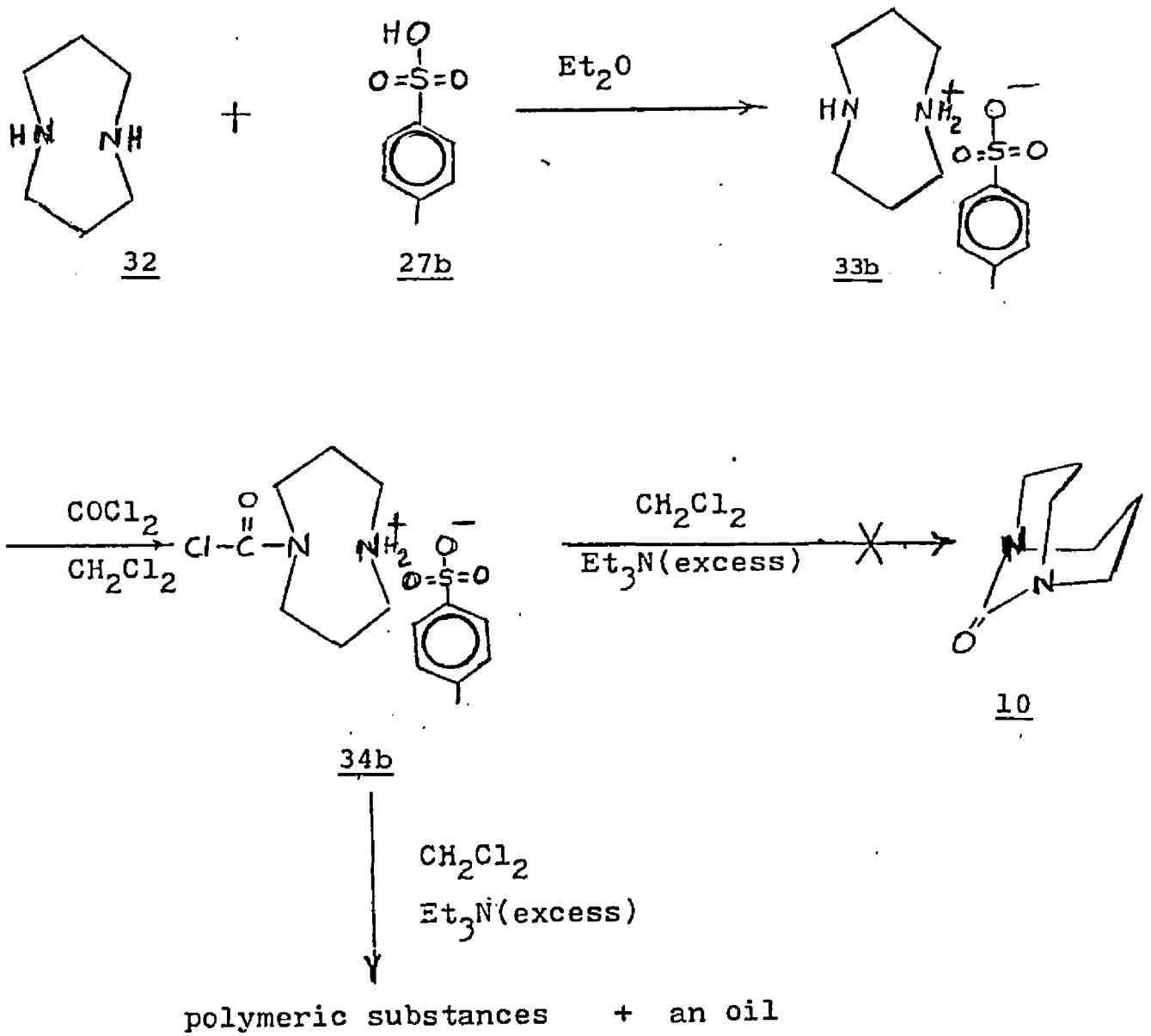


Figure 8. An Unsuccessful Attempt to Adapt the Reaction of Figure 5 to Prepare 8



(a) with 27a as the protecting acid

Figure 9. An Unsuccessful Attempt to Adapt the Reaction of Figure 6 to Prepare 10



(b) With 27b as the protecting acid

Figure 9.--Continued An Unsuccessful Attempt to Adapt the Reaction of Figure 6 to Prepare 10

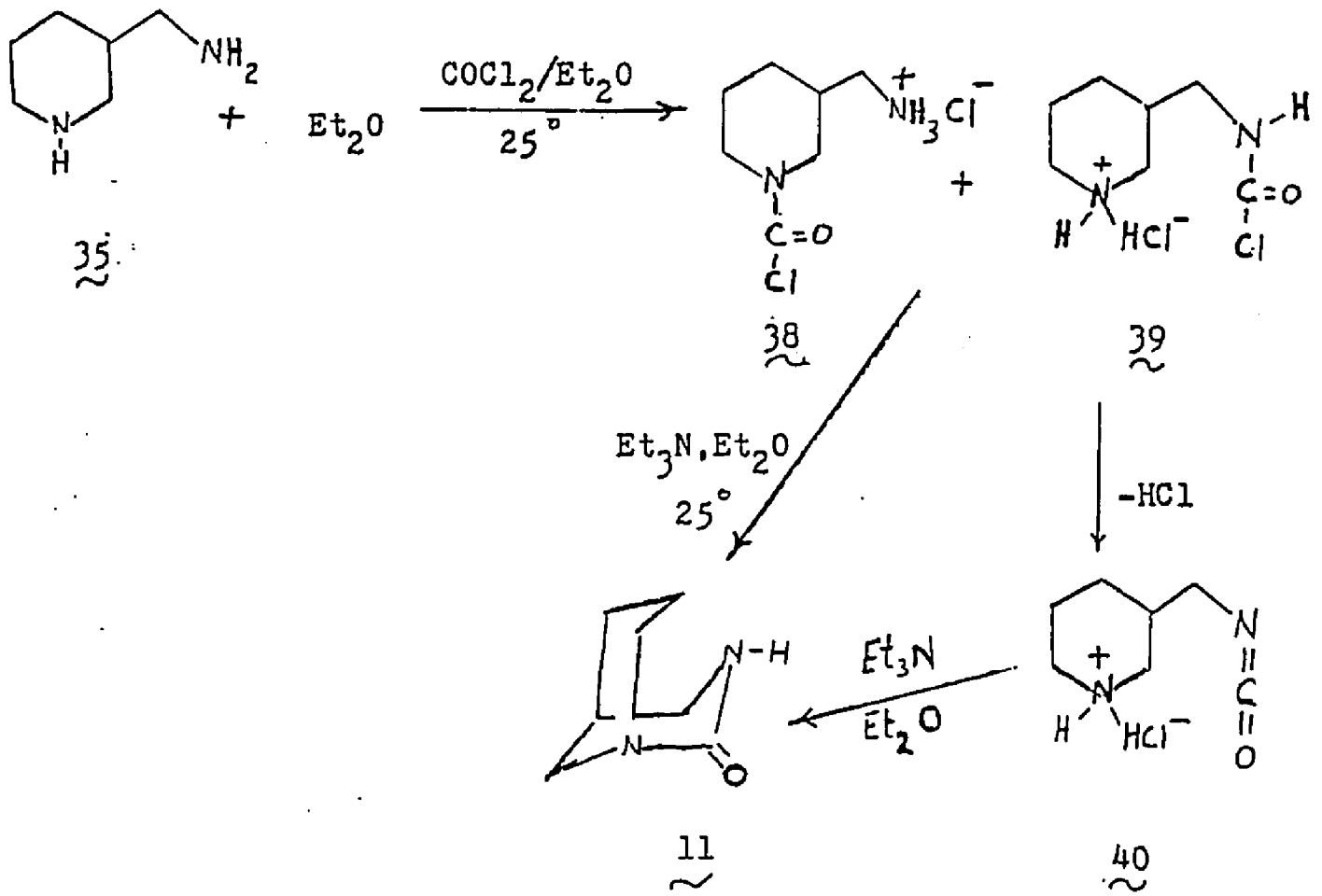


Figure 10. First Successful Synthesis of 11 via Phosgene Route

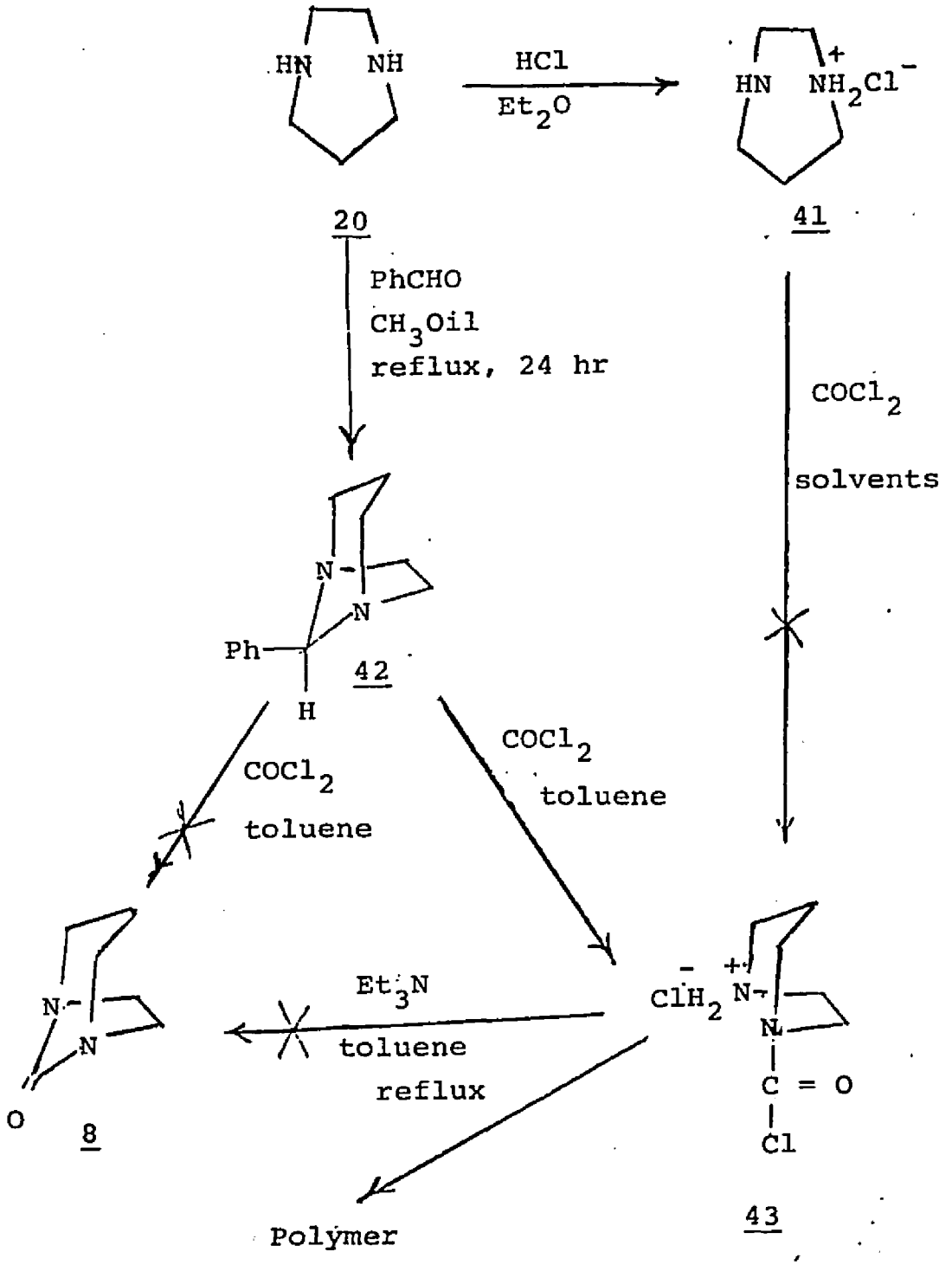


Figure 11. An Unsuccessful Two-Step Synthesis of 8; Indirect Formation of Desired Intermediate 43

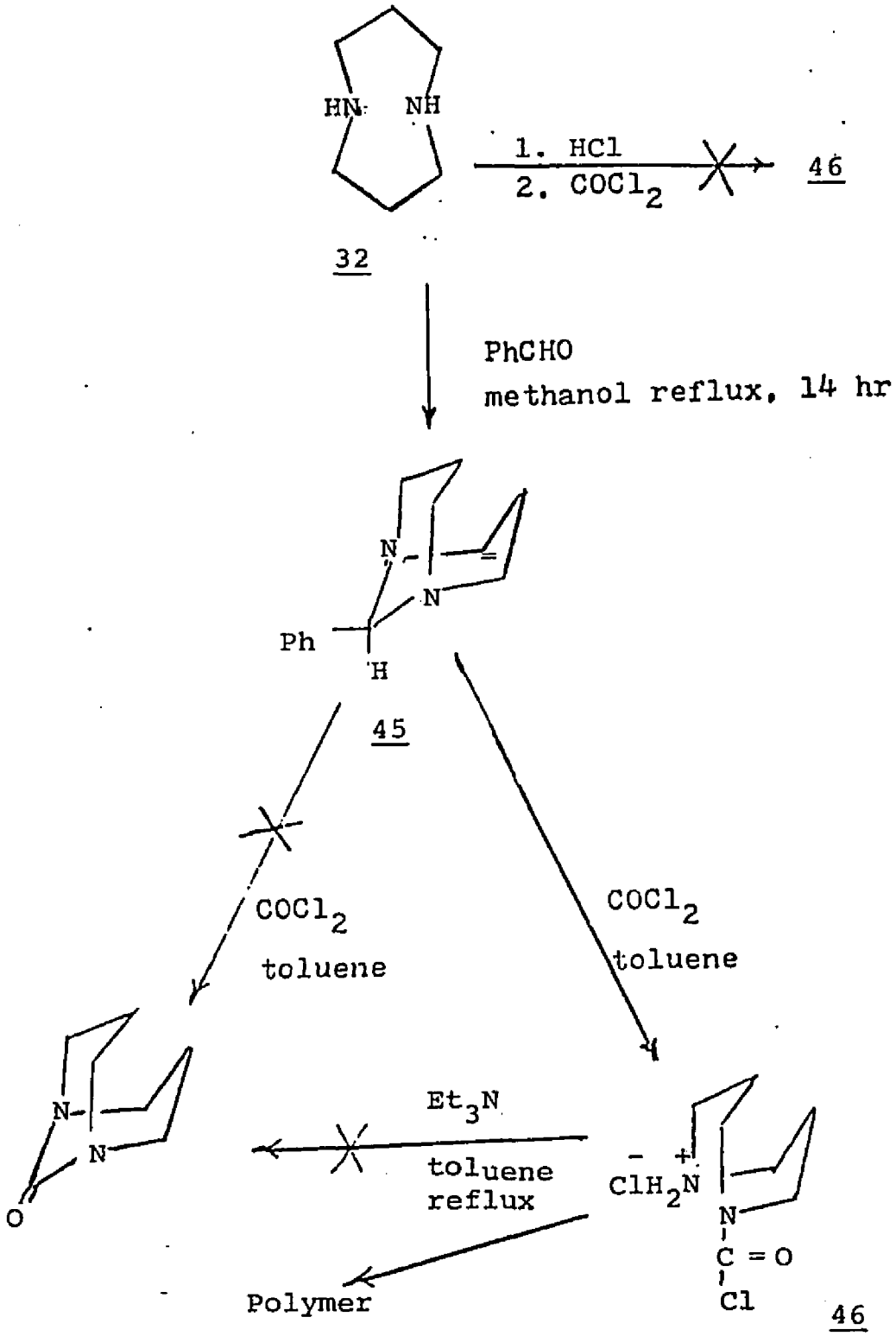
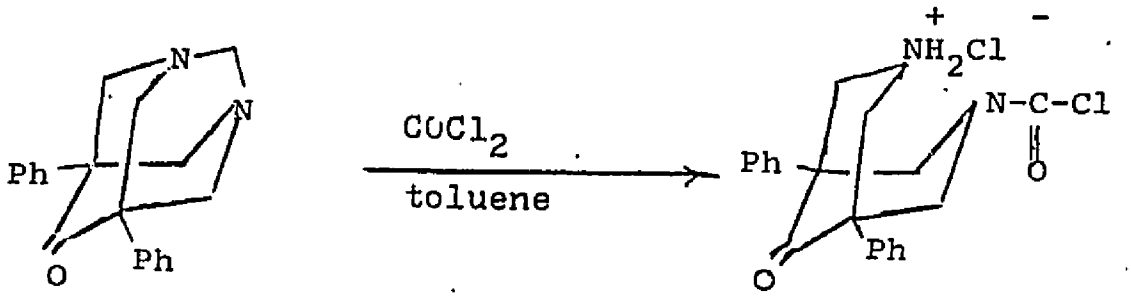


Figure 12. An Unsuccessful Two-Step Synthesis of 10; Indirect Preparation of an Intermediate 46



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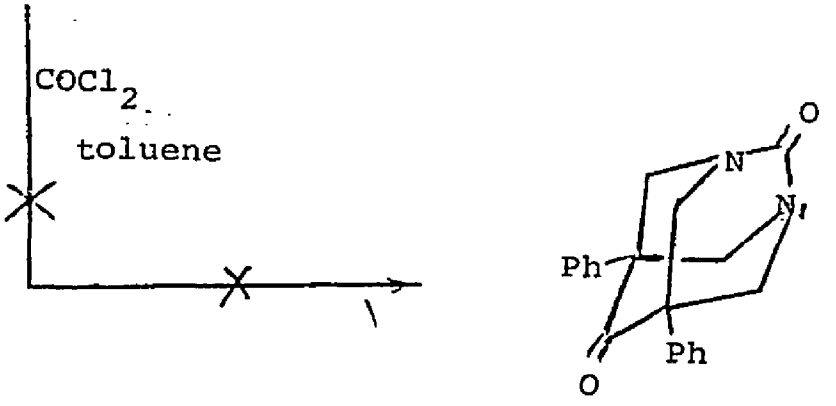

49

Figure 13. The Work of Misiti and Chiavarelli (1966)

anhydrides, acid chlorides, organic acids, and even chloroformates. This approach appeared attractive since it was reported that 2 moles of dimethylaniline reacted with one mole of phosgene to afford one mole of N,N'-dimethyl diphenyl urea (Moller, 1957). Accordingly, the method was investigated for the syntheses of 8 and 10 from homopiperazine 20 and 1,5-diazacyclooctane 32. It was anticipated that one mole of the generalized tertiary amine 50 (Figure 14) would react with one mole of phosgene to yield the corresponding bicyclic urea 56. The methods of Poppelsdorf, Myerly, and Conrow (1961); Jaunin and Godat (1961); Jaunin and Courbat (1961); Misiti and Chiavarelli (1966) were modified and adapted. 8-Phenyl-1,5-diazabicyclo[3·2·1]octane 42 (Figure 11) and 9-phenyl-1,5-diazabicyclo[3·3·1]nonan 45 (Figure 12) were prepared accordingly.

Unfortunately, treatment of 42 and 45 with phosgene in hot toluene did not afford the ureas 8 and 10. Instead a copious, white, hydroscopic, insoluble salt formed in each case. The salt was assigned the general structure 53 (Figure 14) based on the following observations: On exposure of the salt to air, benzaldehyde was expelled (readily detected by its characteristic odor). After washing the exposed mixture well with toluene to get rid of benzeldehyde, the N-carbochloromonoammonium chlorides 43 (Figure 11) and 46 (Figure 12) were obtained in high yields. Thus, this method led to the accessibility of the intermediates 43 and 46 which could not be prepared by the direct method. Unfortunately, 43 and 46 afforded only polymers on treatment with triethylamine.

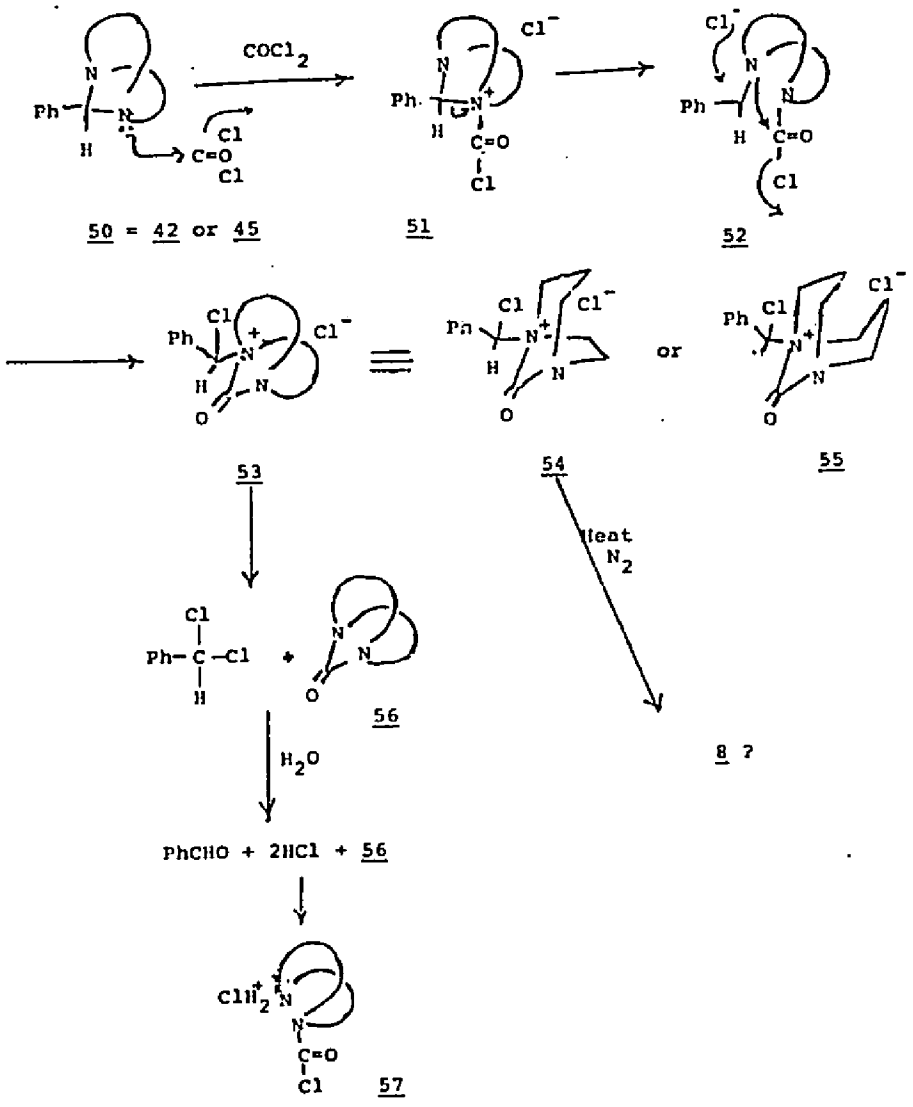

Figure 14. Proposed Generalized Mechanism for the Formation of 43 of Figure 11 and 46 of Figure 12

The postulated mechanism for the formation of 43 and 46 is shown in Figure 14. According to this mechanism, the desired N-bridgehead ureas represented generally by 56 actually formed but probably due to their instability, suffered ring opening in the presence of nucleophilic chloride ions to give 57 (Figure 14). In the case of the product from homopiperazine, an effort was made to isolate 8 by heating 54 (Figure 14) in N_2 atmosphere in the hope that 8 would collect in a trap cooled in a dry ice-isopropanol bath. Only crystalline solids devoid of carbonyl absorption in the IR were found in the trap.

Misiti and Chiavarelli (1966) obtained similar results as described above. These workers did not isolate 49 (Figure 13). Rather they isolated 48 with 47 was reacted with phosgene in hot toluene.

Attempted Synthesis of 4, 8, and 10 via Di-tert-butyltricarbonate 59 (Figures 15, 16, and 17)

The ultimate formation of the nitrogen bridgehead ureas from the diamines 18, 35, 20, or 32 was envisioned to involve a relatively new reagent, di-tert-butyltricarbonate 59 (Pope, Yamamoto, and Tarbell, 1977). To this end, an investigation of the reactions of the model diamines 18 (Figure 6) and 20 (Figure 3) with 59 was undertaken. The generalized anticipated reaction was as shown in Figure 15. Unfortunately, the desired results were not realized. Upon mixing the solutions of 20 and 59 in pentane or ether at 0° or -70°, a white solid precipitated at once with no observed evolution of a gas (Figure 16). The solid was identified as an ammonium salt by IR (3000-2000 cm^{-1}; Bellamy, 1975). The diurethane 63 was isolated from the filtrate.

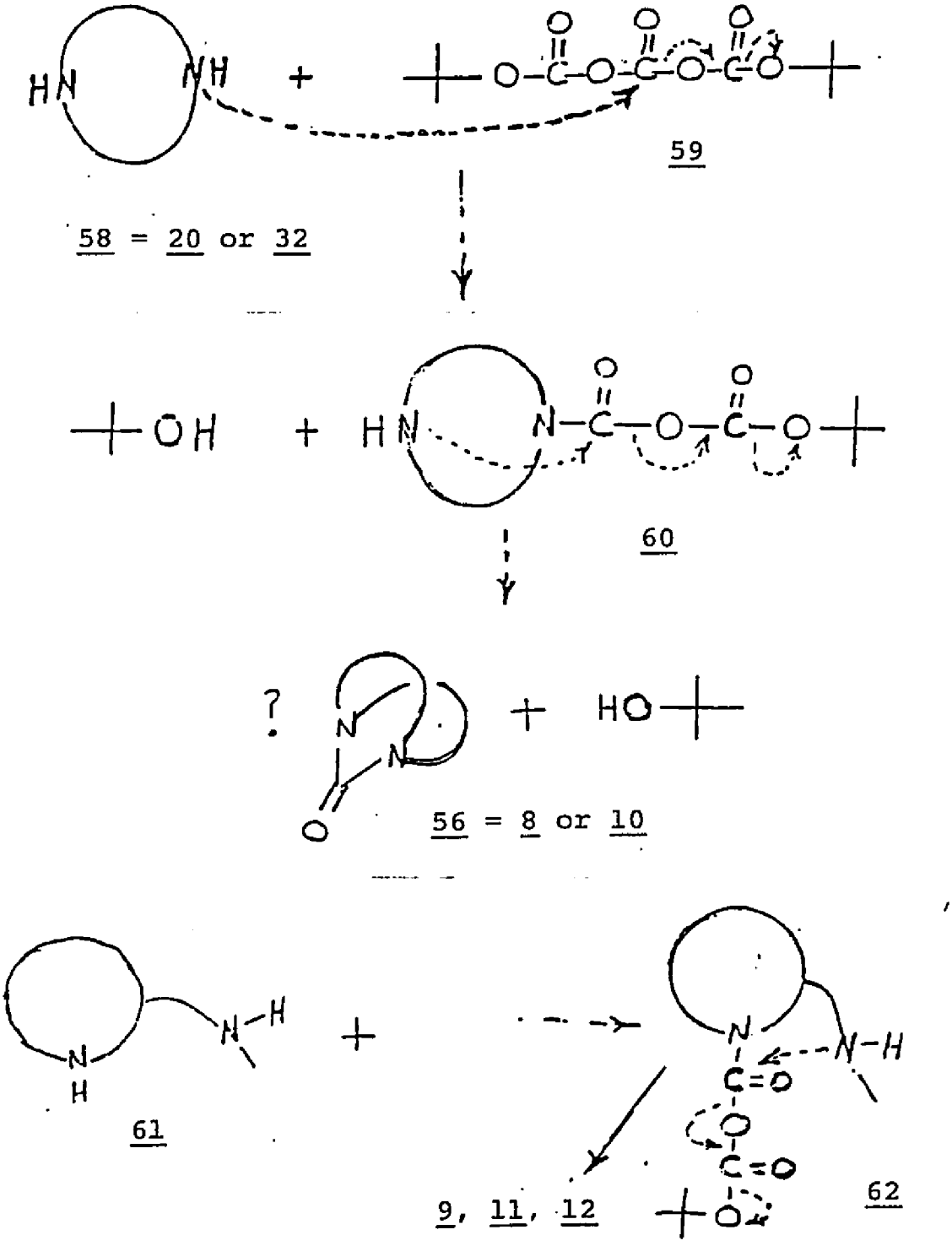

Figure 15. Generalized Proposed Mechanism for the Anticipated Reaction of a Diamine with 59

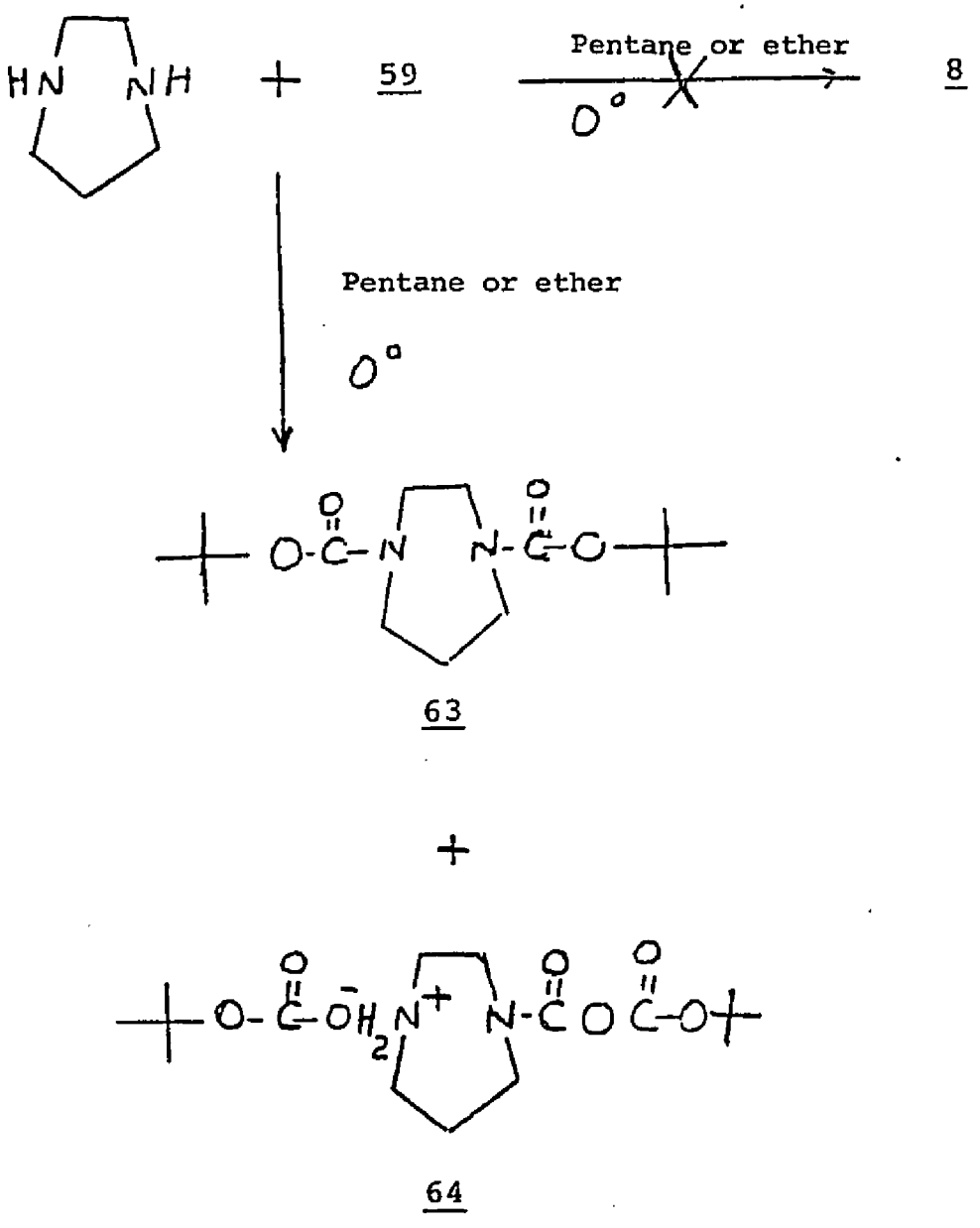

Figure 16. Products of the Reaction of 20 with 59 in Pentane or Ether at 0°

Although 63 did not give a satisfactory elemental analysis,[1] the molecular ion appeared in the mass spectrum at m/e 300 which suggested the composition as $C_{15}H_{28}N_2O_4$. When the ammonium salt was heated in the Kugelrohr at 120°, 0.375 Torr., a liquid (ν_{CO} = 1690 cm^{-1}; ν_{NH} = 3325 cm^{-1}) collected in the cooled bulb. The IR of the liquid was identical in all respects with that of a liquid obtained by refluxing a solution of 20 and 59 in benzene (Figure 17). The latter liquid was identified by IR and by elemental analysis as the monourethane 65 (Figure 17).

A crystalline solid resulting from heating the above ammonium salt settled in the trap chilled by dry ice-isopropanol bath. It had no carbonyl absorption in the IR and so failed to sustain further interest. Furthermore, the ammonium salt reacted with trifluoroacetic anhydride (TFAA) causing effervescence in the NMR tube. The NMR spectra of the contents of the tube suggested that 8 might have formed transiently. Absorptions were apparent at δ 4.1-3.8 (8H, multiplet), 2.4-1.9 (2H, multiplet) (Appendix A, Spectrum #1). The IR of the contents of the tube displayed a band at 1670 cm^{-1}(s) suggesting a urea carbonyl and another at 1800 cm^{-1} ascribed to open chain anhydrides (Bellamy, 1975). In the melting point tube, the salt degassed at 50° and the residue melted at 139-141°.

From the foregoing, the salt was assigned the structure 64 (Figure 16) and its reactions on heating as well as with TFAA are depicted in Figures 18 and 19 respectively. 1,5-Diazacyclooctane 32

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1. Analysis: Calculated for $C_{15}H_{28}N_2O_4$: C, 59.94; H, 9.42; N, 9.32. Found: C, 59.44; H, 9.54; N, 8.79; mp 74-76°; ν_{CO} = 1700 cm^{-1}. MS: m/e 300($M^{+}\cdot$); m-56; M-57.

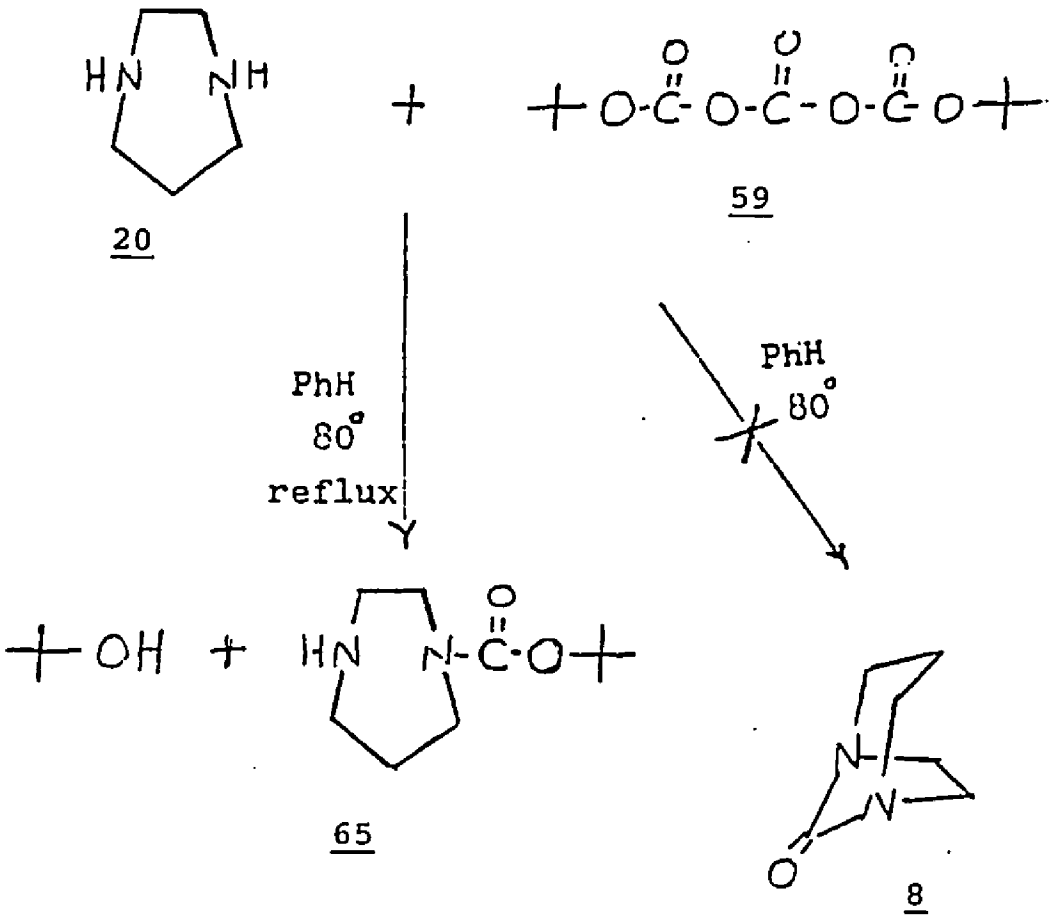


Figure 17. Products of the Reaction of 20 and 59 in Benzene at 80°

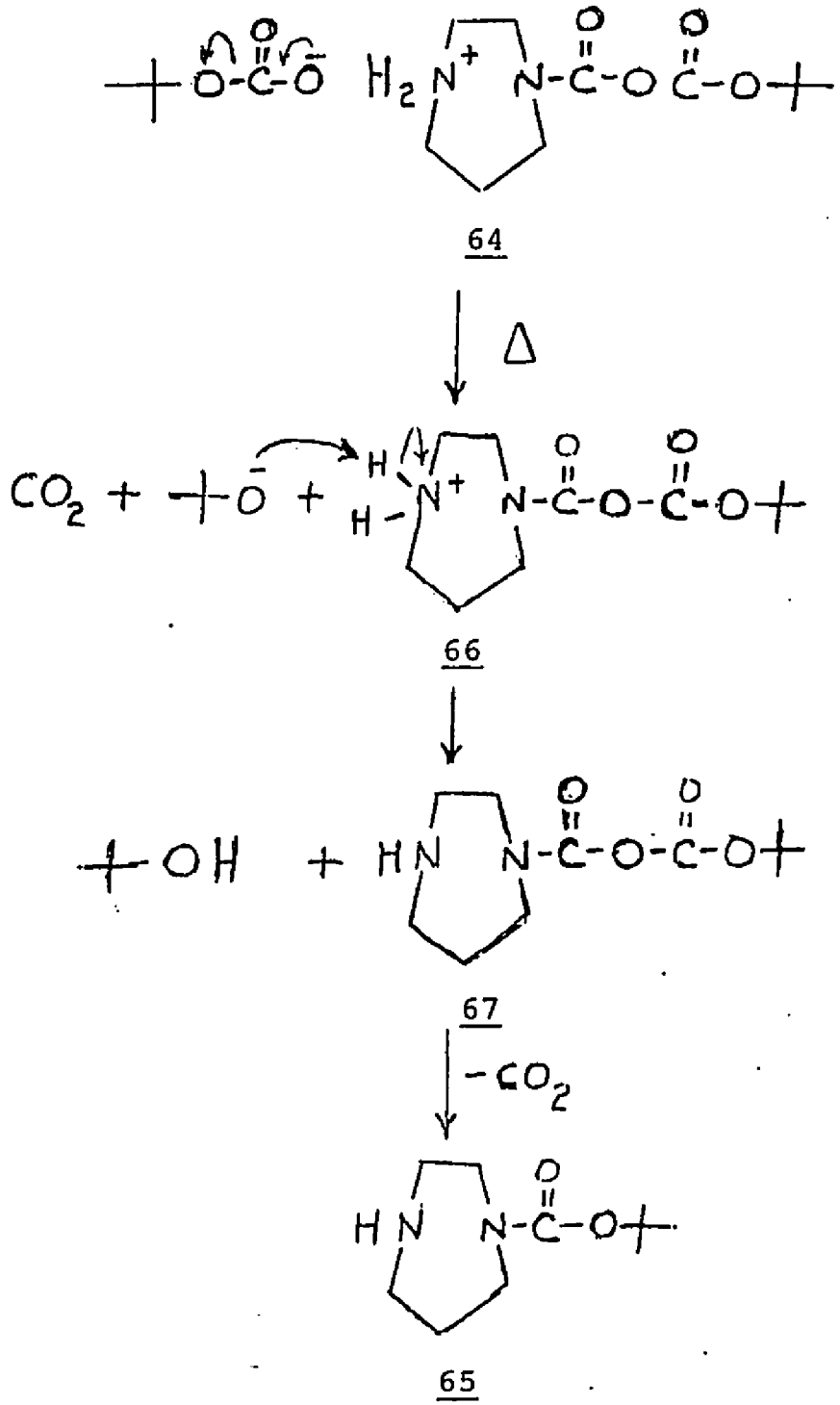


Figure 18. A Postulated Mechanism for the Decomposition of 46 by Heat

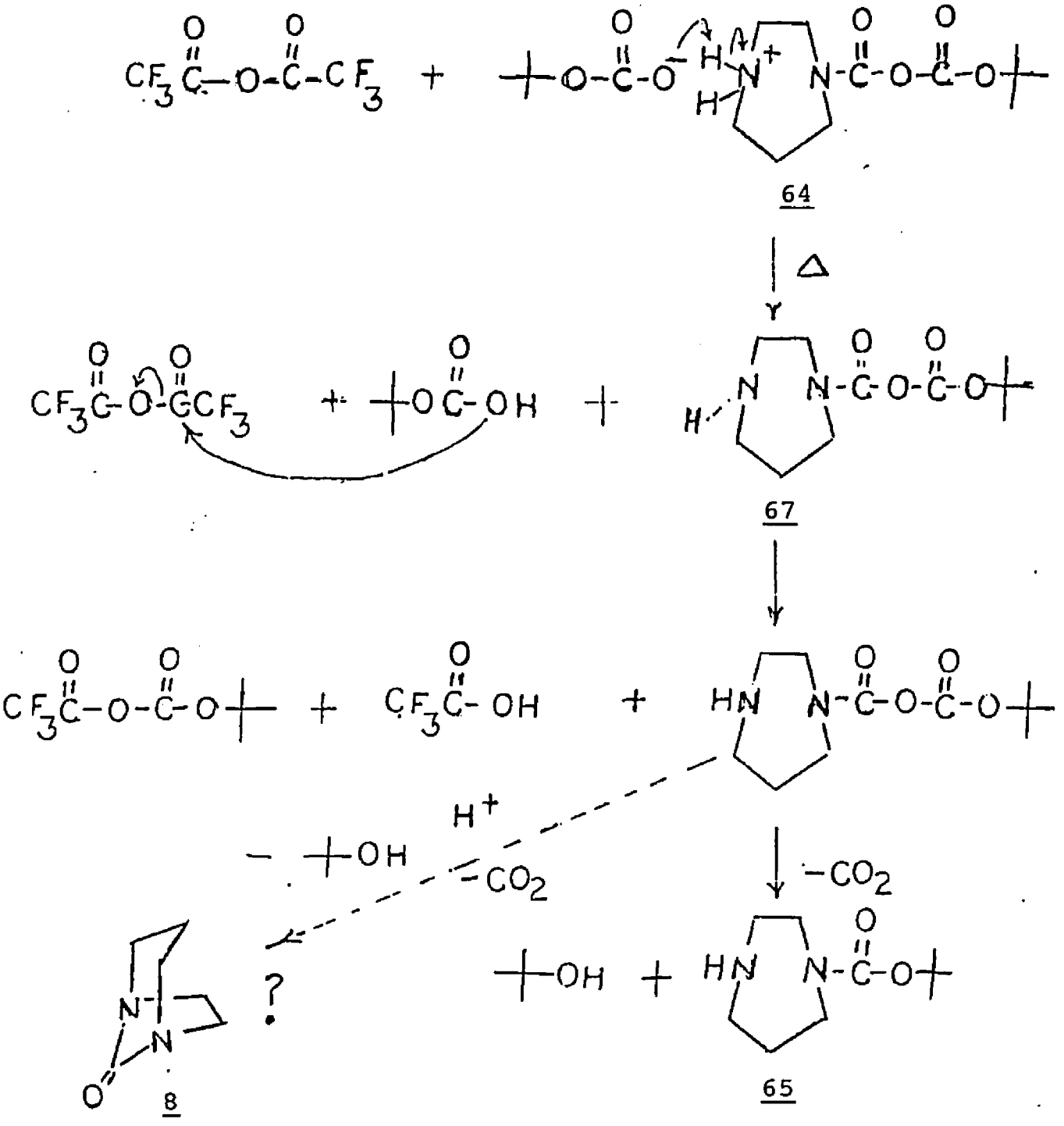
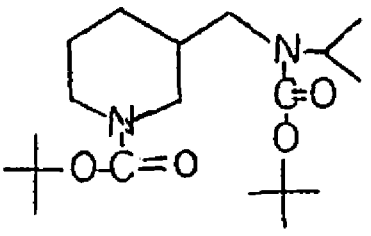


Figure 19. Postulated Products from the Reaction of 64 with Trifluoroacetic Anhydride (TFAA)

reacted in a manner similar to the reaction of homopiperazine 20 with di-tert-butyltricarbonate 59. As before the products were identified by IR. 3-Isopropylaminomethylpiperidine 18 reacted with 59 differently. The urea 4 did not form either, and no precipitate was observed. Instead, a liquid mixture was obtained from which the di- and monourethanes 68, 69, and/or 70 were isolated and identified by IR (ν_{NH} = 3375 cm^{-1}; ν_{CO} = 1700 cm^{-1}). The monourethane 69 and/or 70 distilled at 112-120°, 0.37 Torr. and the diurethane 68 distilled at 104°, 0.37 Torr.



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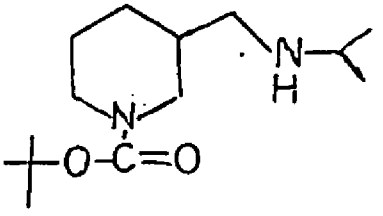

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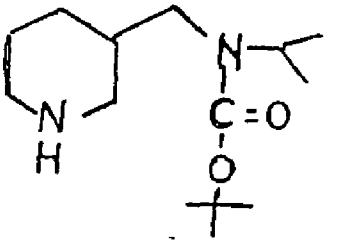

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Attempted Synthesis of 8 and 10 via Depolymerization of 71 and 76 (Figures 20 and 21)

Non-olefin chain-growth polymers show many characteristics of olefin polymers. For example, when heated at or above their ceiling temperatures they tend to depolymerize. In particular, polymers prepared from 5- and 6-membered cyclic ethers, lactams and lactones show a reversible polymerization-depolymerization behavior with an associated low ceiling temperature. In some cases, high yields of the monomer are recovered by the thermal degradation process (Lenz, 1967). It was, therefore, considered that since 8 and 10 contain 5- and 6-membered

ureas, they could be obtained by thermal degradation of their deliberately prepared polymers or oligomers.

The polymer or oligomer 71 (Figure 20) (ν_{CO} = 1620-1630 cm^{-1}, ν_{NH} = 3450 cm^{-1}) was prepared by an interfacial polycondensation reaction (Wittbecker and Morgan, 1959; Morgan and Kwolek, 1959; Magat and Strachem, 1955; Lenz, 1967; Figure 20). Thermal depolymerization of 71 above 360°, 0.1-0.05 Torr. generated a complex mixture of ureas. The IR spectra of this mixture displayed absorptions at 1690 and 3300 cm^{-1}. The thin layer chromatography of the mixture on silica gel with benzene, chloroform, dichloromethane, ether, tetrahydrofuran, and their various combinations as solvents did not effect a separation. However, Kugelrohr distillation gave three main fractions. One which collected in the dry ice trap as a viscous faint yellow liquid had no carbonyl absorption in the IR. It therefore invoked no further interest. A "fraction" (87-90°, 0.075 Torr.) was a green liquid which later partially crystallized. It displayed a rather broad absorption in the IR(neat) at 3250 cm^{-1}, a strong carbonyl absorption at 1690 cm^{-1} and another small sharp band at 2210 cm^{-1} (-N=C=O). Its NMR spectra discouraged any meaningful interpretation. On redistillation a fraction which later solidified on trituration with a 50/50 mixture of ether and dichloromethane came over at 60-70°, 0.05 Torr. It exhibited in the IR(KBr) sharp absorptions at 3210 cm^{-1}(NH) and at 1680 cm^{-1} (C=O). In comparison, the carbonyl absorption of a melt of bispentamethylene urea 72 occurs at 1645 cm^{-1} (KBr). A conclusion could be that the presence of two nitrogen atoms in the ring system of the "dimer" 73 or "trimer" 74 had conceivably raised their carbonyl absorptions by 35-45 cm^{-1}. Else,

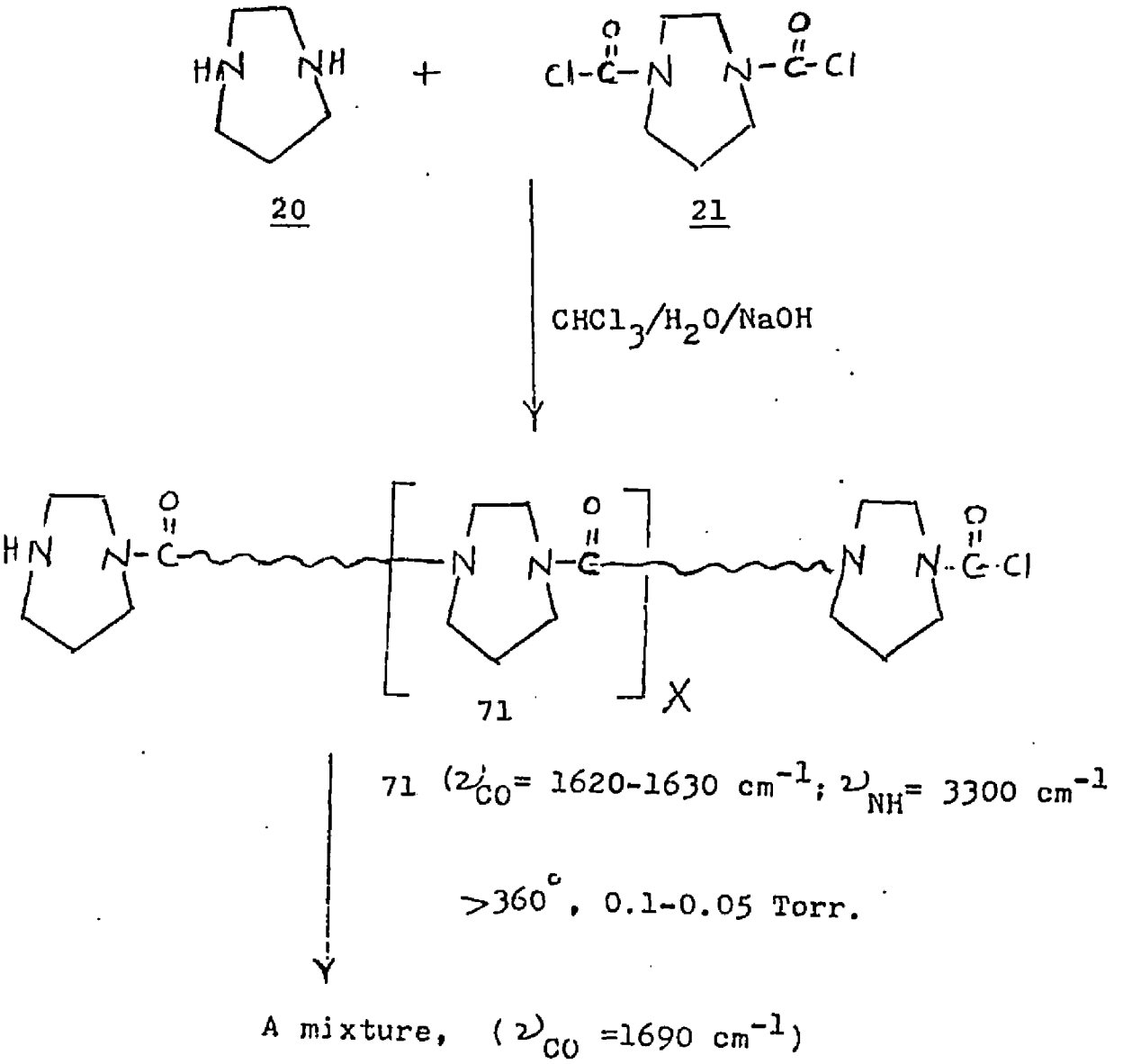
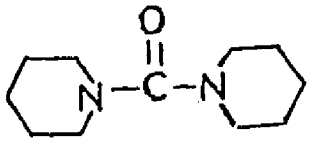


Figure 20. Interfacial Polycondensation of 20 with 21 and Depolymerization of 71

the products obtained contained the bicyclic urea which unfortunately could not be isolated.



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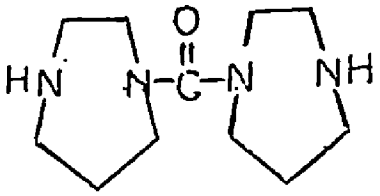

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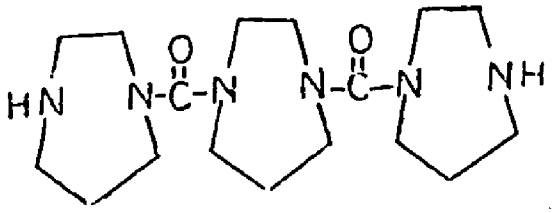

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In a similar manner, polycondensation of 32 with 75 gave a polymer 76 (Figure 21). It had a pronounced carbonyl absorption at 1620 cm^{-1} and melted at 128-155°. Its depolymerization was carried out in a horizontal 1/8" tube in which the polymer was sandwiched between glass wool. The end very near the polymer was sealed. Depolymerization of the polymer 76 at 233°, 0.05 Torr. yielded a soft solid. On subjecting the solid to sublimation at 90°, 0.05 Torr. a crystalline hygroscopic product was obtained. It had no sharp melting point. It showed an absorption at 1650 cm^{-1} (KBr) (C=O), and a weak doublet at 3280 and 3220 cm^{-1} (NH). A weak absorption was also observed at 3060 cm^{-1}, and a sharp one at 1520 cm^{-1}, probably an amide II band.

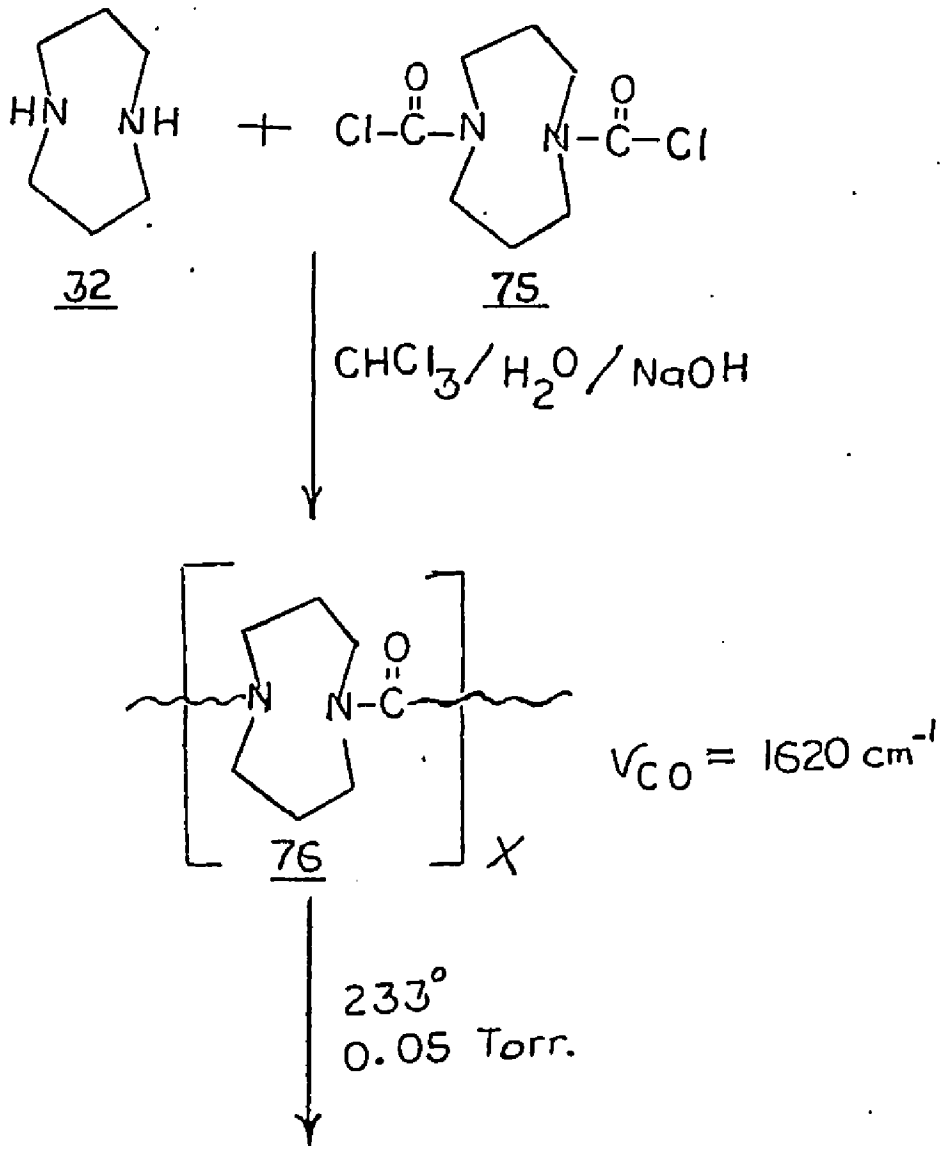
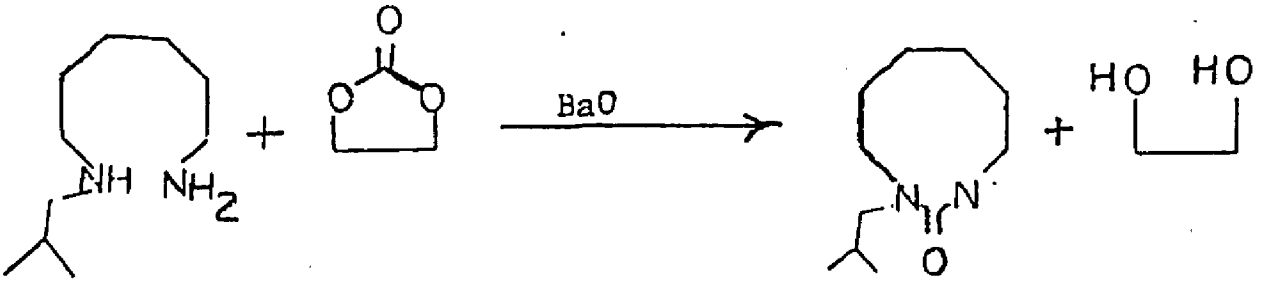


Figure 21. Interfacial Polycondensation of 32 with 75 and Depolymerization of 76

The mass spectrograph, the NMR, and the combustion analysis of this solid were not helpful in characterizing the material. The conclusion was that it was a mixture of the degradation products of 76.

Diphenyl Carbonate as a Carbonylating Reagent for the Synthesis of the Ureas 8-13 (Figures 22-25)

Since phenoxide ion is a good leaving group it was of interest to investigate diphenyl carbonate as a carbonylating agent in place of di-tert-butyltricarbonate-N,N'-carbonyldiimidazole or phosgene for the conversion of the diamines 20, 32, 35, 79, 80, and 82 to their corresponding N-bridgehead bicyclic ureas. Dyer and Scott (1957) have described a reaction in which a bulk mixture of N-isobutyl-1,6-hexanediamine and ethylene carbonate in the presence of catalytic amounts of barium oxide reacted to give N-isobutylhexamethylene urea as shown below:



In the same manner, when a bulk mixture of 3-aminomethylaminopiperidine 35 (Figure 22), diphenyl carbonate, and a catalytic amount of dibutyltin oxide was heated in vacuo, a hard brittle glass formed after the removal of the condensed phenol. The glassy material was successfully depolymerized at 208-240°, 0.05 Torr. High Pressure Liquid

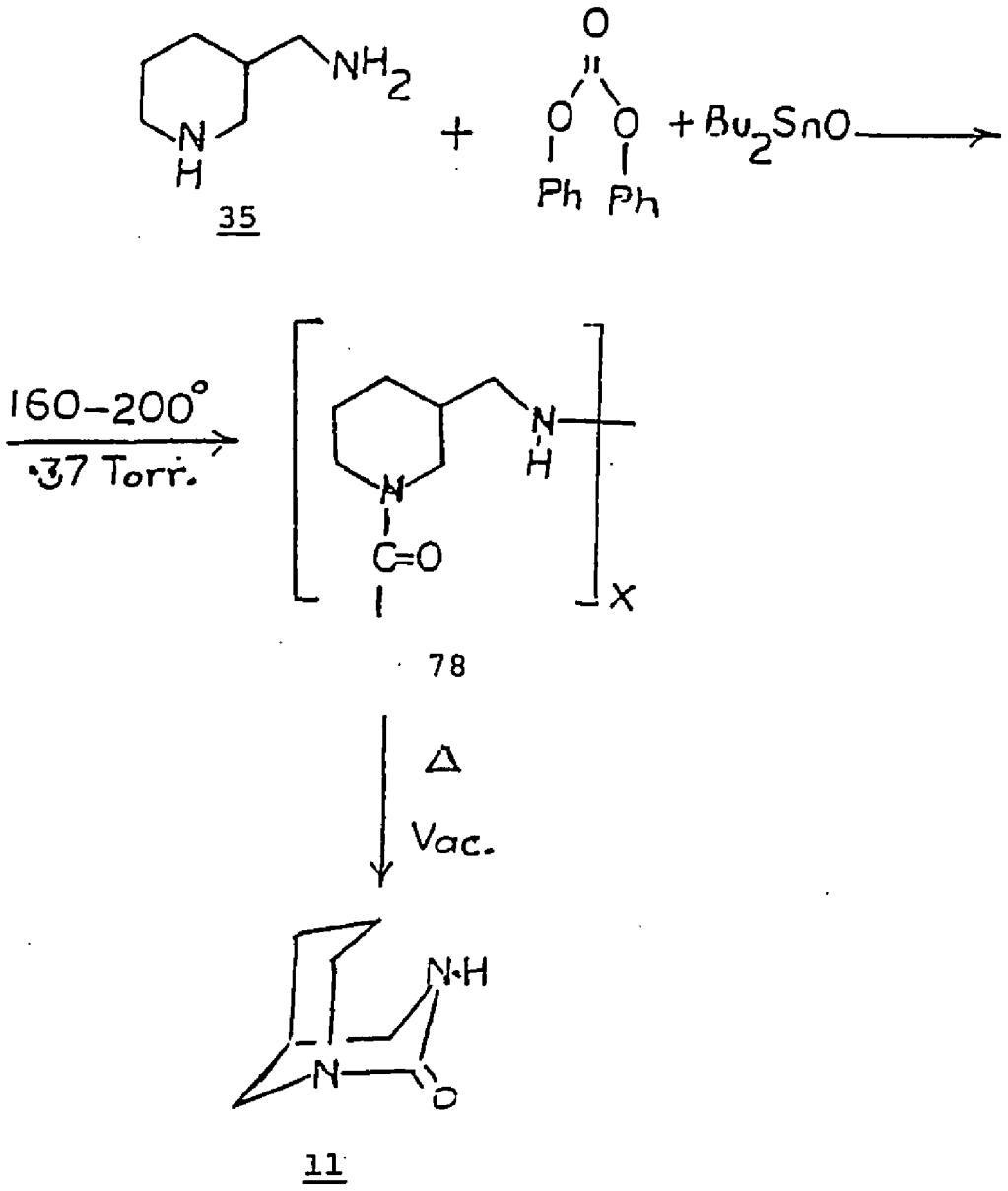


Figure 22. A Successful Carbonylation of 3-Aminomethylpiperidine 35 to Afford 11 via the Diphenyl Carbonate Route

Chromatography (HPLC) of the depolymerized material on silica gel gave 11 in 27% yield (Figure 22). Its spectra were identical in all respects with 11 obtained via phosgene route (Figure 10). A similar treatment of 2-aminomethylpiperidine 79 (Figure 23) by-passed the glassy stage and afforded 12 directly in 50% yield. But when 4-aminomethylpiperidine 80 (Figure 24), 3-aminopiperidine 82 (Figure 25), and 1,5-diazacyclooctane 32 (Figure 26) were each reacted in bulk with diphenyl carbonate in the presence of Bu_2SnO, the expected ureas 13, 9, and 10 respectively were not obtained.

The hot, bulk mixture of 4-aminomethylpiperidine 80 and diphenyl carbonate polymerized to a glass which decomposed extensively during the "depolymerization" step. A low yield (10%) of the urethane 81 mp 180-182° was obtained (Figure 24) along with a liquid which had no carbonyl absorption in IR. The identity of 81 was established by IR and NMR[1] only. Thus, at the high temperature (200-240°) and low pressure (0.05 Torr.) employed in the reaction, 81 resisted cyclization to 13.

The reaction of 3-aminopiperidine 82 with diphenyl carbonate followed by depolymerization at 290-305°, 0.3-0.4 Torr. and HPLC gave an anomalous result. The mass spectra of the solid cyrstalline sublimate (mp 173-175°, Kofler Hot Stage) suggested that the product was not the monomer 9 but rather the dimeric urea 83 existing in a

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1. NMR($CDCl_3$): δ 1.0-2.0 (5H, multiplet); 2.8-3.0 (4H, multiplet); 4.0-4.4 (9.2H); 4.9-5.2 (1H, multiplet); 7.0-7.4 (5H, multiplet). IR(KBr): 3375, 3300, 3150, 3075, 1710, 1630, 1580 cm^{-1}.

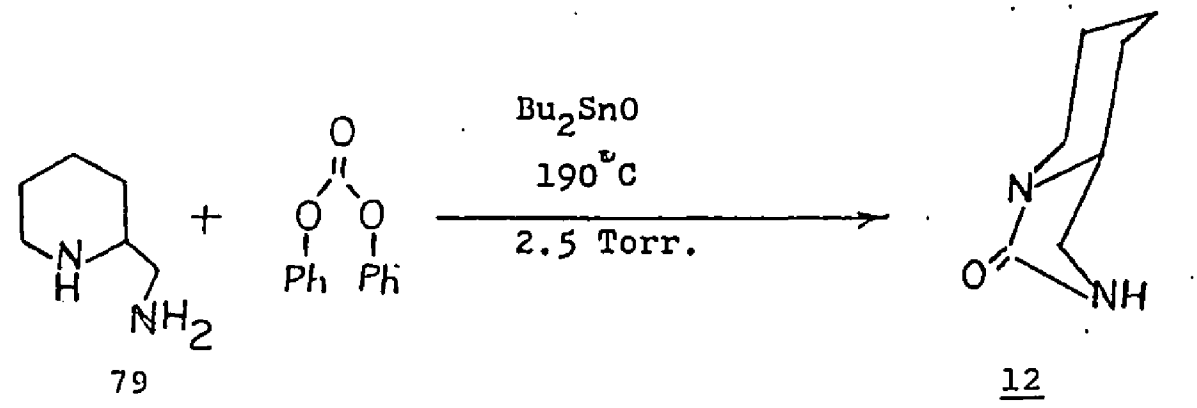


Figure 23. A Successful Synthesis of 12 via the Diphenyl Carbonate Route

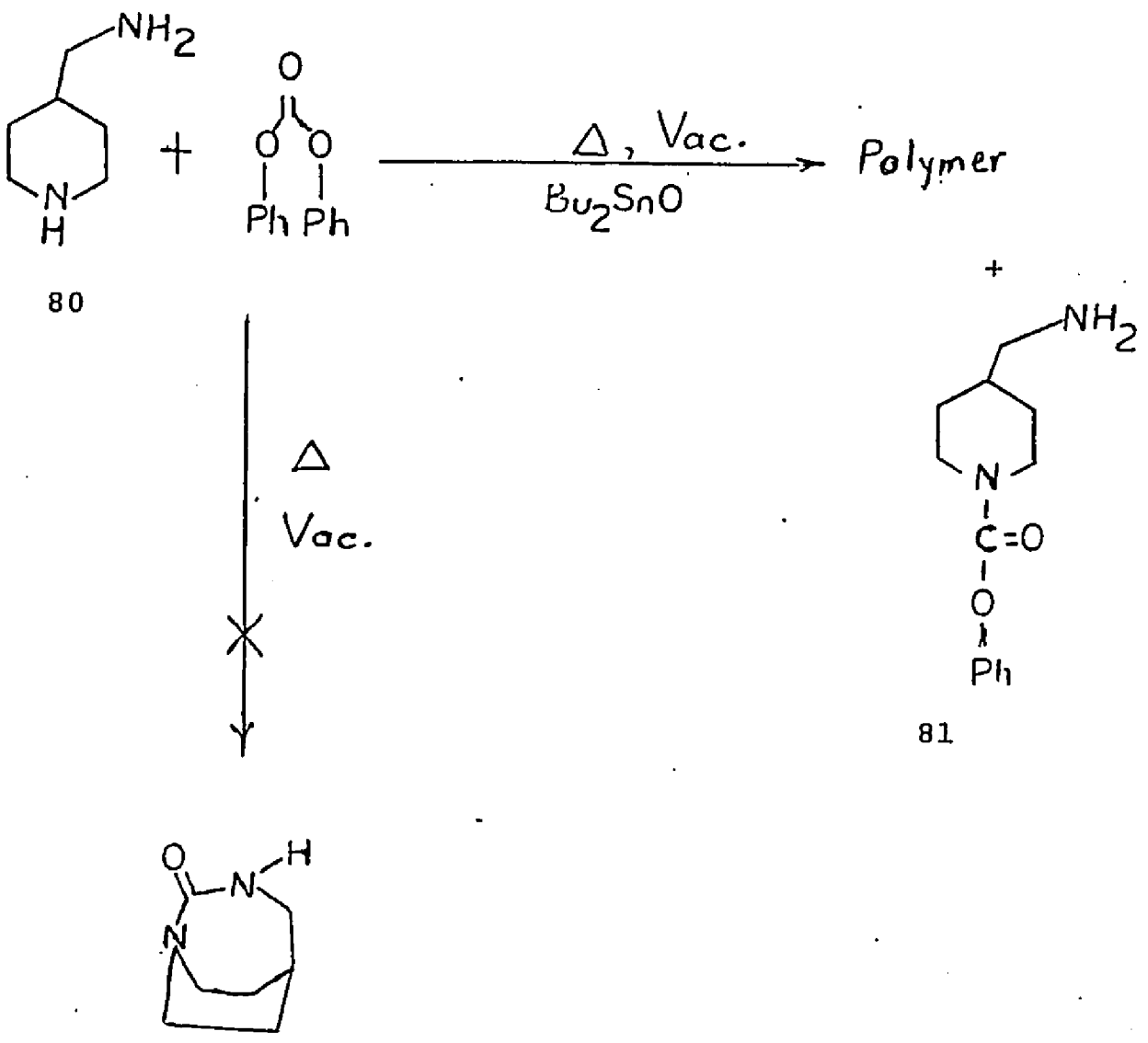


Figure 24. Attempted Synthesis of 13 via Diphenyl Carbonate Route

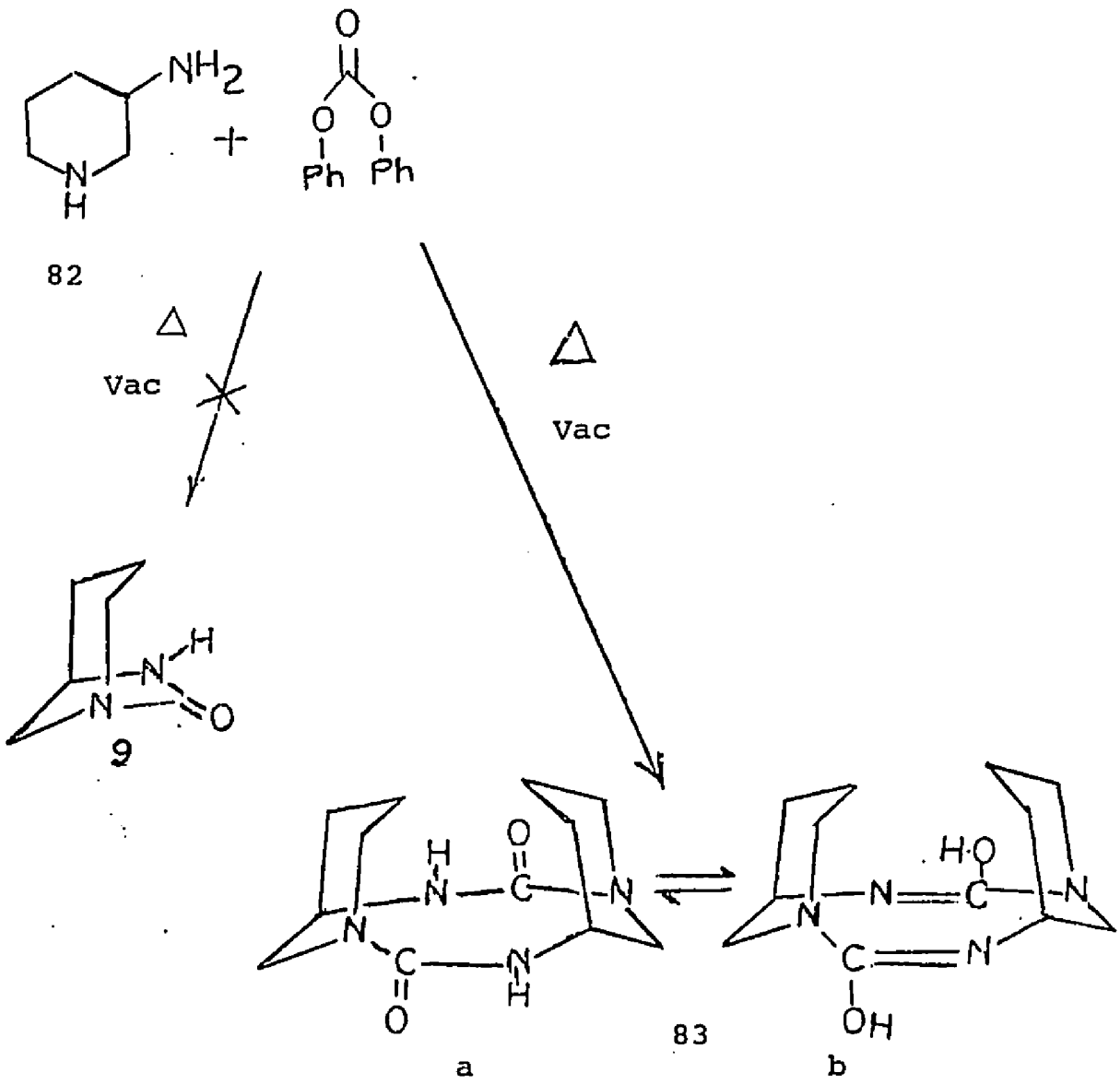


Figure 25. Attempted Synthesis of 9 via Diphenyl Carbonate Route; Formation of Dimer of 9

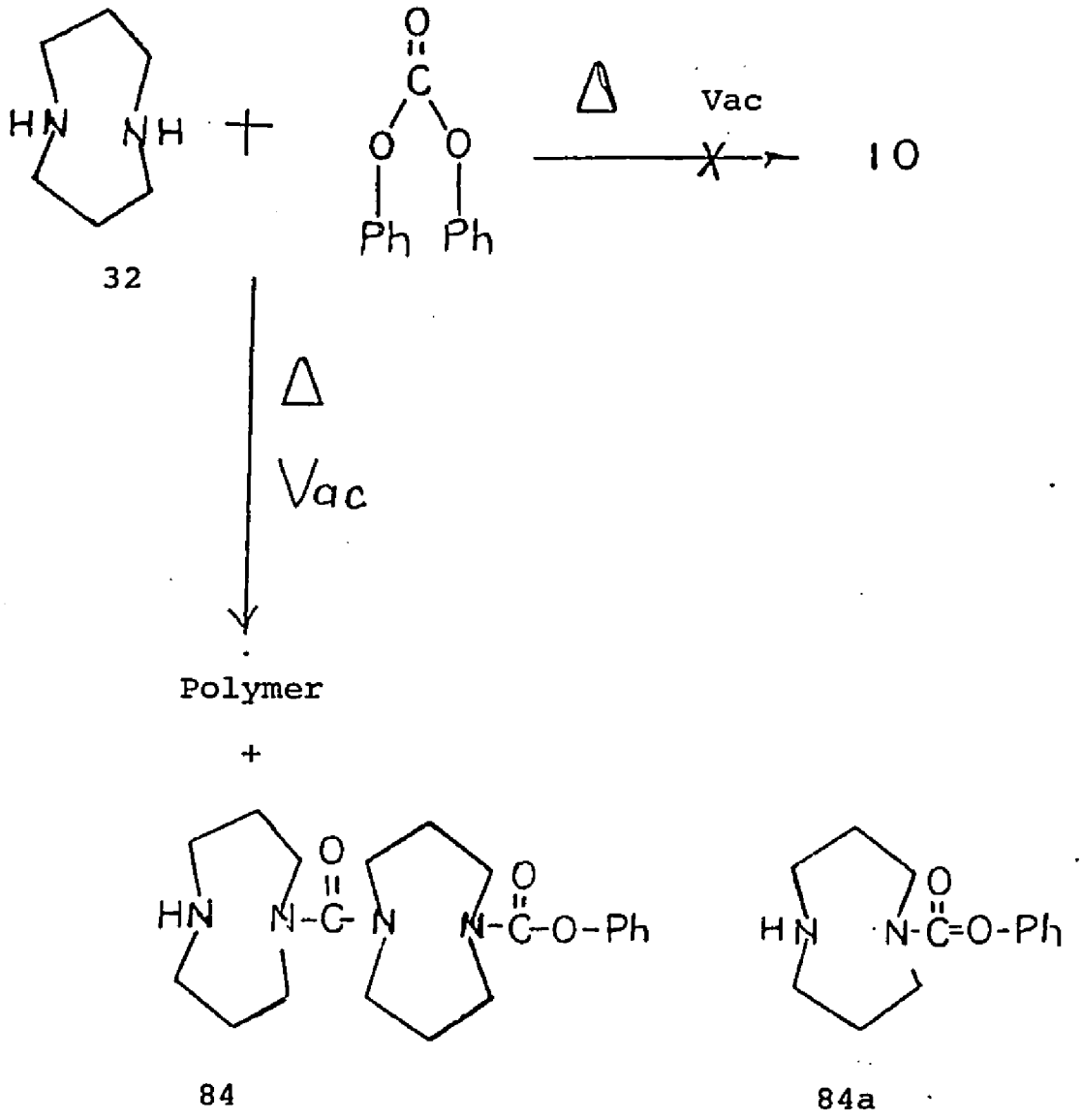


Figure 26. Attempted Synthesis of 10 via Diphenyl Carbonate Route

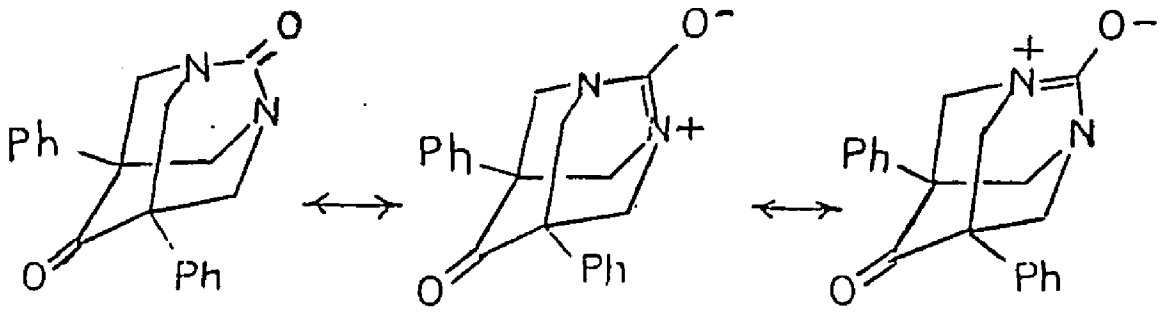
keto-enol form (Figure 25). The evidence for this conclusion was supported by the following observations:

1. The mass spectra showed an absence of a molecular peak at m/e 129 expected of structure 9. Instead a base peak at m/e 234 was observed (Appendix C, Spectrum #1). This strongly suggested a dimer of molecular weight equal to 252 minus a molecule of water. The enol structure 83b (Figure 25) could conceivably lose a molecule of water in the mass spectrograph.
2. Unlike the other two bicyclic ureas 11 and 12 which displayed sharp, prominent N-H absorptions in the infrared (Appendix B, Spectra #1 and #2), the N-H absorption of this product was vestigial and almost undetectable at 3500-3300 cm^{-1} (Appendix B, Spectrum #3). Again, the enol form 83b could account for this. The dominant carbonyl absorption around 1660 cm^{-1} showed some splitting probably indicating a HO-C=N- contribution known to occur around 1673-1620 cm^{-1} (Bellamy, 1968). The carbonyl absorption of this compound generally appeared to be in accord with a urea in which the possibility of the existence of the enolic form was recognized by Gompper and Herlinger (1956) and by Bellamy (1958, 1968).
3. The Chemical analysis was consistently in agreement with formula $C_{13}H_{19}N_4O$ instead of $C_{12}H_{20}N_4O_2$ for dimer 83. The history of the compound makes $C_{13}H_{19}N_4O$ an unlikely candidate indeed.
4. NMR($CDCl_3$): δ 4.7-2.4 (12H, multiplets), 2.4-1.2 (8H, multiplets). Appendix A, Spectrum #6.

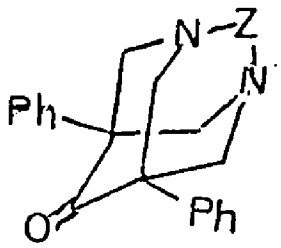
The reaction of 1,5-diazacyclooctane 32 with diphenyl carbonate with Bu_2SnO as a catalyst largely gave a polymer (Figure 26). A small quantity of a liquid was also isolated. Its IR and NMR suggested that it was an oligomer probably the urethane-urea 84 rather than the urethane 84a (Figure 26). IR (neat): 1720, 1700, 1640, 1600, 700 cm^{-1}; NMR ($CDCl_3$): δ 6.6-7.4 (5H, multiplet), 3.8-1 (25H, multiplets).

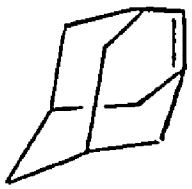
Comments on the Unsuccessful Syntheses of 8, 10, and 13 (Figures 27 and 28)

Some of the promising synthetic methods applied in the present work were adapted from the literature (Hall and Johnson, 1972; Moller, 1957; Misiti and Chiavarelli, 1966; Dyer and Scott, 1957). They proved unsuccessful in the synthesis of 8, 10, and 13. The two nitrogen atoms of 8 and 10 are located at the bridgeheads. The N-atoms of 1,5-diphenyladamantan-9,10-dione 49 are similarly located. As indicated in Figure 13, Misiti and Chiavarelli (1966) also failed to prepare 49, although they succeeded in synthesizing the homomorphic sulfoxide 85 and sulfone 86. These sulfur compounds were stable and isolable because of sulfur d_π-p_π orbital overlap. In comparison, adamantene 87, similar in structure to the resonance forms 49b and 49c, has been generated only as a transient intermediate (Liebman and Greenberg, 1976; Grant et al., 1972; Lenoir, 1972; Gano and Eizenberg, 1973; Burns and McKerney, 1974). Therefore, it should not be very surprising that Misiti and Chiavarelli (1966) were unable to prepare 49. Although it was disappointing that 8, 10, and 13 eluded accessibility in the present study, the reason for the difficulty seemed obvious. An



49 49b 49c





85, Z = SO

86, Z = SO_2

87

examination of 87, 49b, and 49c, above, 8b-c, 10b-c, and 13b-c (Figure 27) reveals a common feature: each incorporates in the largest ring, either a cis cycloheptene or a cis cyclohexene type of structure. According to Wiseman and Pletcher (1970) a bicyclic bridgehead alkene should be isolable if the larger of the two rings containing the double bond is at least eight membered, and possibly isolable only if the double bond is trans in a seven membered ring. In other words, bridgehead trans cycloheptene is about the lowest limit of isolable bridgehead bicyclic alkene structures. Therefore cis cycloheptene and cis cyclohexene bridgehead compounds would appear to be totally inaccessible (Buchanan, 1974).

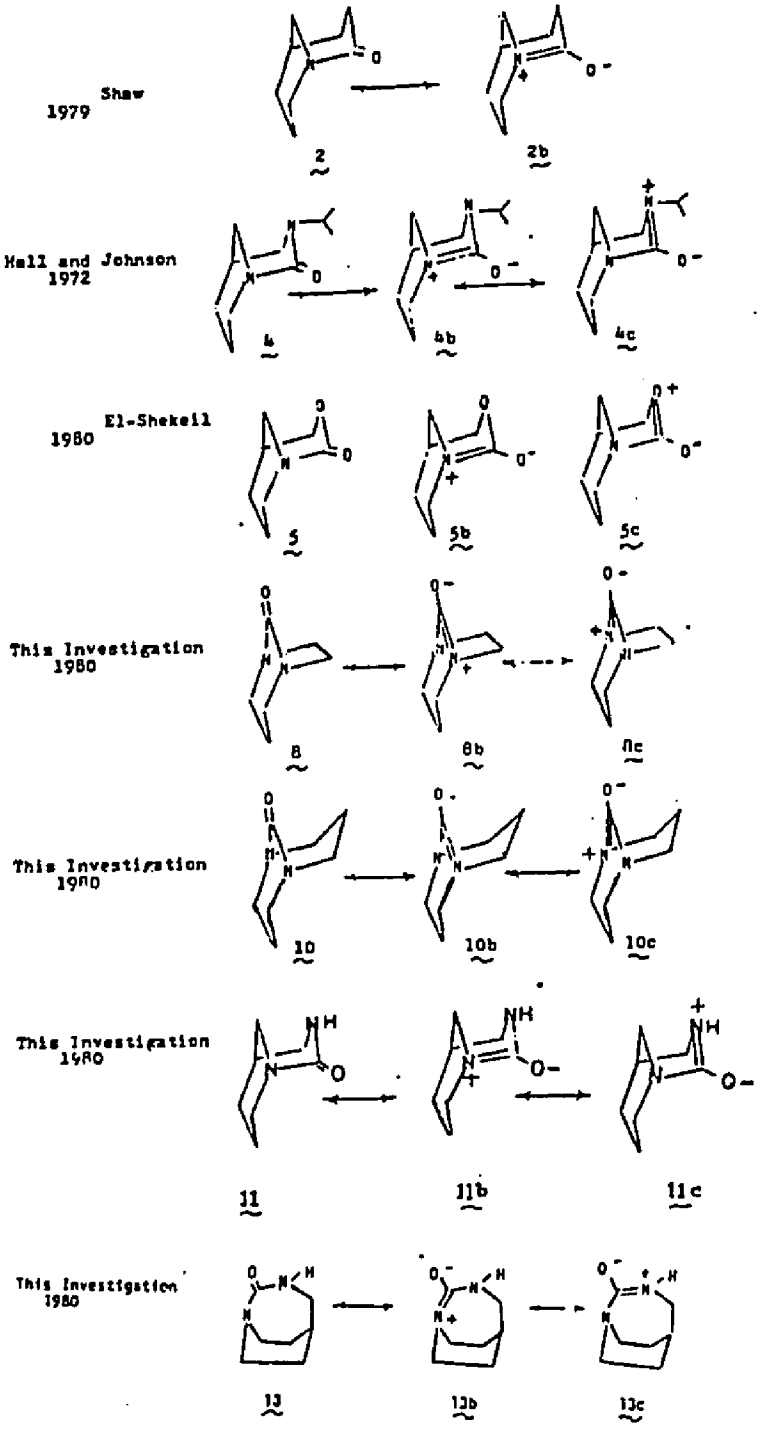


Figure 27. A Comparison of the Structures of 2, 4, 5, 8, 10, 11, and 13 to Explain the Unsuccessful Syntheses of 8, 10, and 13

This consideration severely dampered the prospects for the existence or isolation of 8, 10, and 13 under the conditions of the present study. These ureas could conveniently be termed "anti-Wiseman" compounds.

On the other hand, the largest rings in 2b, 4b-c, 5b-c, and 11b-c (Figure 27) embody bridgehead trans cyclooctenes. The largest ring of 12b-c (Figure 28) is a cyclononane structure. In addition, in this bond bridged system, overlap is allowed. In agreement with Wiseman's rule, Hall and Johnson (1972) and El-Shekeil (1980) had little difficulty in preparing 2, 4, and 5. Also in the present study, 11 and 12 were easily prepared.

The canonical form 9b-c (Figure 28) harbors a cis cycloheptene structure. Therefore, as observed in adamantene 87, the distortion of the double bond in 9b-c must be very severe (Buchanan, 1974; Kobrich, 1973). A Dreiding model of 9b confirmed this proposition. To relieve the strain, 9 "dimerized" to a 10-membered ring conformation to give 83 isolated in this study.

Comments on the Preparation of the Starting Materials

Homopiperazine 20 and 4-Aminomethyl-piperidine 80

These diamines were purchased from the Aldrich Chemical Company Inc. Homopiperazine 20 was purified by extraction with anhydrous ether if exposed to air for long periods of time. The commercially available 99% 4-aminomethylpiperidine 80 was dried over analytical reagent grade sodium hydroxide and redistilled therefrom.

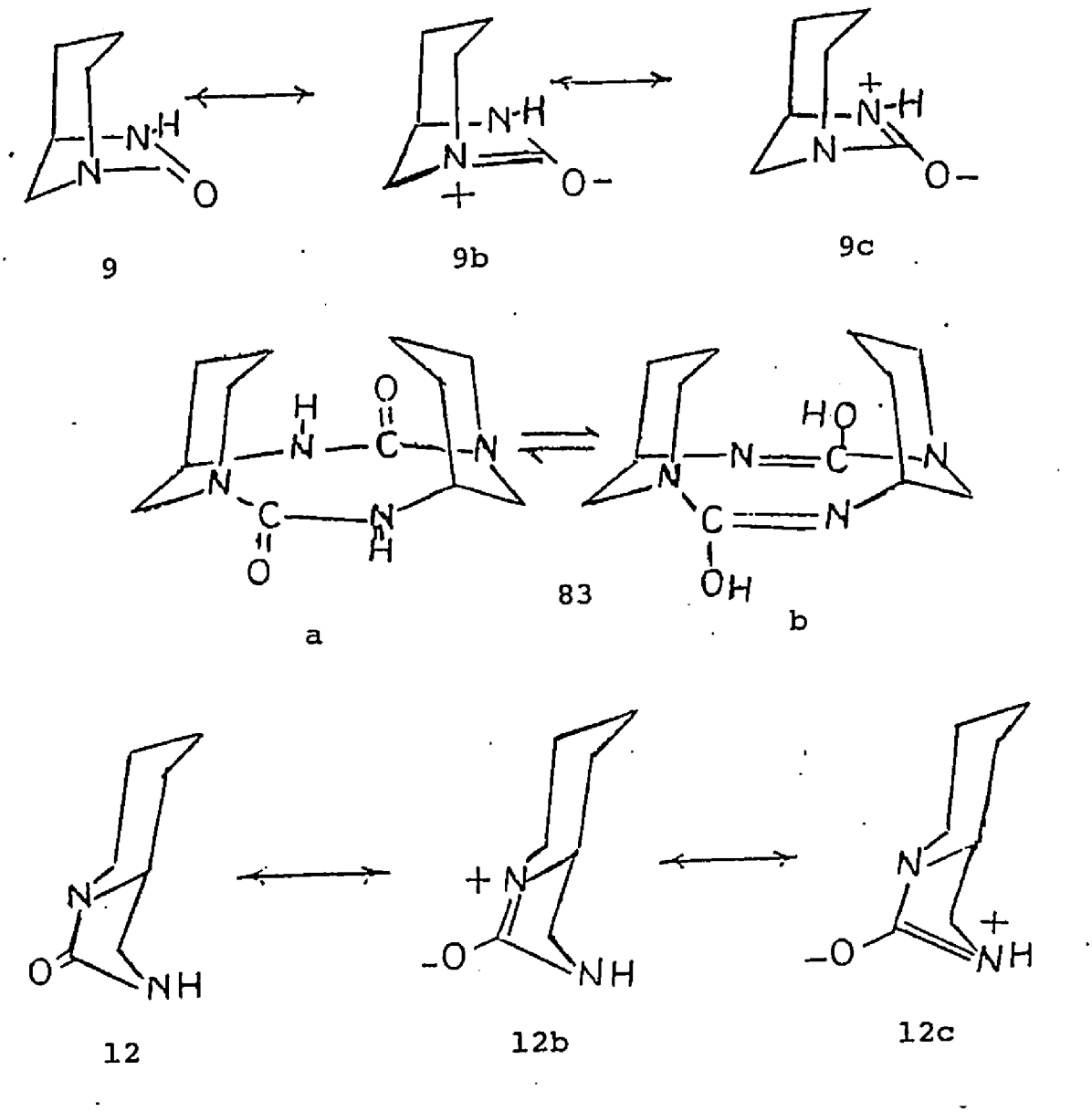


Figure 28. A Comparison of Structure 9 with Its Dimer 83 and with 12

1,5-Diazacyclooctane 32

Several methods for the preparation of 1,5-diazacyclooctane 29 and some of its derivatives appeared in the literature (Kost and Chursing, 1951; Buhle, Moore, and Wiselogle, 1943; Howard and Marckwald, 1899; Kemp, Chabala, and Marson, 1978; Hall, 1958a). Of these, a modification of the procedure of Howard and Marckwald (1899, Figure 29, Method A) and a variant of Hall's (1958a) method (Figure 30, Method B) were the most convenient and unambiguous to apply in this investigation. The method of Buhle et al. (1943), though oft-referred to in the literature, could not be reproduced.

A Synthesis of 32; Method A (Figure 29)

A Schotten-Bauman two-phase reaction of 2 moles of tosyl chloride with one mole of 1,3-diaminopropane afforded 1,5-diaza-1,5-ditosyl pentane 88 in 90% yield; 88 was sufficiently pure for the next synthetic step. A phase-transfer catalysis reaction of 88 with 2,3-dibromopropane generated 1,5-diaza-1,5-ditosyl cyclooctane 89 in 50% yield. For the hydrolytic cleavage of 89 utilizing 48% HBr, the procedures of Koyama and Yoshino (1972), Yang and Zompa (1976), and White et al. (1979) were slightly modified and employed in the present study. The method advanced by Richman and Atkins (1974), Weitl and Raymond (1979), and Smith, Ekstrand, and Raymond (1978) using 98% H_2SO_4 for the hydrolytic cleavage of -N-Ts bond was found in the present study to be either unworkable or tedious and hazardous. Deprotonation of the dibromide 90 afforded 32 in 73% yield based on 89.

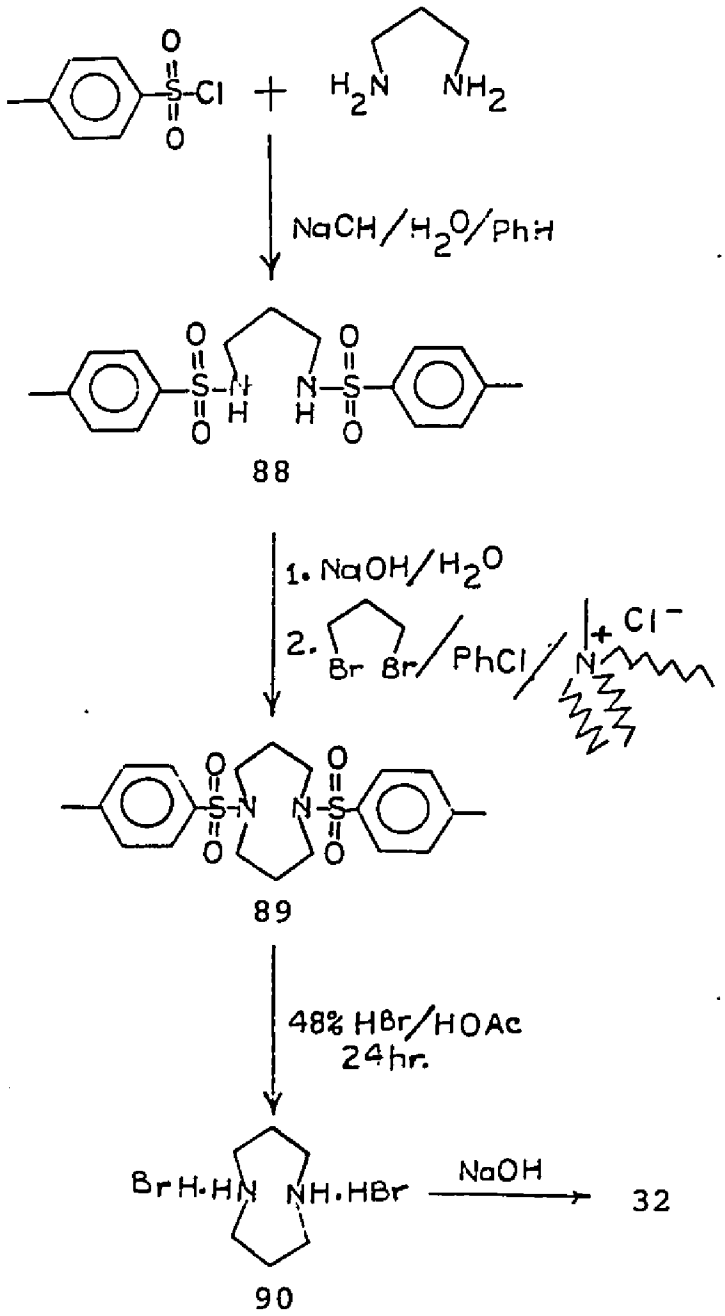


Figure 29. A Synthesis of 1,5-Diazacyclooctane, 32; Method A

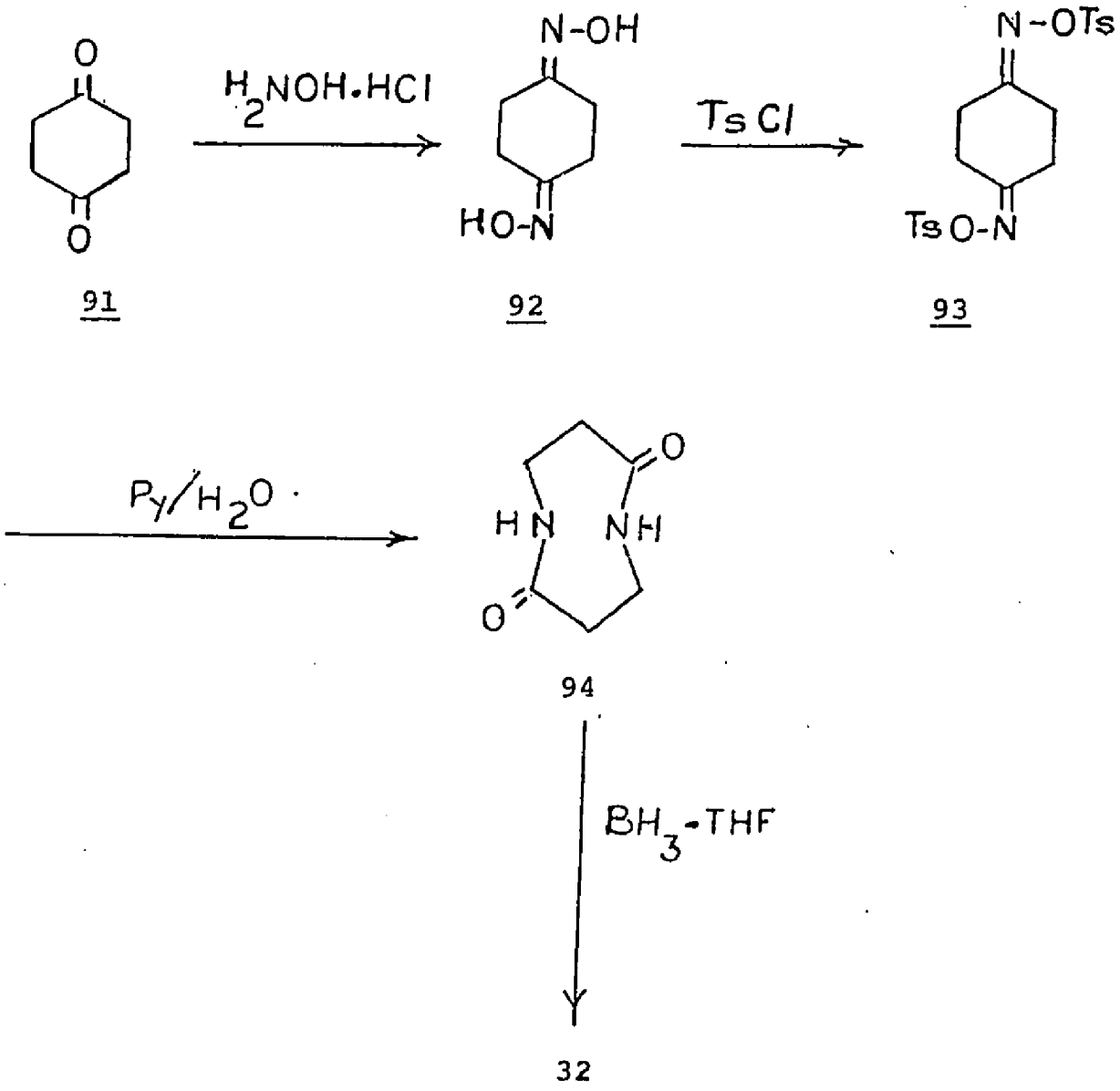


Figure 30. An Alternative Route to Prepare 32; Method B

A Synthesis of 32; Method B
(Figure 30)

During the preparation of 1,4-cyclohexane-dioxime ditosylate 93 subsequent to conversion to 1,5-diazacyclooctane-2,6-dione 94 as described in the literature (Hall, 1958a) an interesting observation was made. The conversion of cyclohexene-1,4-dioxime 92 to the ditosylate 93 proceeded normally as reported in the literature (Iwakura et al., 1969). Hall (1958a) caused the ditosylate to undergo a Beckman rearrangement by heating it in a solution of sodium acetate and glacial acetic acid. In the present study, it was found that this step was unnecessary. The ditosylate underwent a facile Beckman rearrangement to the 2,6-dione 94 during the process of its recrystallization from hot aqueous pyridine as described in the literature (Knunyants and Fabrichnyi, 1949), thus saving one step.

Preparations of the Diamines 35, 79, and 82

3-Aminomethylpiperidine 35, 2-aminomethylpiperidine 79, and 3-aminopiperidine 82 were prepared by high pressure hydrogenation of the corresponding pyridines with 5% ruthenium-on-carbon as a catalyst. The pyridine rings were resistant to hydrogenation. So in each case rehydrogenation was necessary under severe conditions and with fresh catalysts.

Preparation of 2,4,6-Triisopropylphenylsulfonic Acid 27

The alkaline hydrolysis of the commercially (Aldrich Chemical Co. Inc.) available 2,4,6-triisopropylphenylsulfonyl chloride gave 27 in 100% yield.

Preparation of Di-tert-butyltricarbonate 59

The tricarbonate 59 was prepared exactly as described in the literature (Pope et al., 1977).

Reactivities of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11 and 1,3-diazabicyclo[4·3·0]nonan-2-one 12

The chemical reactivities of 11 and 12 were of interest. At ambient temperature, urea 11 was sparingly soluble in D_2O in the NMR tube. Except for the N-H to N-D isotopic exchange and minor differences in chemical shifts, there were no significant differences in the spectra with D_2O and $CDCl_3$ as NMR solvents. After 13 days at ambient temperature or 2 hours at 70° there was also no change in the NMR spectra. Under identical conditions, similar results were obtained with a mixture of 11, D_2O, and potassium carbonate in one NMR tube, and 11, D_2O, and potassium tertiary butoxide in another. However, when HCl gas was bubbled into the mixture of D_2O and 11 at ambient temperature, 11 dissolved and there was a dramatic change in the NMR spectra. The conclusion was that urea 11 was surprisingly and remarkably stable under basic conditions at ordinary temperatures, but would hydrolyze under strongly acidic conditions.

Essentially similar results were obtained with 1,3-diazabicyclo-[4·3·1]nonan-2-one 12.

Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11 and 1,3-diazabicyclo[4·3·0]nonan-2-one 12

Polymerizability of the bicyclic ureas was one of the objectives of this work. At any temperature no bulk or solution polymerization was

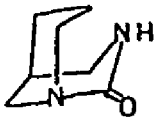
observed for urea 12 with or without catalyst. Urea 11 however, bulk polymerized thermally. But it did not polymerize in solution (diglyme) with or without catalyst even at 120°. On bulk polymerization its carbonyl absorption in the IR shifted from 1660 to 1620 cm^{-1}, the sharp NH absorptions of the monomer at 3310, 3200, and 3100 cm^{-1} collapsed to a broad one at 3200 cm^{-1}. The fingerprint region was almost featureless. These changes in IR spectra were exploited in monitoring the polymerizability of 11 under various conditions.

The urea 11 was sealed in the melting point capillary tubes. Duplicates were heated in thermostated oil baths at various times and temperatures. Their IR spectra were taken in KBr pellets. The results are shown in Table 1. From Table 1 the observation was that uncatalysed bulk polymerization of 11 began within 30 minutes of heating at 120°.

Next, the effects of anionic, cationic, and metal coordination catalysts in bulk polymerizations were investigated. A bulk mixture of about 20 mg of urea 11 and trace amount of the catalyst was heated at 120-135° for 6 hours in evacuated sealed vials. The catalytic initiators were potassium tertiary butoxide, phenyl phosphonic acid, and dibutyltin oxide.

The uncatalysed and the catalysed polymerization reactions of 11 yielded hard glassy, transparent polymers which were insoluble in 1,2-dichloroethane, dimethylformamide, tetrahydrofuran, and glyme, but significantly soluble in warm absolute ethanol. Purification was attempted by slurrying the crude polymer first, in 1,2-dichloroethane and later in dimethylformamide to remove unreacted monomers. It was then washed with water, methanol, and ether in that order. Later it was

Table 1. Thermal Uncatalysed Bulk Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one, 11



Time (min)	Temperature °C	IR (KBr) ν_{NH} cm^{-1}	IR (KBr) ν_{CO} cm^{-1}	IR (KBr) Finger Print Region Characteristic	Other Observation	Inference
0	25	3310 3200(s) 3100	1660(s)	Sharp outline	--	Monomer
5	120	3310 3200(s) 3100	1660(s)	Sharp	--	Monomer
10	125	3200(s) 3100	1660(m)	Partly sharp or keen, partly broad	--	Mostly monomer
30	125	3200(s) 3310 3100	1600	Featureless	--	Onset of polymerization
60	120	3200	1620	Featureless	Tough polymer isolated	Polymer/ monomer
180	95	3200(s) 3310	1660	Sharp	--	Monomer
63 hr	95	3200	1660- 1620(dull	Sharp outlines	--	Mostly monomer

found that the polymer dissolved completely in 1,1,1-3,3,3-hexafluoro-2-propanol (HFIPA) from which analytical samples were precipitated with anhydrous ether. Viscosity measurements at 32° were made in this solvent after removing spurious particles by filtration through a cotton wool. The results are shown in Tables 2 and 3. In Tables 2 and 3, the important viscosity term, the intrinsic viscosity, was computed from Huggins equation (Huggins, 1942).

$$\frac{\eta_{sp}}{C} = \text{Reduced Viscosity} = [\eta] + k'[\eta]^2 C$$

in which, for many polymers in good solvents $k' = 0.4 \pm 0.1$ (Rodriguez, 1970).

$$[\eta] = \text{Intrinsic Viscosity} = \lim_{C \to O} \frac{\eta_{sp}}{C}$$

$$\eta_{sp} = \text{Specific Viscosity} = \eta_r - 1 = \frac{t - t_o}{t_o}$$

$$C = \text{Concentration, } \frac{\text{g polymer}}{100 \text{ ml solution}}$$

where: t = time of flow of polymer solution,

t_o = time of flow of solvent in the Ostwald-Fensk capillary viscomets

In this calculation k' was assumed to be 0.40. From $[\eta]$ calculated, the viscosity average molecular weight $\overline{Mv}$ (Stevens, 1975) could be estimated from the Mark-Houwink equation $[\eta] = K\overline{Mv}^a$, if K and a could be evaluated. In Table 2, however, the molecular weights of polymers 1-4 have been estimated from the range of molecular weights customarily

Table 2. Catalysed Bulk Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11

Sample No.	Weight of Urea (mg)	Catalyst	Polymerization Temperature °C	Monomer Heating Time (hr)	Weight and Yield of Polymer (mg)	m.p. of Polymer °C	Inherent Viscosity $\eta_{inh} = \frac{\ln \eta_r}{c}$	Specific Viscosity $\eta_{sp} = \eta_r - 1 = \frac{t-t_o}{t_o}$	Intrinsic Viscosity $[\eta] = \frac{\eta_{sp}}{c}$	Estimated Molecular Weight from η_{inh}
							$\frac{100 \text{ ml solution}}{\text{g polymer}}$			
1	202	None	120	6	100(55%)	200-210	0.64	0.89	0.696	Medium 10,000-15,000
2	204	$PhPO_3H_2$	120	6	150(74%)	200-210	0.81	1.26	0.921	Medium 15,000-50,000
3	202	Bu_2SnO	120	6	120(60%)	201-212	0.89	1.45	1.028	Medium 10,000-50,000
4[a]	227	tBuOK	120	6	170(75%)	>220	1.23	2.1	1.45	High 50,000
	202	None	95	24	None	--	--	--	--	--
	211	PhNCO + KOtBu	112	24	Discoloration (Trace?)	--	--	--	--	--
5	204	H_3PO_4	98	2	110(54%)	>220	0.13	0.15	0.14	Low 10,000-15,000

[a]Polymer #4 was so electrostatic that manipulating it was difficult.

Table 3. Viscosity Measurements at 32° of Polymers from 1,3-Diazabicyclo[3·3·1]nonan-2-one 11

Polymer #	Solvent Flow Time, t_o (sec)	Polymer Solution Flow Time, t (sec)	Polymer Solution Concentration C=g/100 ml Solution	Relative Viscosity η_r, $\frac{\eta}{\eta_o}$ $\frac{t}{t_o}$	Specific Viscosity η_{sp}, $\eta_r - 1 = \frac{t-t_o}{t_o}$	Inherent Viscosity η_{inh}, $\frac{\ln\eta_r}{C}$, $\frac{100\ ml}{g}$
1	56.4	106.5	1.0	1.89	0.89	0.64
2	56.4	127.2	1.0	2.26	1.26	0.81
3	56.4	138.0	1.0	2.45	1.45	0.89
4[a]	56.4	174.6	0.9195	3.096	2.10	1.23
5	56.4	65.2	1.1	1.15	0.15	0.13

[a]Polymer #4 was so electrostatic that weighing it was difficult.

(Hall, 1978) assigned from inherent viscosities, η_{inh}, as shown in Table 4.

Table 4. Molecular Weight-Inherent Viscosity Relationship

η_{inh}, Deciliter/g	Polymer Description	Molecular Weight
< 0.1	Oligomers	< 10,000
0.1-0.5	Low Polymer	10,000-15,000
0.5-1.0	Medium Polymer	15,000-50,000
1.0 and over	High Polymer	50,000

Ureas 11 and 12 failed to polymerize in solution with or without catalysts. For the solution polymerization tests, the initiators investigated were methyltrifluoromethylsulfonate, $CF_3SO_3CH_3$, in 1,2-dichloroethane and sodium methoxide in glyme, at 24°, 55°, and 120° (Table 5).

The general conclusions concerning the reactivity and polymerization of ureas 11 and 12 were:

1. Ureas 11 and 12 were stable to hydrolysis under normal conditions.
2. At any temperature no bulk or solution polymerization was observed for the [4·3·0] system with or without catalytic initiators.

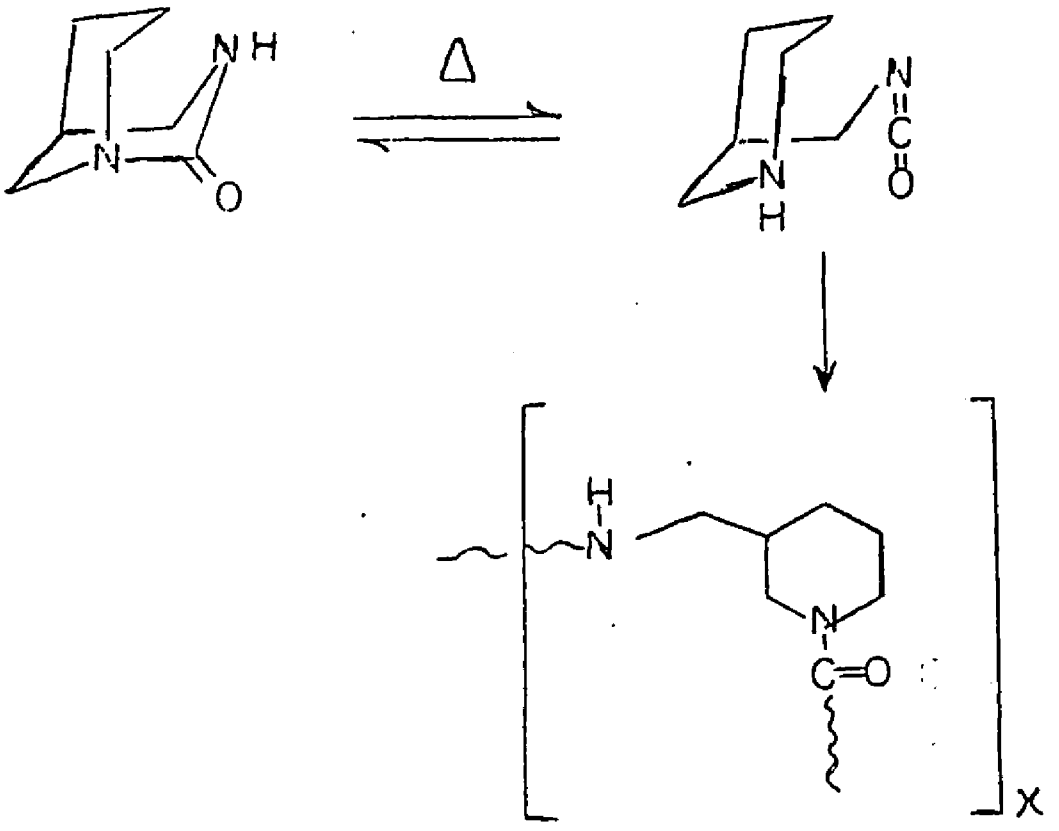
Table 5. Attempted Solution Polymerization of 11 and 12

Monomer	Weight of Monomer (mg)	Solvent (0.8 ml)	Catalyst (5 mole %)	Time (hr)	Temperature °C and Polymerizability
11	100	CH_2ClCH_2Cl	$CF_3SO_3CH_3$	24	24
	100	CH_2ClCH_2Cl	$CF_3SO_3CH_3$	36	55 No Reaction
	100	Glyme	$NaOCH_3$	24	120
	100	Glyme	$NaOCH_3$	36	
12	100	CH_2ClCH_2Cl	$CF_3SO_3CH_3$	24	24
	100	CH_2ClCH_2Cl	$CF_3SO_3CH_3$	36	55 No Reaction
	100	Glyme	$NaOCH_3$	24	110
	100	Glyme	$NaOCH_3$	36	

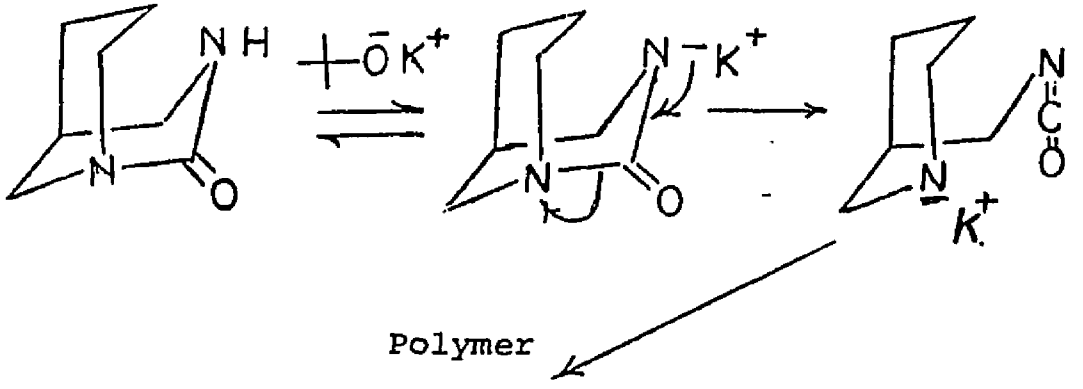
3. At 95°, no polymerization of the [3·3·1] urea was observed with or without catalyst.
4. At 120°, the [3·3·1] urea would polymerize in bulk with or without catalyst.
5. Higher molecular weight polymer would be generated by the [3·3·1] urea in bulk in the presence of a catalyst than in the absence of a catalytic initiator. Anionic catalyst gave the highest molecular weight polymer and in the highest yield. The transparent melt would be drawn into short lengths of brittle fibers.

A Postulated Mechanism of Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one, 11

From the foregoing it was reasonable to postulate the following schemes for the polymerization of the [3·3·1] urea 11:

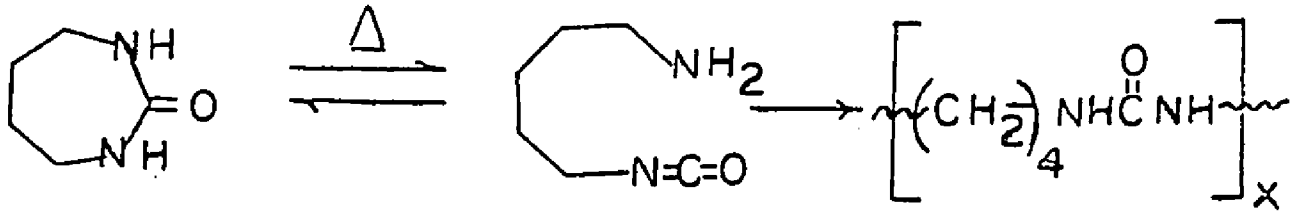


The presence of a basic catalyst wuch as KOtBu would enhance the initiation step:



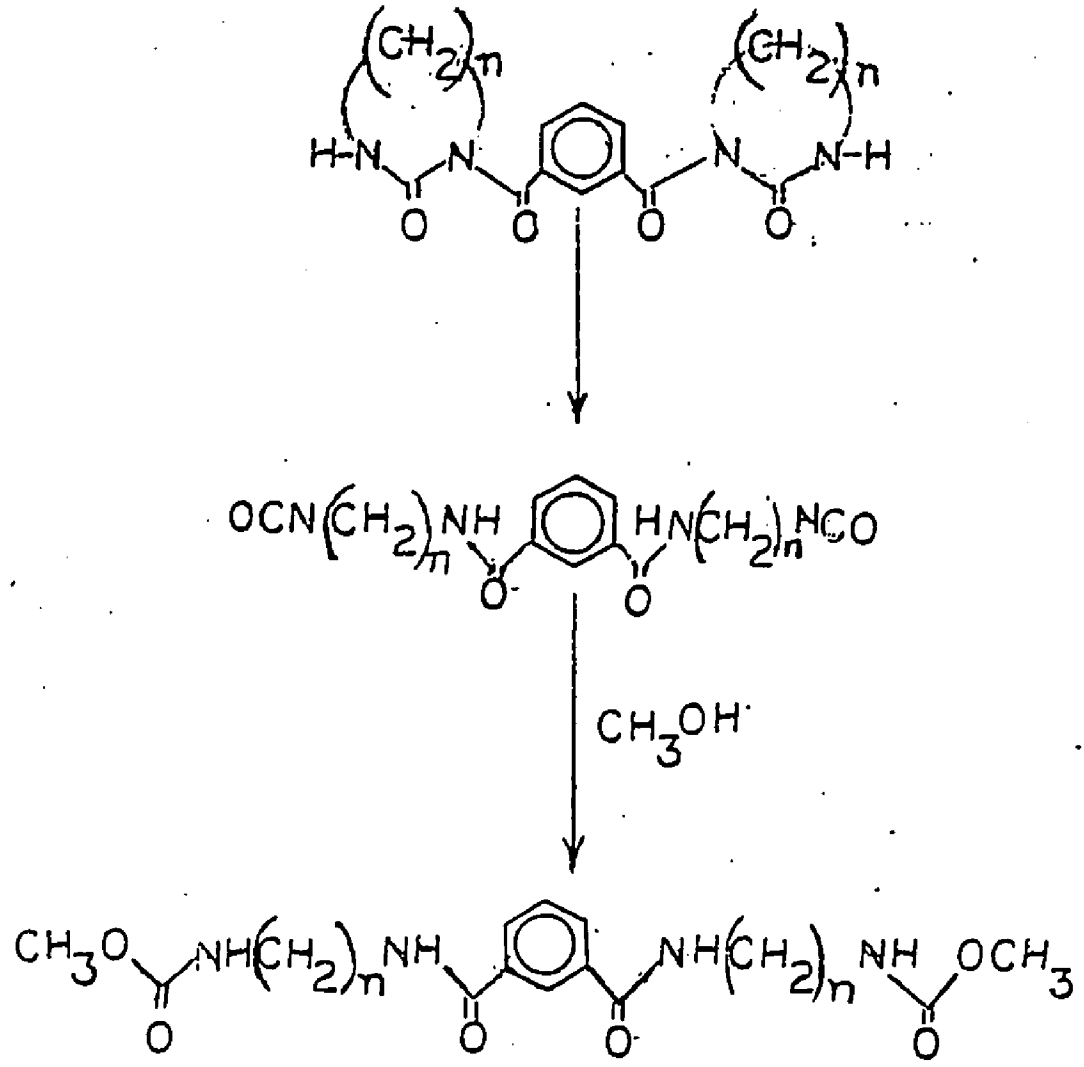
In accord with the above mechanism, the failure of 11 to polymerize in solution might be attributed to a slow dissociation in liquid media due to solvation.

The above mechanism is not without precedence. As opined by Hall and Schneider (1958) the polymerization of tetramethylene urea by heat occurs via an aminoisocyanate:

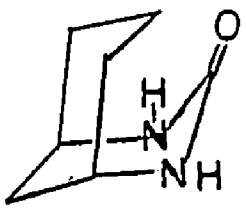


Five- and six-membered ureas dissociate to an aminoisocyanate, albeit, one-fortieth (Ozaki, Mukaiyama, and Uno, 1957) as rapidly as the 7-membered compound and their failure to polymerize on heating was attributed to this property (Hall and Schneider, 1958). Recently, Ulrich et al. (1978) have demonstrated the generation of diisocyanate by heating macrocyclic ureas and trapping the diisocyanate with methanol. The failure of Hall and Johnson (1972) to polymerize 3-iso-ropyl-1,3-diazabicyclo[3·3·1]nonan-2-one 4 is in accord with the above postulated mechanism; there is no mechanistic path for such a polymerization reaction.

The bulk polymerization of 11 is probably the first example of a rapid polymerization of a six-membered urea. It is also one of the rare cases of polymerization of a bicyclo[3·3·1]nonane derivative. The driving force for the polymerization could be the so-called "steric



inhibition to resonance" occasioned by the bridgehead N-C=O. The failure of the isomeric bond bridged reference compound 12 (Appendix



95

D) to polymerize, and the observation by Hall (1958b) that another isomeric urea, 2,4-diazabicyclo[3·3·1]nonan-7-one 95 also failed to polymerize, support this conclusion.

EXPERIMENTAL

Instrumentation

Unless otherwise stated all melting points were uncorrected and were determined in a Thomas-Hoover capillary melting point apparatus. Melting points, boiling points, and reaction temperatures are recorded in degrees Celsius (°C). Nuclear Magnetic Resonance (NMR, 60 MHz) spectra were determined on a Varian Model T-60 spectrometer. NMR peak positions (chemical shifts) were expressed in parts per million (δ) downfield. Tetramethylsilane (TMS) was an internal standard. Mass spectra were recorded on a Hewlett-Packard 5930A quadrupole mass spectrometer of The University of Arizona Analytical Center. Gas chromatogram (GC) was performed on a Varian Aerograph 1700 using a 5' x 1/4" column B packed with 20% S.E. 30 on 70/80 mesh chromosorb. Helium flow rate was 60 ml/min. Column temperature was 180. High performance liquid chromatography (HPLC) was accomplished using Altex, Inc., units. The HPLC was equipped with Spectra-Physics (SP 8200) 254 nm UV detector, linear recorder, and Altex pump primed with isopropyl alcohol. The column was 3-1/2' x 1" packed with Woelm dry column chromatography silica gel activity 111/30 from Water Associates. Solvent flow rate was 2.0 ml/min. Infrared (IR) spectra were obtained with a Perkin Elmer 710A grating infrared spectrophotometer. Inherent viscosities were determined with an Ostwald-Fenske Viscometer. All hydrogenations were done at The University of Arizona High Pressure Laboratory equipped with various reactor sizes (Magnadrive) autoclaves.

Some of the combustion analyses were performed by Chemalytics, Inc., Tempe, Arizona. The others were done by The University of Arizona Analytical Center.

Chemicals

Most of the solvents used in this work were purified as described in the literature (Perrin, Amarego, and Perrin, 1966). Pyridine was distilled from BaO and stored in brown bottles over KOH pellets. The commercially available canned anhydrous diethyl ether was used as received. Dichloromethane (CH_2Cl_2) was shaken with portions of concentrated H_2SO_4 and then aqueous 5% Na_2CO_3, NaOH, and again with water. It was dried with $CaCl_2$, distilled from P_2O_5, and stored in a brown bottle containing molecular Sieve 4A. Chloroform was washed three times to remove ethanol, dried with $CaCl_2$, distilled, and stored in a brown bottle. Tetrahydrofuran (THF) was refluxed with and distilled from CaH_2. 1,2-Dichloroethane, glyme, diglyme, and dimethylformamide (DMF) were purified likewise. They were stored over CaH_2 in brown bottles. Benzene was distilled from Na and stored in a brown bottle containing molecular Sieve 4A. Triethylamine was purified by distillation from P_2O_5 and stored in a brown bottle. The solvent system used for TLC and subsequently for HPLC was as follows: 100% CH_2Cl_2, 50/50 THF/CH_2Cl_2, and 100% THF.

Preparation of 2,4,6-Triisopropylbenzenesulfonic Acid, 27

2,4,6-Triisopropylbenzenesulfonyl chloride (20.0 g, 66.0 mmole, Aldrich Chemical Co.) and a solution of analytical grade sodium

hydroxide (12.8 g, 0.32 mole) in 600 ml of water were mixed and refluxed with stirring for 12 hours. On cooling to ambient temperature, snow-white flakes of the sodium salt of 2,4,6-triisopropylbenzene sulfonic acid precipitated from the clear solution. It was removed by filtration. Later, an additional crop of the salt was obtained from the filtrate. The salt was treated with a large excess of concentrated hydrochloric acid. On cooling, the mixture was extracted 6 times with 80 ml portions of water. The combined ether extract was dried with anhydrous sodium sulfate, filtered, and the solvent was rotoevaporated. The final traces of ether were removed by vacuum pump to afford a white solid. Yield 18.8 g (100%), mp = 119-120°.

Preparation of 3-Aminomethylpiperidine, 35

A mixture of 3-aminomethylpyridine (190 g, 1.76 mole) and 5% ruthenium on carbon (4.0 g) in analytical grade methanol (1300 ml) was hydrogenated at 100-150° and 133 atm (200 psi) pressure for 11 hours. After cooling, the mixture was filtered and the filtrate was re-hydrogenated for 5 hours, using a fresh amount (4 g) of 5% Ru/C. After the reaction mixture was cooled it was filtered from the catalyst and the methanol rotoevaporated. Upon distilling at 0.1 Torr and oil bath temperature of 120°, the title compound 35 came over at 40°. Yield: 117 g (58%), (Lit. bp = 114-118°, 50 Torr, Freifelder and Stone, 1961). It was stored over anhydrous K_2CO_3 and the container placed in a dessicator. IR (neat): NH, 3250(m), 3350(s), 1600 cm^{-1}(s); CH, 2900-2700 triplets(s), 1400 and 1460 cm^{-1}. NMR ($CDCl_3$): δ3,2-2.8; 2.6-2.0, 2.0-2.6, multiplets.

Preparation of 3-Aminopiperidine, 82

A mixture of 3-aminopyridine (100 g, 1.06 mole) and 5% Ru/C (2 g) in analytical grade THF (1000 ml) was hydrogenated at 150° and 133 atm pressure for 11 hours. After cooling and filtering off the catalyst, the filtrate was rehydrogenated using a fresh amount (2 g) of catalyst. The mixture was filtered and the solvent rotoevaporated. The product was distilled at 0.075 Torr in a 2-foot Vigreaux column wherein it sublimed over at 70°. Yield of needles: 42.71 g (40%); mp 56-57° (Lit. mp 55-57°; bp 68°/17 Torr, Nienburg, 1937). IR (KBr): consistently featureless. IR (neat, a melt on NaCl): NH, 3275, shoulder at 3350 cm^{-1} (broad), 1590; CH, 2925, 2851, 2725(s), 1470 cm^{-1} (s). NMR ($CDCl_3$): δ3.2-1.0 (multiplets).

Preparation of 2-Aminomethylpiperidine, 79

The hydrogenation of 2-aminomethylpyridine was done exactly as described for 3-aminomethylpyridine except that the mixture consisted of 2-aminomethylpyridine (50 g, 0.46 mole) and 5% Ru/C (2 g) in 50 ml of AR methanol.

The distillation of the rotoevaporated crude product was carried out in a 4-foot Vigreaux column packed with 1/2" glass rings, bp 22-23°/0.05 Torr. Yield: 40.0 g (76%). It was stored over anhydrous K_2CO_3.

Preparation of 1,4-Diazacycloheptan-1,4-diformoyl Chloride, i.e., Homopiperazine Biscarbamoyl Chloride, 18 (Figure 3)

Phosgene (7.06 g, 71.3 mmole, 5.05 ml) condensed in a graduated cold finger condenser, was swept with dry nitrogen into a vigorously stirred solution of homopiperazine (7.15 g, 7.13 mmole) in 300 ml of anhydrous ether. The solution was chilled in a dry ice-isopropanol bath. White solid immediately precipitated. The vigorously stirred mixture was allowed to attain the ambient temperature. The precipitate was removed by gravity filtration in the hood. It was extracted with a Soxhlet extractor in the hood using the ether contained in the filtrate as the extraction solvent. Evaporation of the solvent afforded needles, 5.97 g. On sublimation 4.0 g of the title compound was obtained. Yield, 50%, mp 106-107°. Mass spec.: m/e 224, 226, 227; base peak, 189. IR: ν_{CO} 1720 cm^{-1}. Analysis: Calcd for $C_7H_{10}N_2O_2Cl_2$: C, 37.30; H, 4.49; N, 12.43. Found: C, 37.55; H, 4.39; N, 12.40. IR (neat): NH, 3275(s), 3375 (shoulder), 1600 cm^{-1} (s); CH, 2900-2700 triplets (s), 1400 cm^{-1} (s). NMR ($CDCl_3$): δ3.3-2.0; 2.0-0.8 multiplets.

Preparation of 1,5-Diazacyclooctane, 32 Method A (Figure 29)

This method is a three-step synthesis.

Step 1. Synthesis of 1,5-Diaza-1,5-ditosylpentane, 88 (Figure 29)

To a hot solution of 1,3-diaminopropane, 88 (Figure 29) in 300 ml water placed in a 3-necked 2000 ml flask equipped with an efficient mechanical stirrer and two 500 ml dropping funnels, were added dropwise

and simultaneously from the two funnels, solutions of tosyl chloride (115.65 g, 606.6 mmole) in 600 ml dry benzene and AR grade sodium hydroxide (24.26 g, 606.6 mmole in 300 ml water).

After the addition of the two solutions, one of the funnels was removed and replaced by a reflux condenser. Then the mixture was stirred and refluxed for 3 hours. The precipitated granular white product was filtered hot and dried in air. Yield: 104 g (90%), mp 147-148° (Lit. mp 148°; Howard and Marckwald, 1899). The product was sufficiently pure for the next step, but if desired, could be recrystallized from 95% ethanol. IR (KBr): 3255(s), 3025, 1595(s), 1325, 1160 cm^{-1}. NMR: (Appendix A, Spectrum #1).

Step 2. Synthesis of 1,5-Diaza-1,5-ditosylcyclooctane, 89 (Figure 29)

To a vigorously stirred, clear, hot solution of a mixture of 73 prepared above (24 g, 62.8 mmole), 250 ml of water, and AR grade sodium hydroxide (11 g, 725 mmole) was added 125 ml of chlorobenzene. This was followed immediately by the addition of a mixture containing 1,3-dibromopropane (60 g, 297 mmole), 125 ml of chlorobenzene, and a phase transfer catalyst, methyl tricaprylylammonium chloride (200 mg). The batch was refluxed with vigorous stirring for 18 hr. Upon cooling, the chlorobenzene layer was separated and rotoevaporated. Recrystallization of the residue from acetonitrile afforded 9.03 g electrostatic silver-white plates. Later a second crop crystallized from the supernatant solution. Total yield: 13.25 g (50%), mp 214-216° (Lit. mp 215°; Howard and Marckwald, 1899). The yield tended to decrease when the batch was scaled up; therefore, several runs were made in order to

obtain enough material for the next step. The yield was not significantly improved when the ditosylate of 1,3-propanediol (Nelson et al., 1957) was employed in place of 1,3-dibromopropane. IR (KBr): 3075, 3030, 2950, 2775, 1598, 1500, 1460, 1380, 1330, 1150, 1090, 720 cm^{-1}. NMR ($CDCl_3$): (Appendix A, Spectrum #3).

Step 3. Hydrolytic Cleavage of 89 (Figure 29)

The procedures of Koyama and Yoshino (1972), Yang and Zompa (1976), and White et al. (1979) were slightly modified and employed here for the hydrolytic cleavage of the cyclic ditosylate 89.

A mixture of 89 (37.6 g, 89 mmole), 303 ml of 48% hydrobromic acid, and 170 ml of glacial acetic acid was refluxed with efficient stirring for 36 hours. The mixture was rotoevaporated completely. The resulting brown solid was treated with a very large excess of NaOH (150 g) dissolved in as little ice as possible so that the alkaline solution remained supersaturated. The cooled mixture was extracted 10 times with 100 ml portions of ether. The ether extract was dried over KOH for 2 days. Rotoevaporation of the ether followed by distillation 23°, 0.05 Torr, gave 32. Yield 7.38 g (73%).

IR (neat): Appendix B, Spectrum #4. NMR ($CDCl_3$): N-H sharp and migratory; 2.8-3.0(8H, t); 2(2H, s); 1.6(4H, peaks?). MS: m/e 114 (M^+), 43 (M-71, base), M-17, M-29, M-43, M-44.

Preparation of 1,5-Diazacyclooctane, 32
Method B (Figure 30)

This method involves two steps.

Step 1. Preparation of 1,5-Diazacyclooctane-2,6-dione, 94 (Figure 30)

The methods employed in this synthesis were those of Hall (1958a), Knunyants and Fabrichnyi (1949), Brown and Heim (1973). Cyclohexane-1,4-dioxime 92 was prepared as described in the literature (Iwakura et al., 1969).

Cyclohexane-1,4-dioxime (19.16 g, 127.8 mmole), 130 ml of pyridine, and tosyl chloride (54.5 g, 285.8 mmole) were mixed and stirred at -8°. The mixture was then allowed to stand at 0° for 24 hr. Crystals precipitated. These were poured into ice. The crude product (66 g) was removed by filtration. In the process of recrystallizing it from a hot 50/50 pyridine/water mixture as described in the literature (Hall, 1958a), the oximeditosylate underwent a facile Beckman rearrangement, the title compound 94 precipitating from the solution after standing in the hood for 3 days. Yield 6.64 g (34%), mp 299-300° (Lit. mp 298°; Hall, 1958a). IR (KBr): $\nu_{CO} = 1645$ (amide I); 1580 cm^{-1} (amide II); $\nu_{NH} = 3150$ cm^{-1}. NMR (trifluoroacetic acid): δ3.6-4.0 (4H,quartet); 2.9-3.2(4H,t), 8.0-8.3(2H, multiplet).

Step 2. Reduction of 1,5-Diazacyclooctane-2,6-dione, 94, to 1,5-Diazacyclooctane 32 with BH_3-THF Complex (Figure 30)

The method adapted here was that developed by Brown and Heim (1973); see also Lane (1977). To 273.4 ml 1M solution (73.4 mmoles) of the commercial borane in THF placed under N_2 in a 500 ml flask equipped

with a reflux condenser, dropping funnel, and a magnetic stirred was added 6.16 g (43.35 mmoles) of 1,5-diazacyclooctan-2,6-dione 94 dissolved in 100 ml THF. The addition took 15 minutes. Temperature was maintained approximately at 0° during the addition. The solution was then refluxed for 2 hours. On cooling to ambient temperature 28.9 ml of 6M hydrochloric acid was added slowly through the dropping funnel. The THF and water were removed on rotoevaporator as hydrogen evolved from the hydrolysis of the amine complex. NaOH pellets were added to saturate the aqueous phase which was later extracted 3 times with 40 ml portions of ether. After drying the ether solution with anhydrous sodium sulfate, distillation of the crude product at 1.1 Torr, bath temperature 88° gave 32 coming over at 30°. Yield, 3.24 g (55%). Its spectra (NMR, IR, Mass) were identical in all respects to the product obtained in Method A (Figure 29).

Attempted Synthesis of 1,3-Diazabicyclo[3·3·1]nonan-2-one, 11, via Piperidinium Aryl Sulfonate (Figure 7)

Step 1. Preparation of Intermediate 3-Ammonium-methylpiperidino-2',4',6'-triisopropyl-benzenesulfonate, 36 (Figure 7)

A solution of 3-aminomethylpiperidine 35 (4.6 g, 0.04 mole) in 100 ml ether was mixed with a solution of 2,4,6-triisopropylbenzenesulfonic acid 27a (11.4 g, 0.04 mole) in 100 ml ether. There resulted a clear solution from which a white solid eventually precipitated. The title compound was removed by filtration. Yield: 11.83 g (87%). Analysis: Calcd for $C_{21}H_{38}N_2O_3S$: C, 63.24; H, 9.63; N, 7.03. Found: C, 63.20; H, 9.90, N, 6.90. IR (KBr): 3310, 2900, 1600, 1020, 680 cm^{-1}.

Step 2. Preparation of Intermediate 1-Chlorocarbonyl-3-ammoniummethyl Piperidino-2',4',6'-triisopropyl Benzenesulphonate, 37 (Figure 7)

To the above ammonium salt (13.05 g, 32.7 mmole) dissolved in 200 ml of dichloromethane was added at room temperature with vigorous stirring phosgene (3.6 g, 36 mmole, 2.54 ml) condensed in a graduated cold-finger condenser. The clear solution was allowed to stir overnight. The dichloromethane was rotoevaporated leaving a viscous material. The viscous substance was slurried in 50/50 mixture of pentane and ether and filtered. The filtrate was chilled at -50° (dry ice/isopropanol bath) for 2 days. The precipitated solid was removed by filtration and dried in air. It was powdery. Yield: 8.25 g (55%), mp 140-170°. Analysis: Calcd for $C_{22}H_{37}N_2O_4ClS$: C, 57.27; H, 8.11; N, 6.07. Found: C, 57.00; H, 8.40; N, 6.4. IR (KBr): 1740(s), 1600(s), 1470(s), 1160-1230, 1020, and 680 cm^{-1}.

Step 3

Successful cyclization of the above N-chlorocarbonyl ammonium salt with triethylamine in refluxing ether or benzene for 15 hr was not realized (Figure 7).

Synthesis of 1,3-Diazabicyclo[3·3·1]nonan-2-one, 11, Phosgene Route (Figure 10)

To a vigorously stirred solution of 3-aminomethylpiperidine (10.07 g, 0.09 mole) in anhydrous ether was added at ambient temperature condensed phosgene (8.73 g, 88.20 mmole, 6.24 ml). After 1.5 hr the emulsion was filtered. The cake was washed by slurrying in anhydrous ether 3 times and filtering to remove any biscarbamoyl chloride which

might have formed. Finally, the white cake (13.7 g) was stirred vigorously with excess triethylamine (85.22 g, 842 mmole) in 1000 ml of dry ether at room temperature for 16 hr. The mixture was filtered and the filtrate concentrated to 30 ml using the rotoevap.

The solution was finally completely evaporated by a stream of dry N_2. The crude crystals (1.70 g) were sublimed at 87°, 0.05 Torr. Yield: 0.63 g (5.1%). It did not have a sharp melting point. When viewed in the Kofler-type hot stage equipped with polarizing microscope, it appeared to soften and swell at 98-100°, transformed to an amorphous material which changed viscosity, and flowed as globules at 133-134°. Analysis: Calcd for $C_7H_{12}N_2O$: C, 59.95; H, 8.65; N, 19.98. Found: C, 59.90; H, 8.80; N, 20.00. IR (KBr): Appendix B, Spectrum #1. NMR ($CDCl_3$): Appendix A, Spectrum #4. MS: m/e 140 (M^+, base), base-57; base-70.

Synthesis of 1,3-Diazabicyclo[3.3.1]nonan-2-one, 11, Diphenyl Carbonate Route (Figure 22)

3-Aminomethylpiperidine (6.0 g, 52.5 mmole), a coordination catalyst, dibutyl tin oxide (200 mg), and diphenyl carbonate (12.7 g, 59.3 mmole) were intimately mixed in a 100 ml round-bottom flask at ambient temperature. They immediately reacted exothermally. The temperature was raised still higher with a heat gun until the mixture became homogeneous. The mixture was distilled in an Aldrich Kugelrohr at 150-160° and 37 Torr (water pump) while the flask and bulb were moderately rocked by the vacuum or air-operated oscillating motor. Figure 31 is a diagrammatic representation of the Kugelrohr used in the present preparation. The buffer bulb 2 prevented a spill over from the

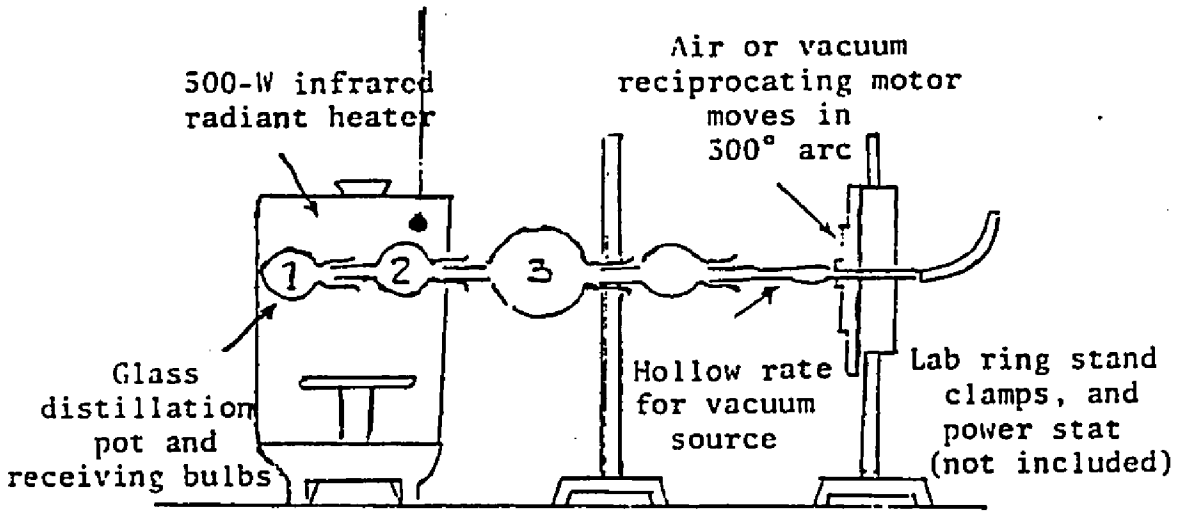


Figure 31. Aldrich Kugelrohr Arrangement Used to Prepare 11, 12, and the Dimer of 9

flask to the receiver 3 which was cooled by a wad of cotton wool drenched with spent dichloromethane. When nearly 2 equivalents of phenol (9.32 g, 99 mmole; theoretical 11.14 g, 118.4 mmole) were collected in bulb 3, the batch was cooled to 60° and another 200 mg of dibutyl tin oxide was added. Bulb 3 was cleaned to receive the crude product. A pressure of 0.05 Torr was applied from a mechanical pump and the temperature of the brittle glassy material in the flask was raised gradually to 215-230° as the flask and the bulbs were rocked. The depolymerized viscous, faint yellow heterogeneous soft solid (5.0 g) was chromatographed on an HPLC over silica gel eluting first with Ch_2Cl_2. When the chart pen returned to the base line, the solvent was changed to THF and the title compound was eluted with it. The THF eluents contained the title compound and were combined. Rotoevaporation followed by recrystallization from methyl acetate afforded 2.0 g of 11, yield 27%. The crystals softened and appeared to swell at 98-100°, transformed to amorphous material which changed viscosity and flowed as globules at 133-135° (Thomas Kofler-type hot stage melting point apparatus). The elemental analysis, IR, NMR, and MS of this product were identical in all respects to the product from phosgene route.

Synthesis of 1,8-Diazabicyclo[4.3.0]nonan-9-one, 12, the Diphenyl Carbonate Route (Figure 23)

A mixture of 2-aminomethylpiperidine (3.03 g, 26.5 mmole), diphenyl carbonate (6.35 g, 29.64 mmole), and dibutyl tin oxide (400 mg) was heated with a heat gun until a wine-red solution resulted. The condensed 2 equivalents of phenol was removed by distillation at Wood's metal temperature of 160-170° and water pump pressure of 37 Torr. After

cooling to about 60°, the dark liquid in the flask was distilled at 190° (Woods metal), 2.5 Torr, using a short path distillation system in the condenser jacket. The receiver was cooled in a dry ice-isopropanol bath. The distillate (2.09 g) was taken up in dry 50/50 ether/THF mixture and chilled at -50° for 2 days. The product was collected by filtration. When the filtrate was concentrated and then chilled at -50° for 2 days a second crop of the product was obtained, after its exposure to air on a filter for 2 days. The combined product was sublimed at 50-65° (oil bath temperature) and 0.05 Torr. Yield: 1.28 g (35%), mp 69-70°. IR: Appendix B, Spectrum #2. NMR: Appendix A, Spectrum #5. MS: Appendix C, Spectrum #2. Analysis: Calcd for $C_7H_{12}N_2O$: C, 59.95; H, 8.65; N, 19.98. Found: C, 59.80; H, 8.40; N, 20.00.

The Aldrich Kugelrohr shown in Figure 31 could also be employed in this preparation. In this case, the redistillation of the crude product at 95°, 0.115-0.175 Torr, removed the residual phenol leaving the crude product in the flask. Distillation of this crude product at 150°, 0.175 Torr, gave a colorless liquid which crystallized on standing. It was recrystallized from THF.

Attempted Synthesis of 1,5-Diazabicyclo[3.2.1]octan-8-one, 8, via Di-tertiary Butyltricarbonate Route (Figures 16 and 17)

Di-tertiary butyltricarbonate 59 was prepared exactly as described in the literature (Pope et al., 1977).

The Reaction of 59 with Homopiperazine 20

To a solution of di-tertbutyltricarbonate 59 (1.31 g, 5.22 mmole) in 315 ml pentane was added dropwise with good stirring at room temperature, a solution of homopiperazine (500 mg, 500 mmole) in 50 ml pentane. There was an instant precipitation of white solid. The solid was removed by filtration under nitrogen. It was insoluble in dimethyl sulfoxide-d_6, acetone-d_6. acetonitrile-d_3, chloroform-d, but dissolved with effervescence in hexafluoroacetic anhydride. Yield: 0.66 g. The product was assigned the structure 64 on the basis of its reaction with trifluoroacetic anhydride (TFAA) and on heating, as discussed earlier.

On heating, in the kugelrohr at 120°, 0.375 Torr, and trapping the products in the bulbs and in chilled traps, the solid decomposed to give a trap product which had no carbonyl absorption in the IR spectra. A liquid product condensing in the bulb of the kugelrohr had IR absorption at 3325(m)., 1690(s), 1545, 990(s), 930(s). This IR was identical in all respects with the single product obtained by refluxing a mixture of 20 and 59 in benzene at 80° for 1 hour (Figure 17).

Attempted Preparation of 1,6-Diazabicyclo[3·2·1]octan-7-one 9 via Diphenyl Carbonate Route (Figure 25)

A mixture of 3-aminopiperidine (5.07 g, 50.6 mmole), diphenyl carbonate (10.84 g, 50.6 mmole), and dibutyl tin oxide (600 mg) was placed in a 100 ml round-bottom flask equipped with short path distillation units. The molten mixture was heated to 210-232° on a Wood's metal, 37 Torr, with magnetic stirring. Phenol (9.04 g expected 9.54 g) distilled over at 145°. The pressure was then lowered to 0.4-0.4 Torr with a mechanical vacuum pump and the temperature raised to

245-250 to depolymerize the glassy residue on the flask. A colorless liquid distilled over at 160-166° followed soon after by a yellow material. Steam was the condensing fluid in the condenser. On further heating to 300-305° to complete the depolymerization more of the yellow material distilled over at 200-210°. The total yield of the crude depolymerized material was 3.50 g. HPLC of this substance on silica gel, as before, using CH_2Cl_2, 50/50 CH_2Cl_2/THF, and THF afforded in the total THF eluents after removing the solvents a crystalline solid (2.0 g) which did not melt even at 210°. It had a doublet carbonyl absorption at 1680 and 1660 cm^{-1}, a weak N-H at 3400 cm^{-1}. On sublimation in a horizontal 1/8" tube sealed at one end in 125°, 0.05 Torr, a crystalline solid was obtained. Yield was 0.75 g, mp 173-175°. Analysis: Calcd for $C_6H_{10}N_2O$ or its dimer $C_{12}H_{20}N_4O_2$: C, 57.07; H, 8.01; N, 22.20. Found: C, 60.0; H, 7.8; N, 23.20. IR: Appendix B, Spectrum #3. NMR: Appendix A, Spectrum #6. MS: Appendix C, Spectrum #1.

Attempted Synthesis of 1,3-Diazabicyclo[3·2.2]nonan-2-one 13 via the Diphenyl Carbonate Route (Figure 24)

The method was similar to the one described earlier for the synthesis of [3·3·1] system, except for minor changes in conditions.

A mixture 4-aminomethylpiperidine (6.07 g, 53.15 mmole), diphenyl carbonate (12.85 g, 60.00 mmole), and dibutyl tin oxide (400 mg) was heated with a heat gun until homogeneous. On distilation at 186°, 37 Torr, phenol (9.14 g; theoretical 10.0 g) distilled over. After adding 200 mg of Pu_2SnO to the residue glassy material, it was heated to 210°, 0.05 Torr, to depolymerize. The depolymerized material

(3.0 g) was chromatographed on the 3-1/2' x 1" HPLC column packed with silica gel. Elution with CH_2Cl_2, CH_2Cl_2/THF (50/50), and THF gave two fractions. Fraction 1 contained essentially phenol. Fraction 2 afforded a white powder (1.24 g) upon removal of the solvent. IR (KBr): ν_{CO} = 1705; ν_{NH} = 3300 and 3375 cm^{-1}. NMR ($CDCl_3$): δ7-7.4 (5H, multiplet), 5.0(1H, multiplet), 4-4.4(2H, doublet broad), 2.6-3.2 (4H, multiplet), 1-2(5H, multiplet); mp 180-182°. The yield of the urethane 81 was 10%.

The Synthesis of N-Methoxycarbonyl Homopiperazine 15a (Figure 1)

The method employed was adapted from the procedure of Jacobi (1933) which was utilized by Hall (1956) to prepare monoacyl piperazines.

To a stirred, cooled aqueous solution (pH = 11.2) of homopiperazine (8.33 g, 83.2 mmole) hydrochloric acid was added dropwise until the pH of the solution was 2-3 by alternating additions of granular potassium carbonate and hydrochloric acid, methyl chloroformate (7.86 g, 83.2 mmole) was added drop by drop. The pH was monitored with an efficient pH meter. After the addition, the pH was allowed to climb to 5.4 and maintained there for 2 hours. After basification to pH 9.2 with solid potassium carbonate, the mixture was evaporated to dryness and the residue extracted in Soxhlet extractor with anhydrous ether. Evaporation of ether and fraction distillation at 90°, 0.05 Torr, gave N-methoxycarbonyl homopiperazine 15a in 62% yield. Analysis: Calcd for $C_7H_{14}N_2O_2$: C, 53.11; H, 8.85, N, 17.71. Found: C, 52.91; H, 8.56; N, 17.57. IR (neat): ν_{CO} = 1700 cm^{-1} (amide I of urethanes; Bellamy, 1958; Randall et al., 1949). NMR ($CDCl_3$): δ3.6(3H, singlet), 3.4

(4H, sextet), 2.8(4H, multiplet), 1.9(1H, singlet, 1.7(2H, quintet). Gas chromatograph displayed only one peak. Attempts to demethanolate 15a at 260° with $Ti(OtBu)_4$ as catalyst failed to give 8 although methanol condensed in a cold finger trap cooled in a dry ice-isopropanol bath.

Phosgenation of N-Methoxy Carbonyl Homopiperazine 15a to Give 1-Methoxy Carbonyl-4-chlorocarbonyl-1,4-diazacycloheptane 15b (Figure 1)

To a stirred cooled phosgene (8 ml) solution in anhydrous ether was added drop by drop an ether solution of 15a (1.6 g, 10.1 mmole). There was an instant precipitation of white solids. After 1 hour, the mixture was filtered (gravity) in the hood and the ether removed from the filtrate with caution. Phosgene! A thick oil resulted. It had no NH absorption in the IR: ν_{CO} = 1750-1700 cm^{-1} (jagged peaks). It was distilled in a 1-foot spinning band at Wood's metal temperature of 105°, pressure 0.1 Torr. The product distilled over at 97-100°, 0.1 Torr. IR (neat): 1750-1700 (4 jagged peaks), 1495, 1320(s), 1250(broad), 1200(broad), 1128(s), 1082(s), 932(s), 778(s), 675(s). NMR ($DMSO_{d_6}$): Appendix A, Spectrum #8.

Hydrolytic cleavage of the product with anhydrous HBr in carbon tetrachloride failed to yield 16 (Figure 1). Instead, 17 was obtained, identified from NMR. NMR (DMSO): δ4.1(3H, singlet), 2.4-2.8(2H, multiplet), 3.6-4.2(8H, multiplet).

Thermal Uncatalyzed Bulk Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11

The urea 11 (about 10 mg) was sealed in the melting point capillary tubes. Duplicates were heated in thermostated oil baths at

various times and temperatures. Their IR spectra were taken in KBr pellets and compared against the IR spectrum of a reference unheated sample. Shifts of the carbonyl absorption from 1660 cm^{-1} to 1620 cm^{-1} and changes in the fingerprint region of the IR spectra indicated polymerization. The results were shown in Table 1.

Thermal Catalyzed Bulk Polymerization of 1,3-Diazabicyclo[3.3.1]nonan-2-one 11

The initiator catalysts tested were phenylphosphonic acid (cationic, $PhPO_3H_2$), dibutyltin oxide (Bu_2SnO) (metal coordination catalyst), potassium tertiarybutoxide (anionic), and potassium tertiarybutoxide containing a trace of phenyl isocyanate (activated anionic catalyst).

A bulk mixture of about 200 mg of urea 11 and trace amounts of one type of initiator catalyst was heated at 120-125° for 6 hours in an evacuated sealed vial. The hard glassy transparent polymer was first stirred in 1,2-dichloroethane, then in dimethylformamide (DMF), tetrahydrofuran (THF), and lastly in glyme, all of which did not dissolve the polymer. The objective was to extract any unreacted monomer. The tough polymer was dried and the melting point taken. Later it was found that the polymer was completely soluble in 1,1,1-2,3,3-hexafluoro-2-propanol in which viscosity measurements were made. The results were tabulated in Table 2. The viscosity measurement results were shown in Table 3. The molecular weight of each polymer was estimated from the inherent viscosity/molecular weight relationship displayed in Table 4.

Attempted Anionic and Cationic Solution Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11 and 1,8-Diazabicyclo[4.3.0]nonan-9-one 12

The solvents employed in these tests were 1,2-dichloroethane and 1,2-dimethoxyethylene (glyme). The cationic initiator catalyst was methyl trifluoromethylsulfonate and the anionic one was sodium methoxide. The catalyst was 5 mole per cent with respect to the urea. Both were dissolved in the appropriate solvent.

In a typical run 0.8 ml of the above solution was pipetted into a tube and seald. The solution was then heated in a thermostated oil bath at a temperature for a certain length of time. After cooling, the IR spectrum was taken and compared against that of the reference unheated sample. The results are tabulated in Table 5.

Attempted Anionic Solution Polymerization of 1,3-Diazabicyclo[3·3·1]nonan-2-one 11 at 120°

The urea 11 (200.49 mg, 1.43 mmole), potassium tertiary butoxide (8.43 mg, 0.075 mmole), and 10 ml of 2,2'-dimethoxy ethylene ether (diglyme) were mixed until homogeneous. This mixture was 5 mole per cent of the anionic catalyst potassium tertiary butoxide with respect to the urea. Six samples of the mixture each 1 ml were contained in NMR tubes and sealed. Five of the samples were heated to 120° in a thermostated oil bath at time intervals of 5, 10, 30, 60 min, and 24 hours. The sixth sample was not heated at all; it was the reference sample. At the end of each period, the sample was cooled and the IR taken.

The IR spectra of the six samples were identical in all respects ν_{CO} = 1680 cm^{-1}(s), ν_{NH} = 3600, 3550 cm^{-1} indicating that no polymerization occurred.

The Preparation of 3-Isopropyl-1,3-diazabicyclo[3·3·1]-nonan-2-one 4; an Alternative Route to Hall's and Johnson's Urea 4 (Figure 6)

Preparation of 3-Isopropylaminomethyl-piperidinium-2',4',6'-triisopropyl-benzenesulfonate 28 (Figure 6)

A mixture of 100 ml anhydrous ether, 20 ml absolute ethanol, 80 ml chloroform, 3-isopropylamineomethylpiperidine 18 (3.95 g, 25.2 mmole), and 2',4',6'-triisopropylbenzenesulfonate acid 27 (7.18 g, 25.2 mmole) was stirred for 18 hr at room temperature. On evaporation of the clear solution, a thick syrupy liquid was obtained. After pumping to remove the last trace of solvents, a very thick oil (10.92 g) was obtained. It was used in the next step without further purification.

Phosgenation of 3-Isopropylaminomethyl-piperidinium-2',4',6'-triisopropyl-benzenesulfonate 28 to give 29 (Figure 6)

The crude salt 28 prepared above (11.0 g, 25 mmole) was dissolved in a mixture of 300 ml anhydrous ether and 185 ml purified chloroform. The material was not soluble in the ether alone. To the cooled solution (-60°, dry ice-isopropanol bath) was added a solution of phosgene (2.48 g, 25 mmole, 1.8 ml) in chloroform. A yellowish solution containing no precipitates resulted. It was stirred overnight and the temperature allowed to climb to ambient conditions. A white emulsion was obtained. The solid was removed by gravity filtration. The solid residue was slurried for 3 hours with a 150/50 ether/$CHCl_3$ mixture and filtered. It was slurried again with 300 ml chloroform and filtered. The filtrates were combined and evaporated to give 8.50 g (68%) of

product which foamed on pumping. A chemical shift downfield of the isopropyl group (compared to its chemical shift in 28) confirmed that the structure was as written for 29 and not the other isomer. The product was used in the next step without further purification.

Successful Cyclization of 3-Isopropyl-N-chlorocarbonyl-aminomethyl-piperidinium-2',4',6'-triisopropyl-benzenesulfonate 29 to 4 (Figure 6)

The crude 29 (8.41 g) prepared above was dissolved in 700 ml of chloroform and stirred at room temperature. Upon addition of triethylamine (34 g, 334 mmole) and stirring overnight, an emulsion was obtained. The solid was removed by filtration and the filtrate evaporated to give an orange viscous liquid. The liquid was slurried in a mixture of pentane (450 ml) and acetone (20 ml) overnight. On filtration and evaporation of the filtrate, a thick liquid (2.32 g) was obtained. It was distilled (110°, 0.05 Torr, 165° oil bath temperature) in a short path column to give a white solid in a receiver cooled in a dry ice-isopropanol bath. Yield 0.97 g (38% based on 29). ν_{CO} = 1650 cm^{-1}(s); mp 47-48° after sublimation (Lit. mp 48.2-49.2°; Hall and Johnson, 1972).

Preparation of Homopiperidinium-2,4,6-triisopropylbenzenesulfonate 30 (Figure 8)

A solution of homopiperazine 20 (2.71 g, 27 mmole), in 200 ml ether was mixed with a solution of 2 ,4 ,6 -triisopropylbenzenesulfonic acid 27a (7.68 g, 27 mmole) in 200 ml of ether. The mixture was stirred at ambient temperature for 1 hour. The precipitated salt was removed by gravity filtration and washed several times with ether. It was dried in air to give white flakes, mp 143-144°. Yield, 7.1 g (69%). IR (KBr):

3225(s), 2925(s), 1590(s), 1205(s), 1140(s), 1000(s), 670(s) cm^{-1}. Analysis: Calcd for 30, $C_{20}H_{36}N_2O_3S$: C, 62.43; H, 9.46; N, 7.28. Found: C, 62.75; H, 9.19; N, 7.28.

Phosgenation of 30 to Give 1-Azonia-[4-chlorocarbonyl]-1,4-diazacycloheptan-2',4',6'-triisopropylbenzenesulfonate 31 and Attempted Cyclization of 31 to 8 (Figure 8)

The above salt 30 (7.69 g, 20 mmole) was dissolved in 560 ml of 3:1 mixture of chloroform/anhydrous ether, and cooled to -50° (dry ice-isopropanol bath). Phosgene (2.18 g, 22 mmole, 1.6 ml) was condensed in a cold finger condenser and added to the chilled stirred mixture. A milky suspension resulted. The flask containing the mixture was securely stoppered and the mixture was stirred overnight as the temperature rose gradually to ambient conditions. Upon filtration (3 g of cake) and evaporation of the solvent, a white solid was obtained; ν_{CO} = 1700 cm^{-1}, ν_{CH} = 1600 cm^{-1} (aromatic). The white solid was slurried in anhydrous ether 2 times to remove any 2,4,6-triisopropylbenzenesulfonyl chloride which might have formed. The final product, a white crystalline solid, was dried. Yield: 3.81 g, 43%, mp 148-150°, foaming at 158°. Analysis: Calcd for 31, $C_{21}H_{35}N_2O_4SCl$: C, 56.39; H, 7.91; N, 6.27; Cl, 7.94. Found: C, 56.44; H, 7.90; N, 6.35; Cl, 7.00. IR (KBr): 2945(s), 2850(s), 2750(s), 2690(m), 2500(s), 1710(s), 1600, 1470, 1205(s), 1130(s), 1005(s), 680(s) cm^{-1}.

The various attempts at ring closure of 31 in dry ether, toluene, dichloromethane, benzene, or hexane in high dilution using as bases, triethylamine, DABCO, DBN, NaH, butyllithium, pyridine,

phenylmagnesium bromide, and sodium hydroxide only led to polymers (ν_{CO} = 1620 cm^{-1}).

Preparation of 1-Azonia-[1,5-diazacyclooctan]-2',4',6'-triisopropylbenzenesulfonate 33a (Figure 9a)

A 200 ml ether solution of 1,5-diazacyclooctane 32 (4.55 g, 39.8 mmole) was mixed and stirred with 300 ml ether solution of 2,4,6-triisopropylbenzenesulfonic acid 27a (11.33 g, 39.8 mmole). When the resulting clear solution was rotoevaporated a viscous clear faint yellow liquid was obtained. The liquid was slurried overnight in pentane (900 ml) and the precipitated solid removed by filtration. The filtrate was discarded. The yield of the product after drying was 14.02 g (88.4%). IR (KBr): 3250(m), 2950(s), 2755, 1600, 1460, 1220(s), 1165(s), 1135(s), 1010(s), 680(s) cm^{-1}. Analysis: Calcd for 33a, $C_{12}H_{38}N_2O_3S$: C, 63.23, H, 9.63; N, 7.03. Found: C, 63.40; H, 9.52; N, 6.74.

Preparation of 1-Azonia-[5-chlorocarbonyl-1,5-diazacyclooctan]-p-toluenesulfonate 33b (Figure 9b)

In the same manner, when 1,5-diazacyclooctane 32 (2.82 g, 24.69 mmole) was reacted with p-toluenesulfonic acid monohydrate 27b (4.0 g, 21.03 mmole) in ether, 1-azonia-1,5-diazacyclooctan-p-toluenesulfonate 33b (4.23 g) was obtained. Yield: 60%, mp 114.5-117°. IR (KBr): Appendix B, Spectrum #5.

Phosgenation of 33a to Give 1-Azonia-[5-chlorocarbonyl-1,5-diazacyclooctan]-2',4',6'-triisopropylbenzenesulfonate 34a (Figure 9b)

The above salt 33a (13.33 g, 32.89 mmole) was dissolved in dry dichloromethane (600 ml). Although the stirred mixture was a little

cloudy, condensed phosgene (4.89 g, 49 mmole, 3.49 ml) was introduced and the mixture stirred at room temperature for 6 hours. After filtration and washing the cake with dichloromethane, the combined filtrate was rotoevaporated. After pumping the resulting viscous liquid overnight to remove traces of solvents, an honey-like syrup was obtained (10.83 g). This material failed to crystallize even when induced by trituration with ether or when stored in the deep freeze. IR (ether): 2950(s), 2850, 1720, 1601, 1580, 1460, 1380, 1170, 890, 680 cm^{-1}. As in the case of 31, the above carbamoyl chloride faile to ring close on treatment with bases. Polymeric substances were obtained.

Phosgenation of 33b to Give 1-Azonia-[5-chlorocarbonyl-1,5-diazacyclooctan]-p-toluenesulfonate 34b (Figure 9b)

The salt 33b (4.15 g, 14.5 mmole) was treated with phosgene (1.43 (1.43 g, 14.5 mmole, 1.02 ml) as described above for 33a. After filtration and evaporation, the resulting viscous liquid was slurried in a 50/50 mixture of ether and dichloromethane. This process was repeated except that in the second time a 30/20 mixture of ether and dichloromethane was used. The final filtrate was concentrated and allowed to crystallize. Yield of title compound 1.36 g (27%), mp 103-104.5°. IR (KBr): Appendix B, Spectrum #6. NMR ($CDCl_3$): Appendix A, Spectrum #7.

Attempted Synthesis of 8 via the Phosgenation of 8-Phenyl-1,5-diazabicyclo[3·2·1]octane 42 (Figure 11)

Step 1. The Preparation of 8-Phenyl-1,5-diazabicyclo[3·2·1]octane 42

Homopiperazine (6.2 g, 61.89 mmole) benzaldehyde (6.38 g, 59.85 mmole) and 500 ml methanol were mixed and refluxed for 24 hr. The clear solution was evaporated to give a light yellow crystalline solid. It was recrystallized twice from hexane at -50° to give 6.11 g of product. A second crop 3.28 g precipitated from the supernatant liquid on standing. Total yield 9.39 g (81%), mp 78-79° (Lit. mp 82-84°; Poppelsdorf et al., 1961). IR (KBr): 2925, 2900, 1601, 1460, 1440, 1340, 1300, 1200, 1140, 1070, 1000, 950, 880, 850, 740, 720, 695 cm^{-1}. NMR ($CDCl_3$): δ7-7.7(5H, multiplets), 5(1H, singlet), 3.6-1.0(10H, multiplet) (see Appendix A, Spectrum #10).

Step 2. Phosgenation of 42 to Give 1-Azonia-[4-chlorocarbonyl-1,4-diazacycloheptan]-hydrochloride 43 (Figure 11)

The procedure applied here was an adaptation of the work of Misiti and Chiavarelli (1966).

To a solution of 42 (1.5 g, 7.97 mmole) in 75 ml of toluene was added 38 ml of a solution of phosgene 0.56 ml in 38 ml of toluene. The mixture was stirred for 24 hr at ambient temperature. The precipitate (2.12 g) was removed by filtration. Its NMR strongly suggested that it was the intermediate salt 54 (Figure 14). NMR ($CDCl_3$): δ8.1-7.5(5H, multiplet), 5.0-3.0(10H, broad multiplet), 2.35 (2H, broad multiplet). IR ($CDCl_3$): Ammonium salt-like, 2950-2300 cm^{-1}, 1720, 1630, 1600, 1410, 1210, 1190, 650 cm^{-1}.

Step 3

Attempts to transform 43 to 8 (Figure 11) also failed.

Attempted Synthesis of 10 via the Phosgenation of 9-Phenyl-1,5-diazabicyclo[3·3·1]octane 45 (Figure 12)

Step 1. Preparation of 45

The procedure followed was exactly as described for the synthesis of 42. The quantities used were 1,5-diazacyclooctane 32 (1.21 g, 10.6 mmole) and benzaldehyde (11.2 g, 10.6 mmole). Yield of 45 was 0.56 g (26%), mp 65-66° (Lit. mp 64-66°; Billman and Dorman, 1962). NMR: Appendix A, Spectrum #9.

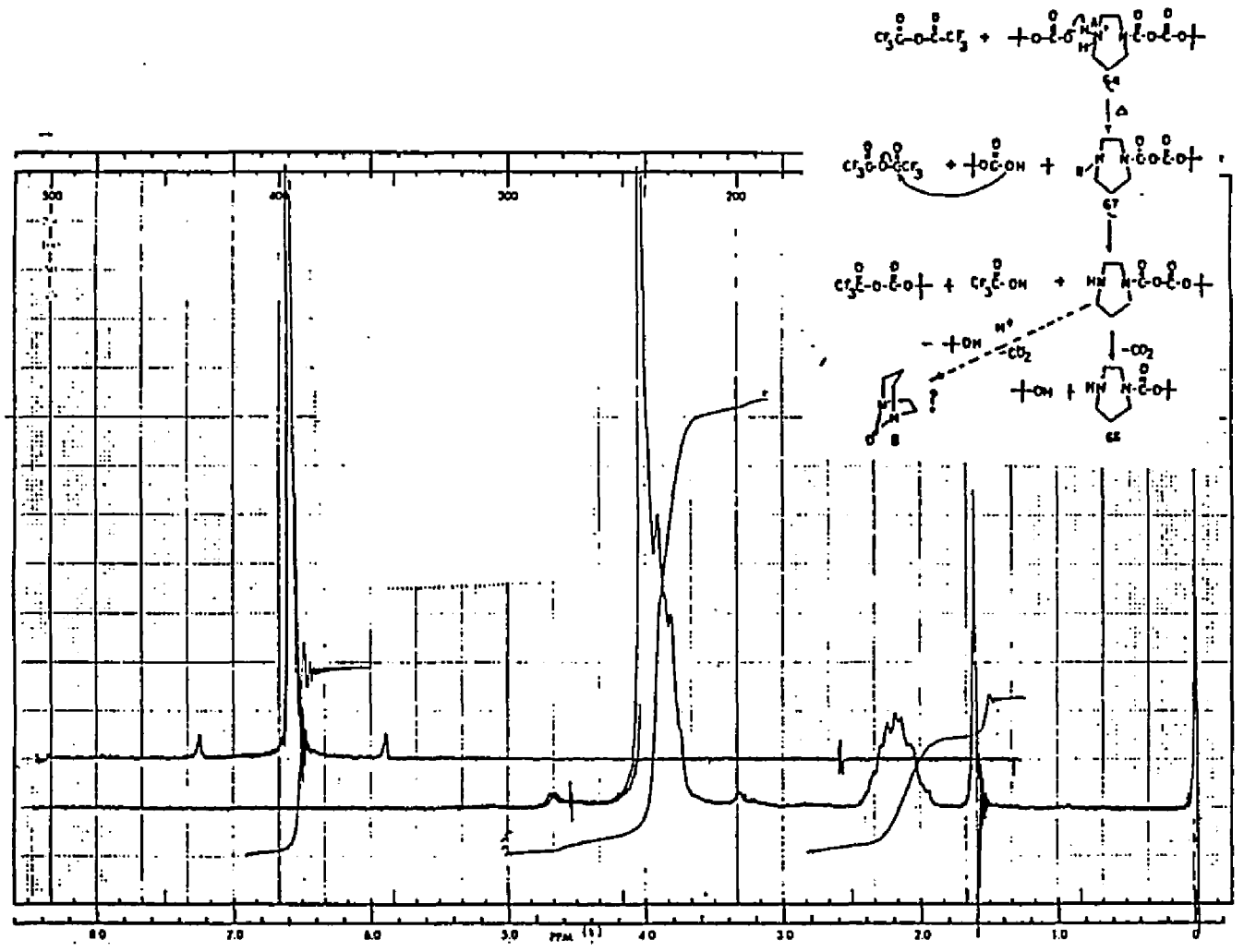
Step 2. Phosgenation of 45 to Yield 1-Azonia-[5-chlorocarbonyl-1,5-diazacyclooctan]hydrochloride 46

The method applied here was exactly as described for the preparation of 43. The yield of 46 was 44%. Analysis: Calcd for 46, $C_7H_{14}N_2OCl_2$: C, 30.41; H, 6.34; N, 13.14. Found: C, 39.70; H, 6.50; N, 13.00.

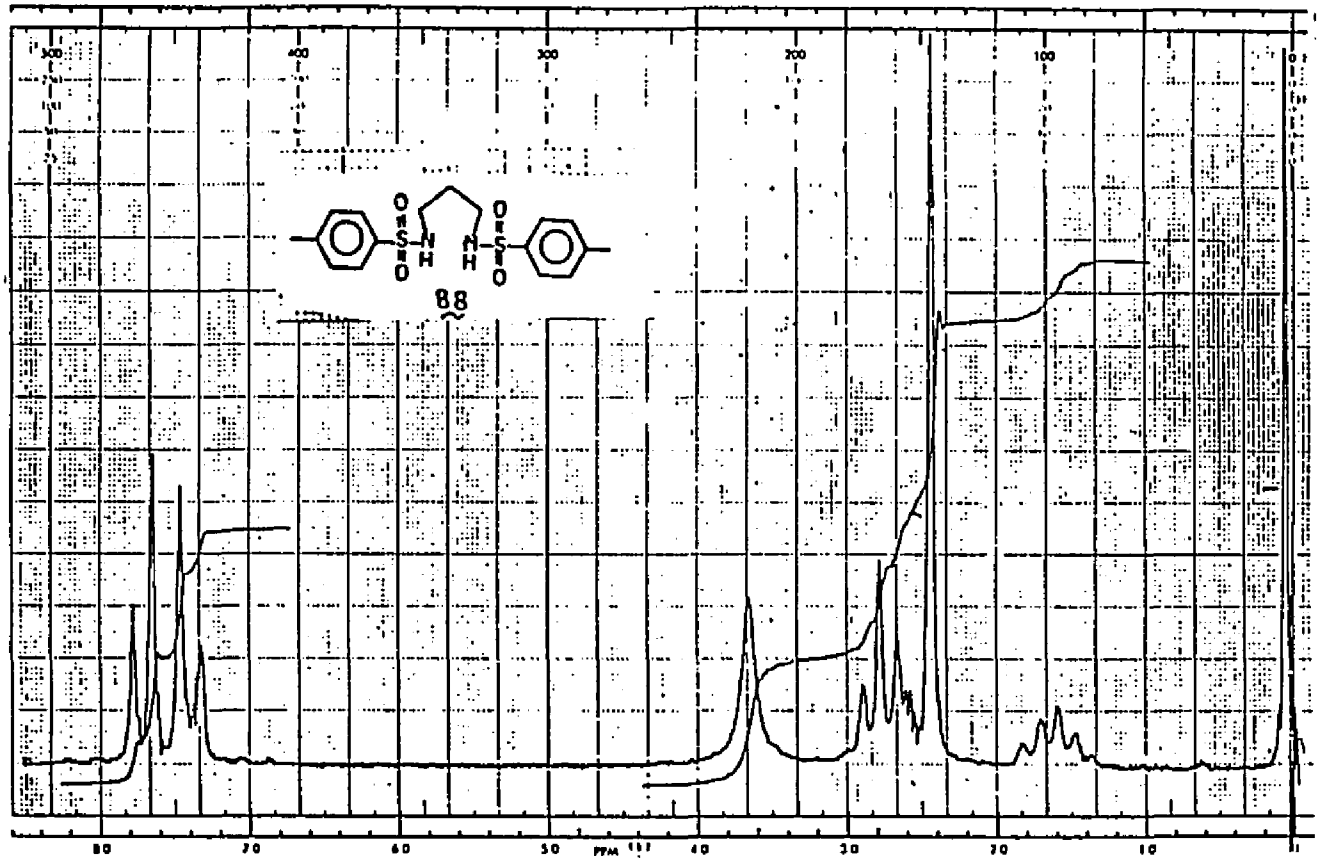
Again, as in the case of 43, 46 gave only polymers on deprotonation with bases.

APPENDIX A

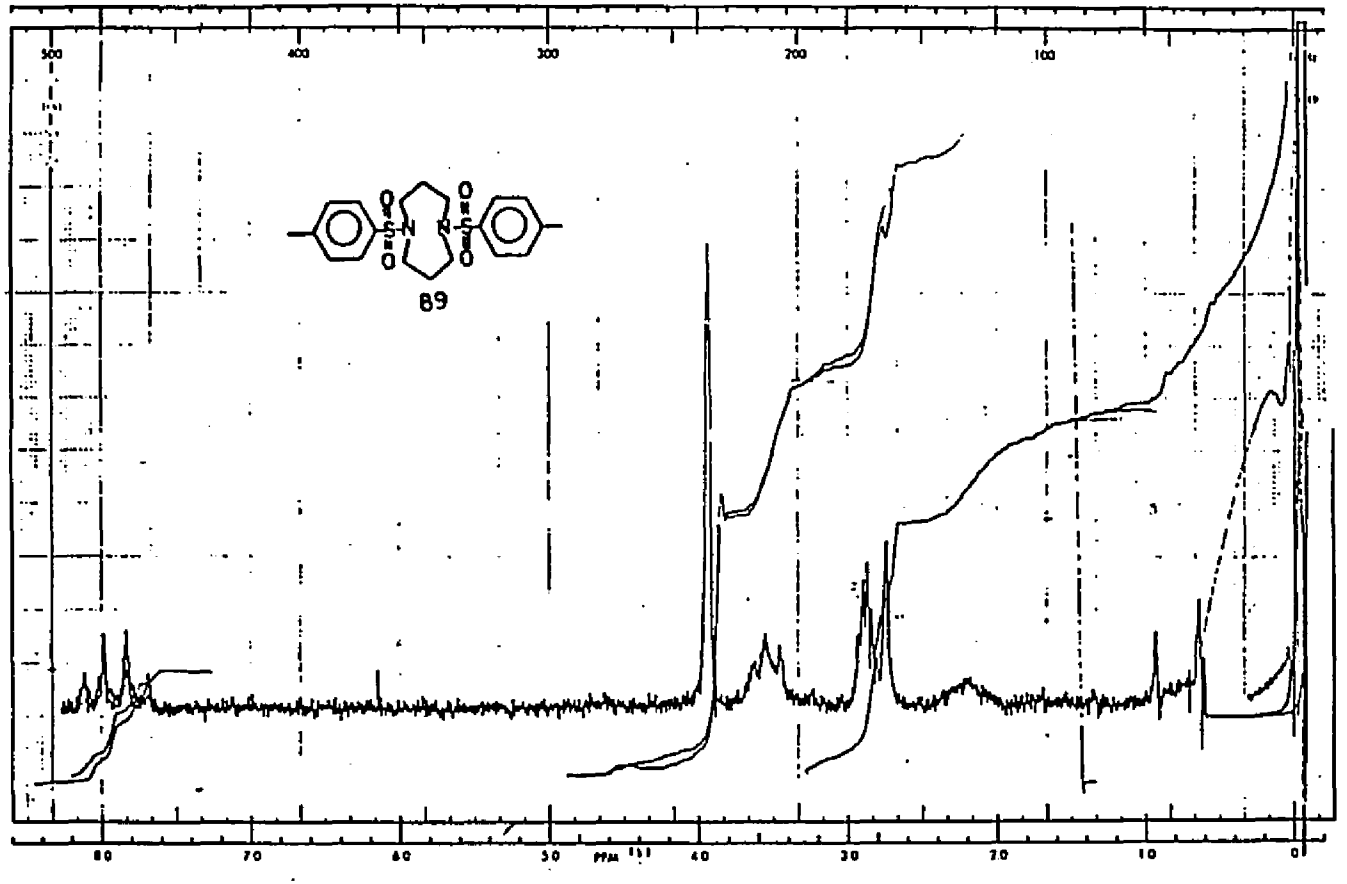
NUCLEAR MAGNETIC RESONANCE SPECTRA



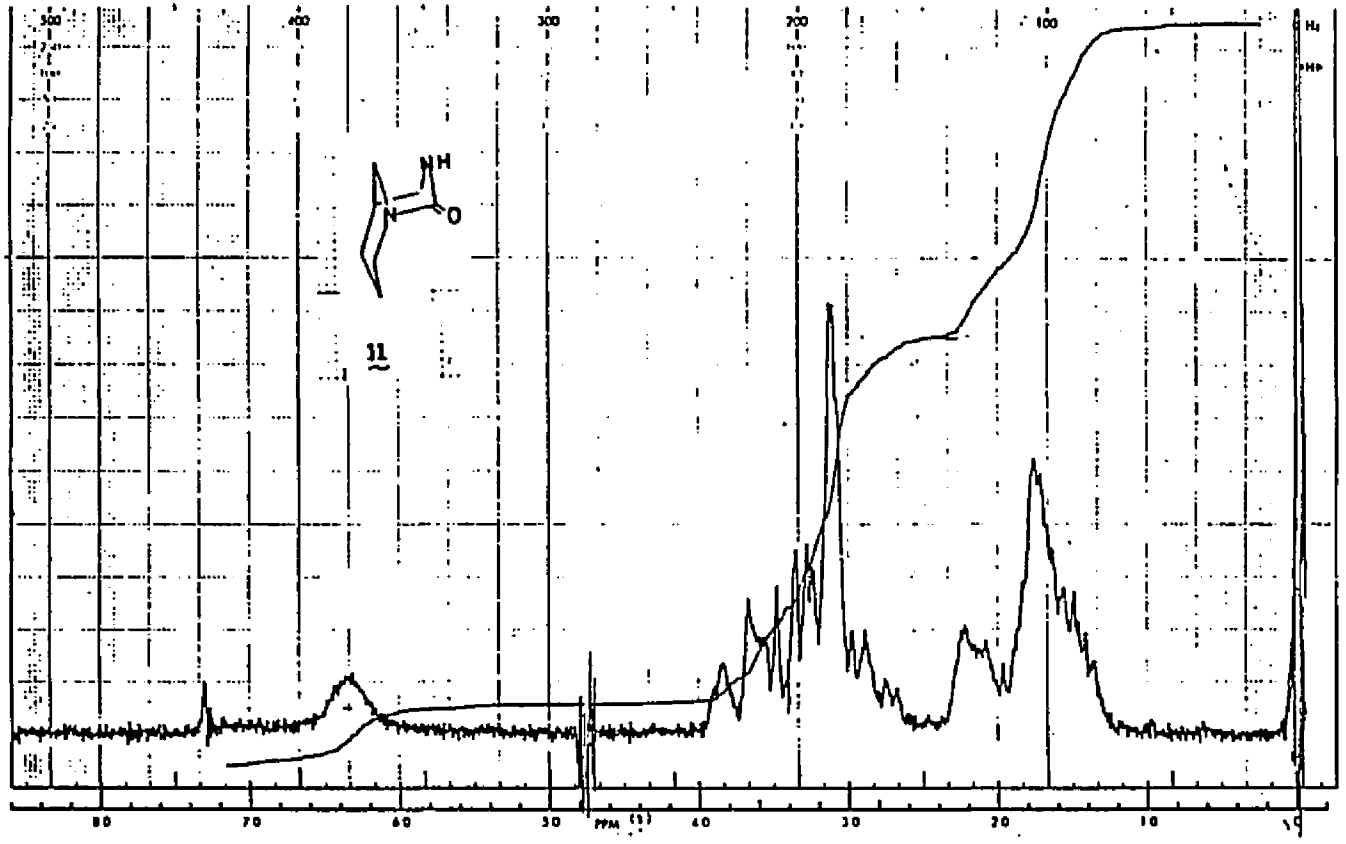
Spectrum #1: 60 MHz NMR Spectrum of the Products of the Reaction of 64 with Trifluoroacetic Anhydride (TFAnh) in NMR Tube (Figures 16 and 19). Probable Formation of 8. Solvent TFAnh.



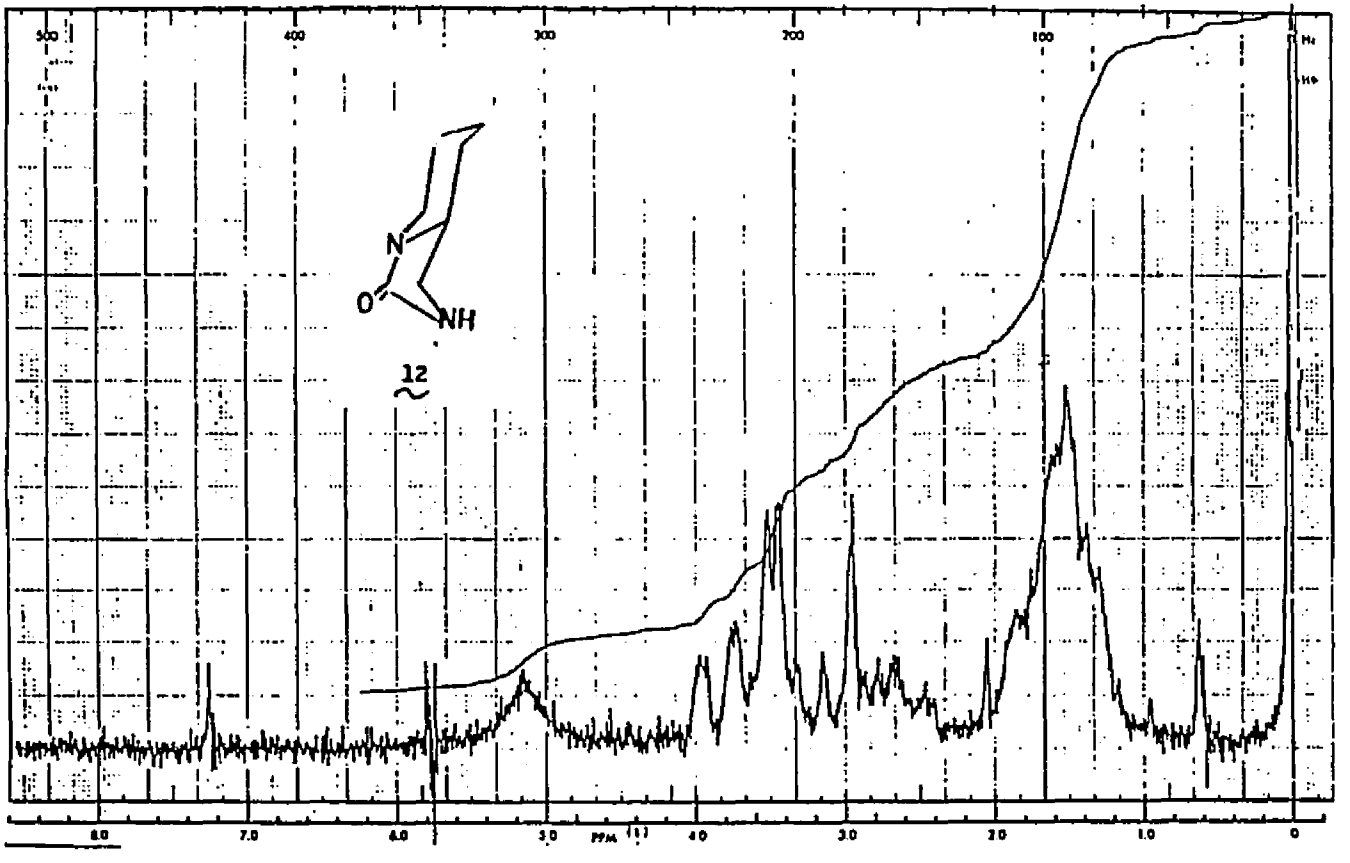
Spectrum #2: 60 MHz NMR Spectrum of 88 (Figure 28) (in $DMSO_{d_6}$)



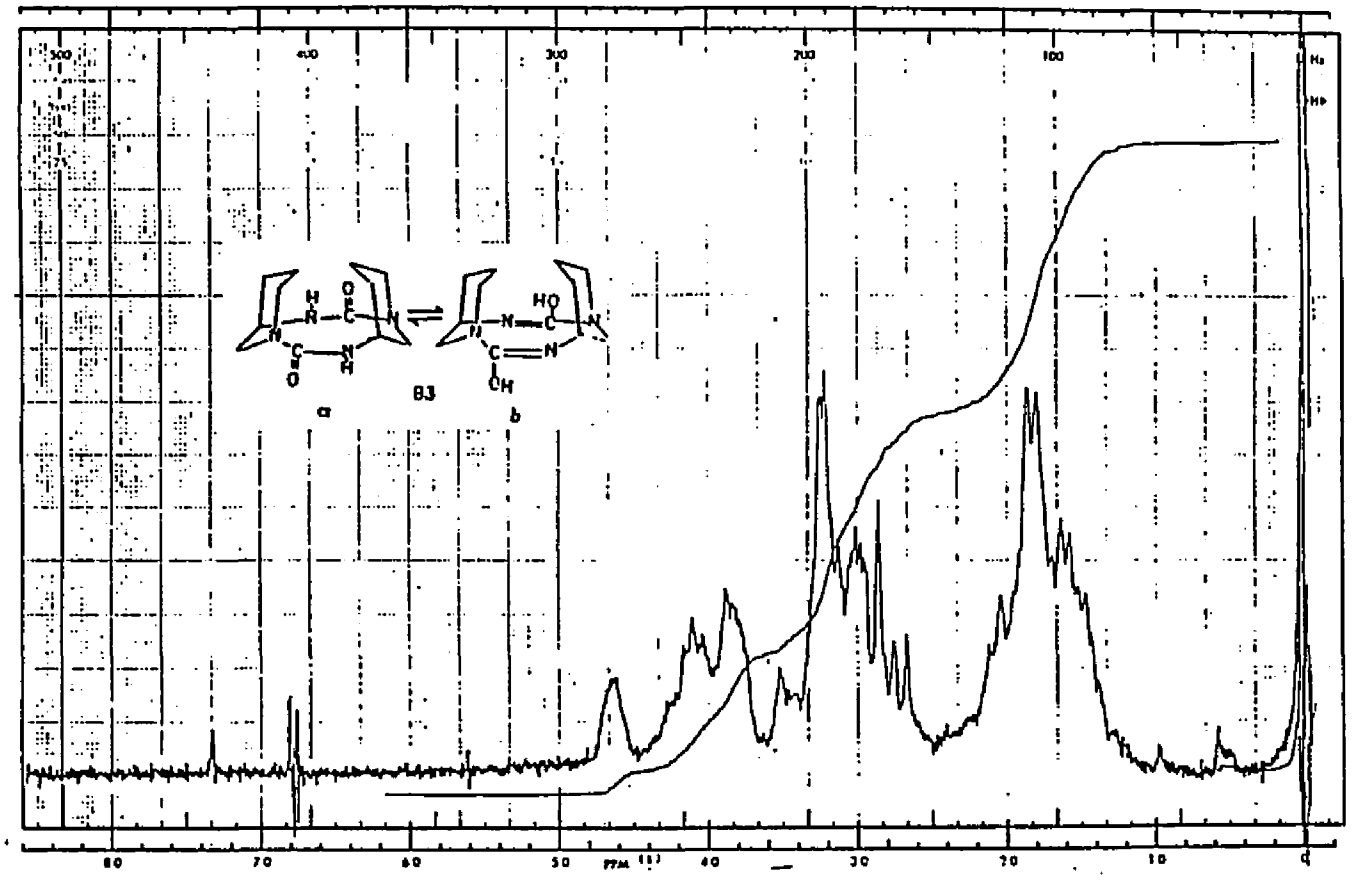
Spectrum #3: 60 MHz NMR Spectrum of 89



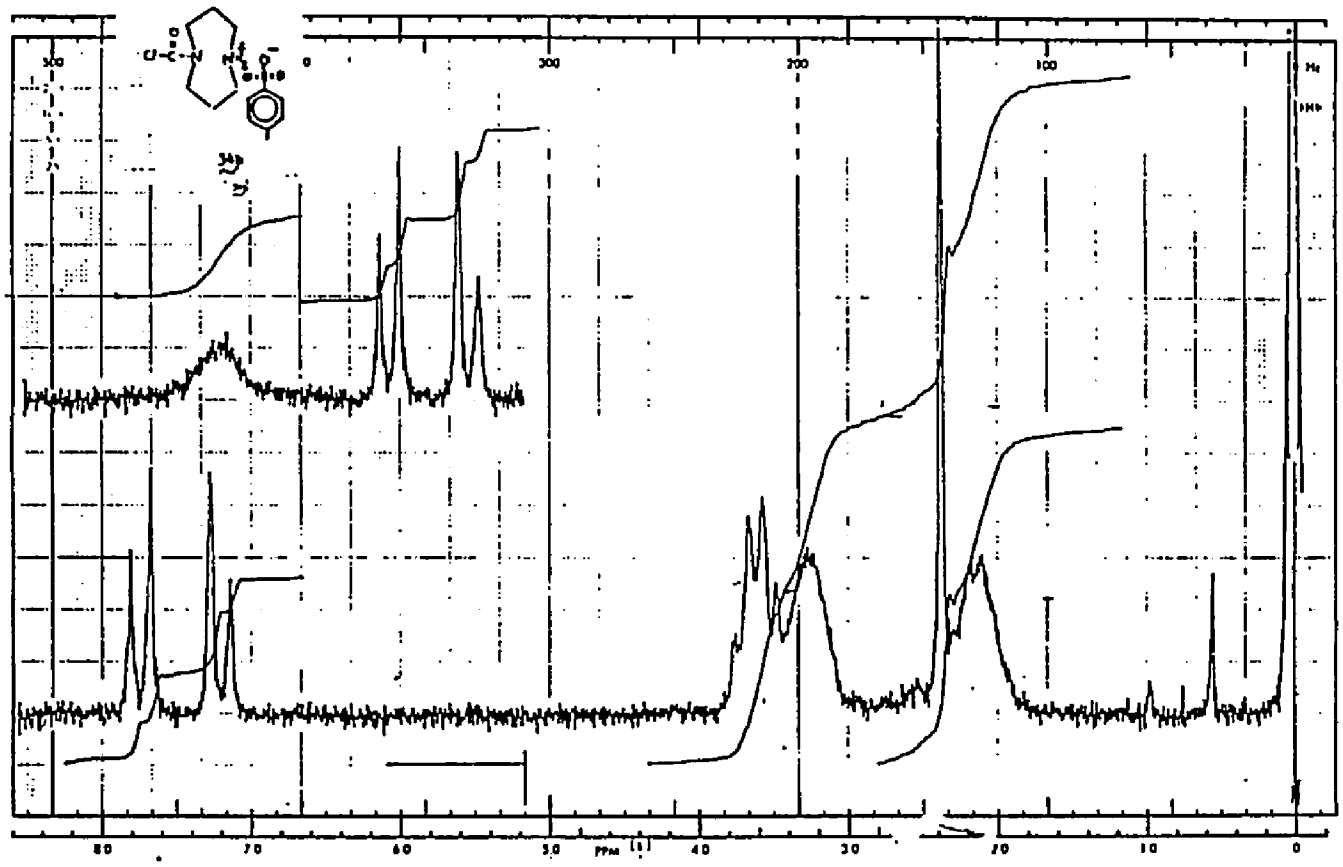
Spectrum #4: 60 MHz NMR Spectrum of 11 (in $CDCl_3$)



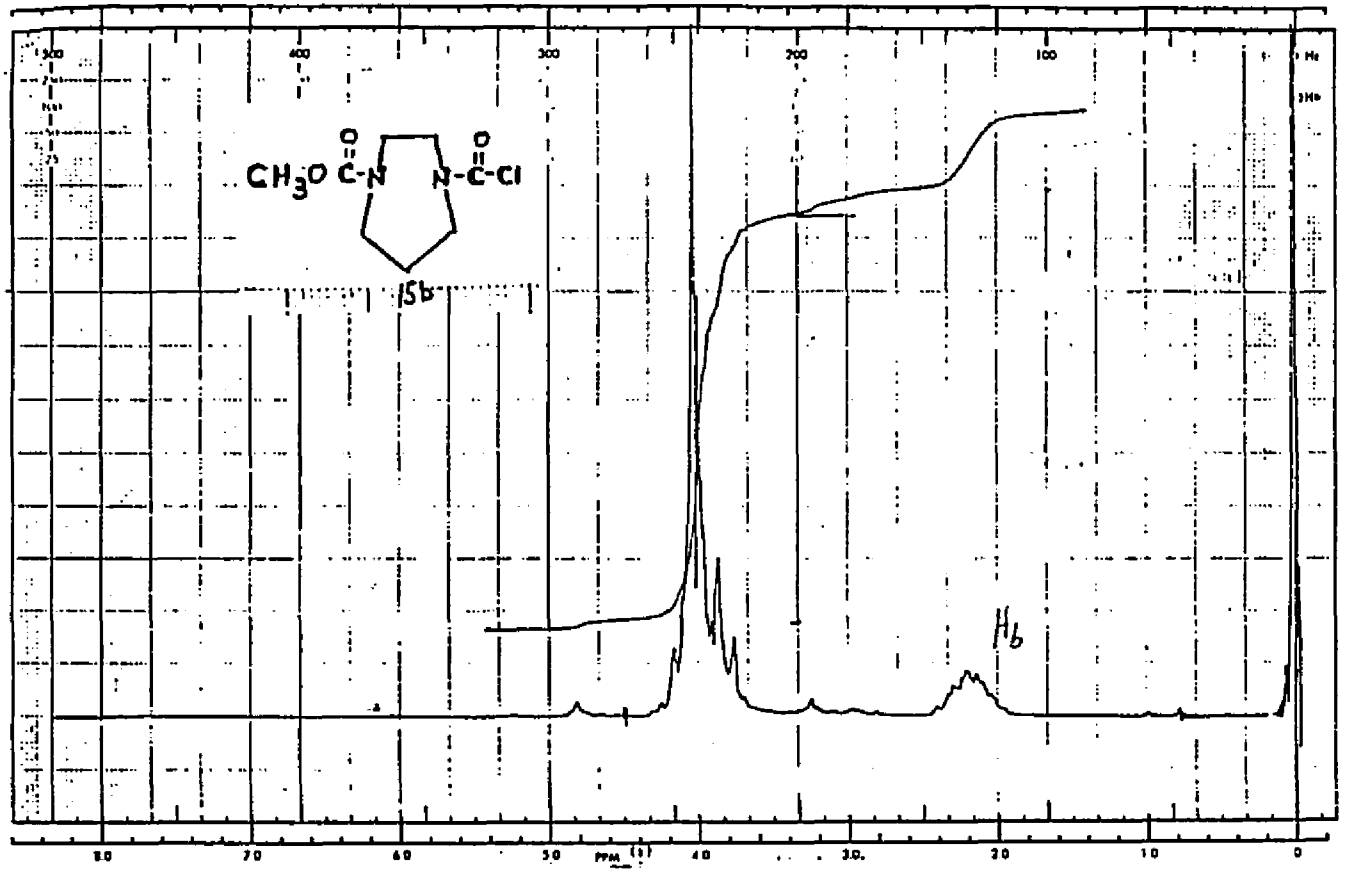
Spectrum #5: 60 MHz NMR Spectrum of 12 (in $CDCl_3$)



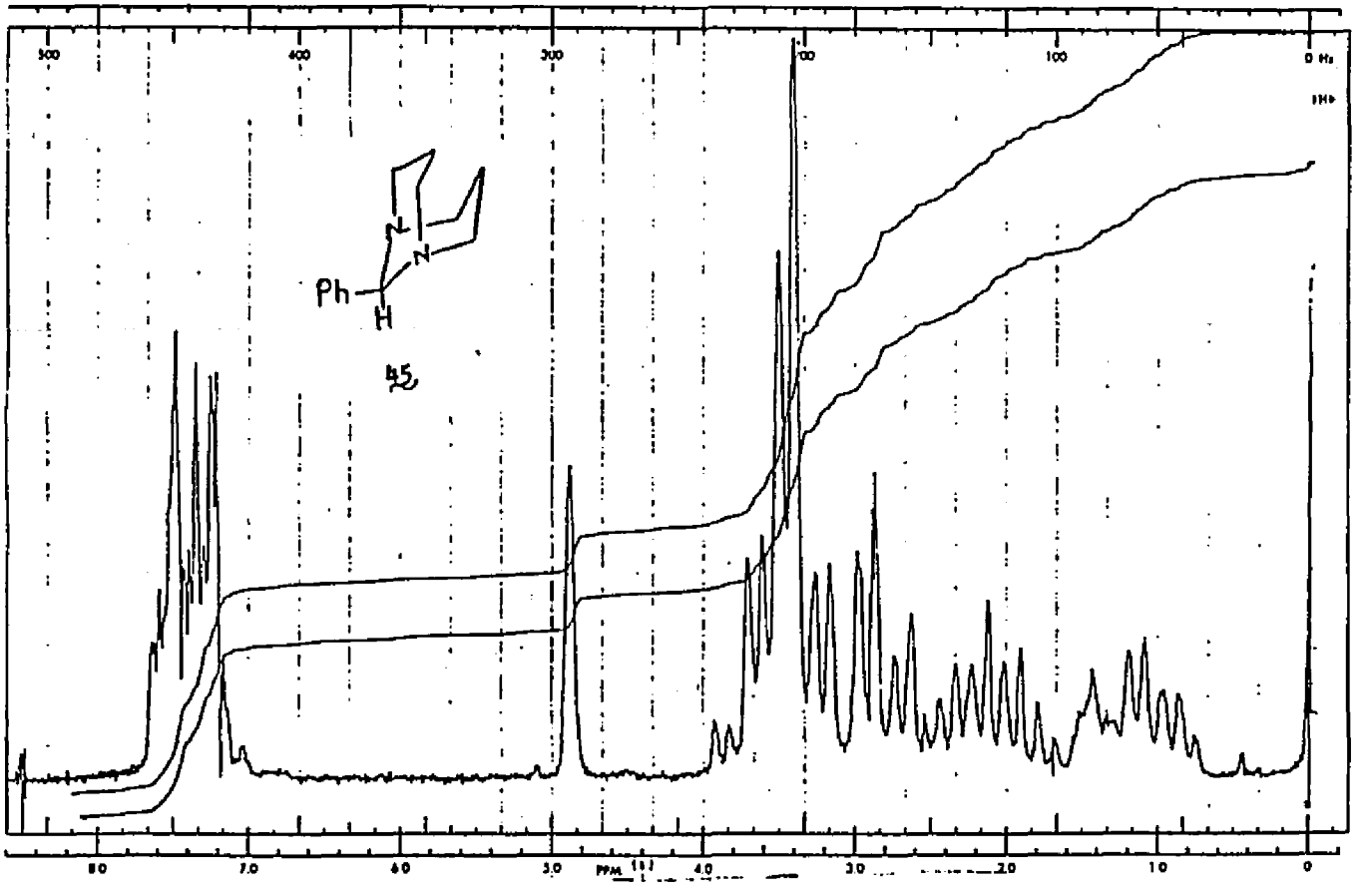
Spectrum #6: 60 MHz NMR Spectrum of a Compound 83 Purported to be a Dimer of 9 (in $CDCl_3$)



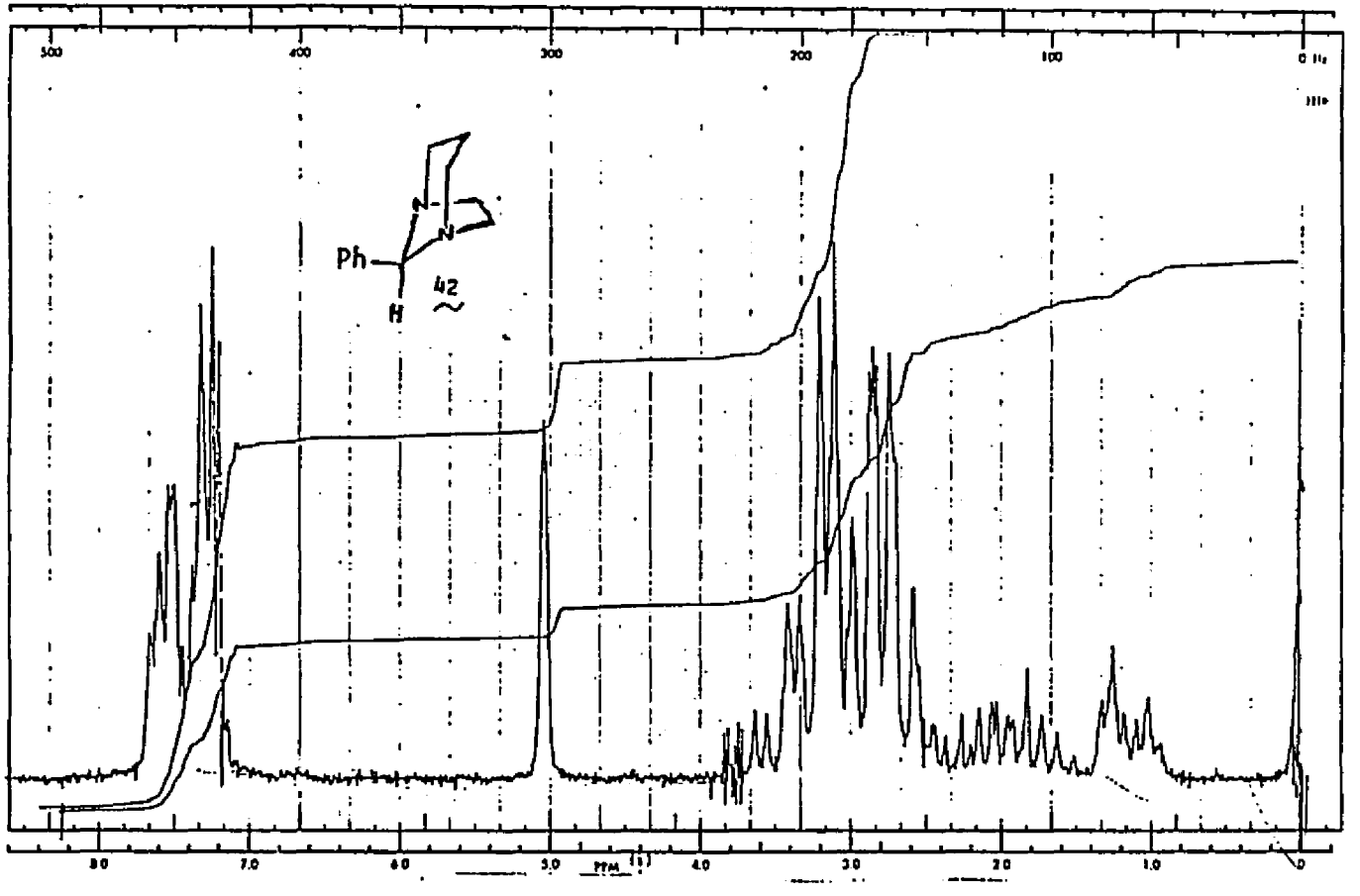
Spectrum #7: 60 MHz NMR Spectrum of 34b (Figure 8b) in $CDCl_3$



Spectrum #8: 60 MHz NMR Spectrum of Phosjenated 15 (Figure 1)



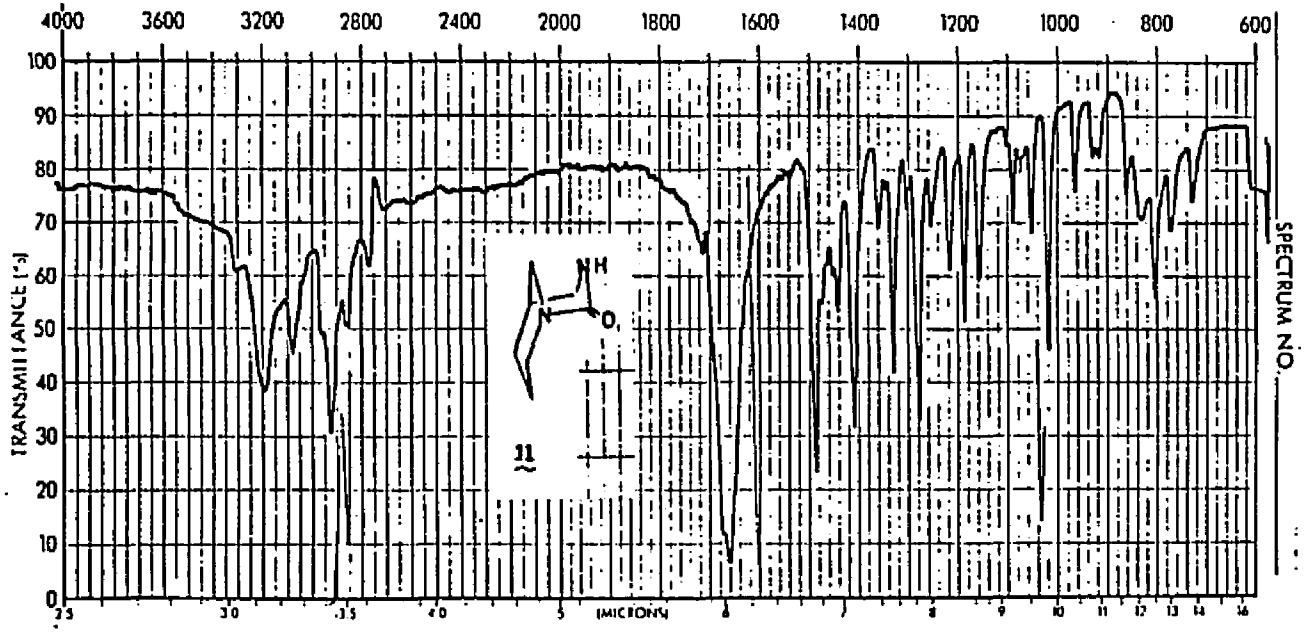
Spectrum #9: 60 MHz NMR Spectrum of 9-Phenyl-1,5-diazabicyclo[3·3·1]nonane in $CDCl_3$



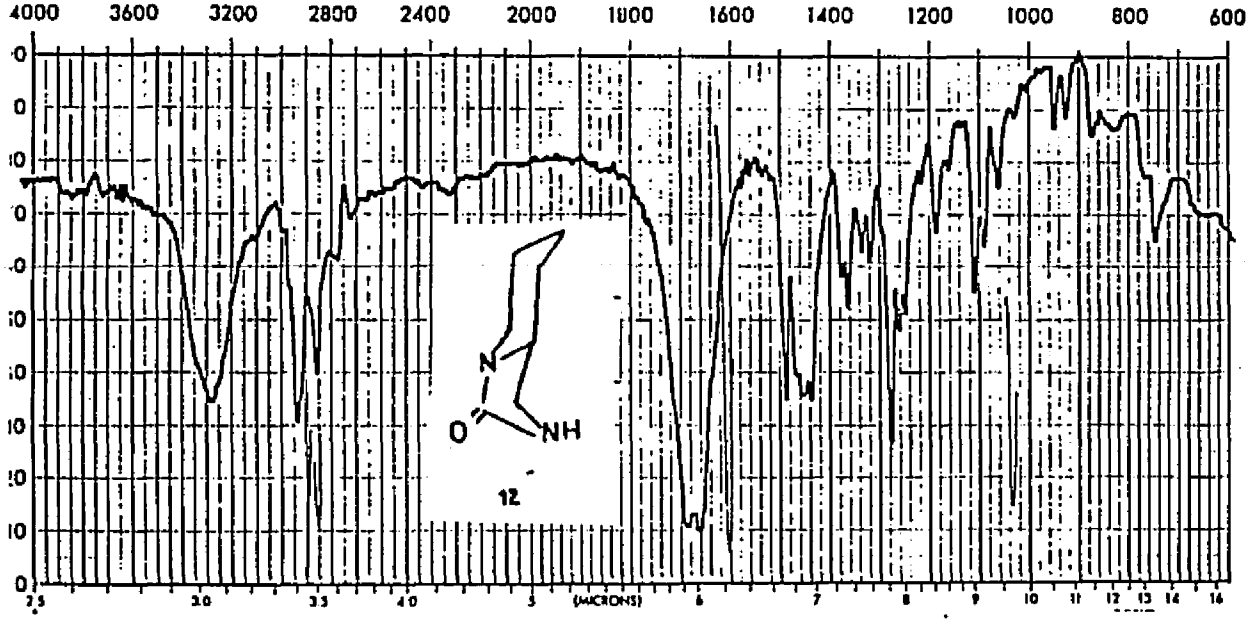
Spectrum #10: 60 MHz NMR Spectrum of 8-Phenyl-1,5-diazabicyclo[3·2·1]octane in $CDCl_3$

APPENDIX B

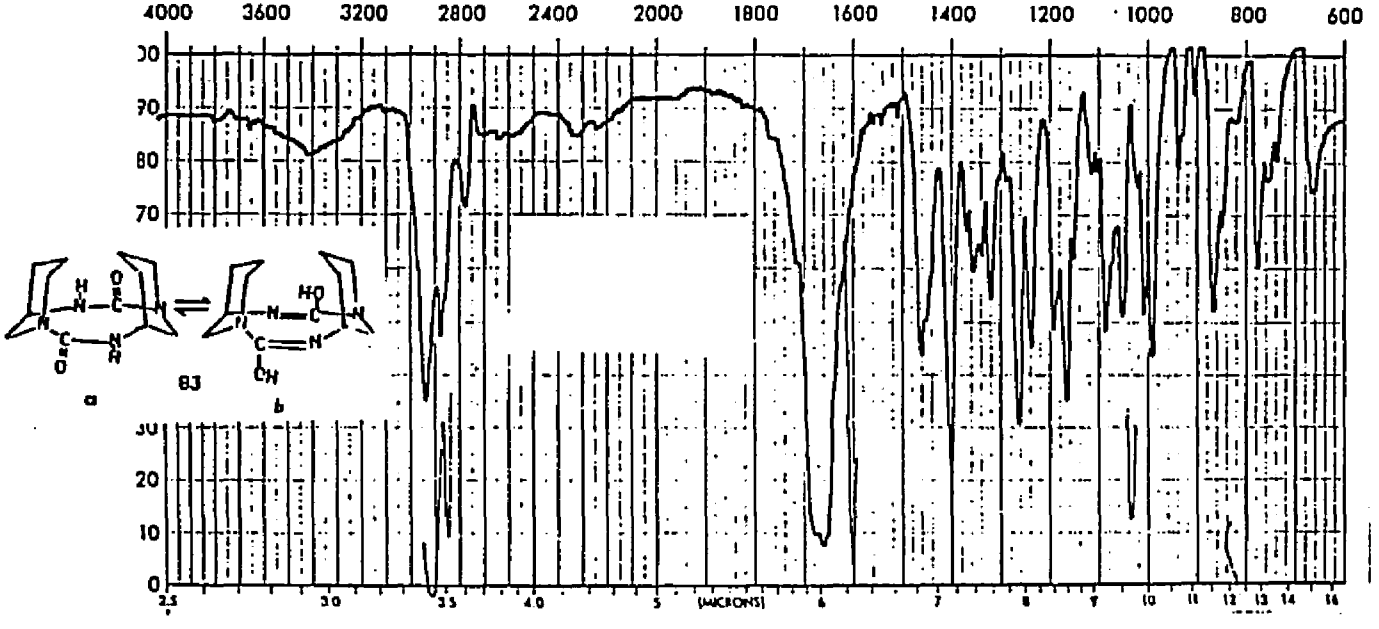
INFRARED ABSORPTION SPECTRA



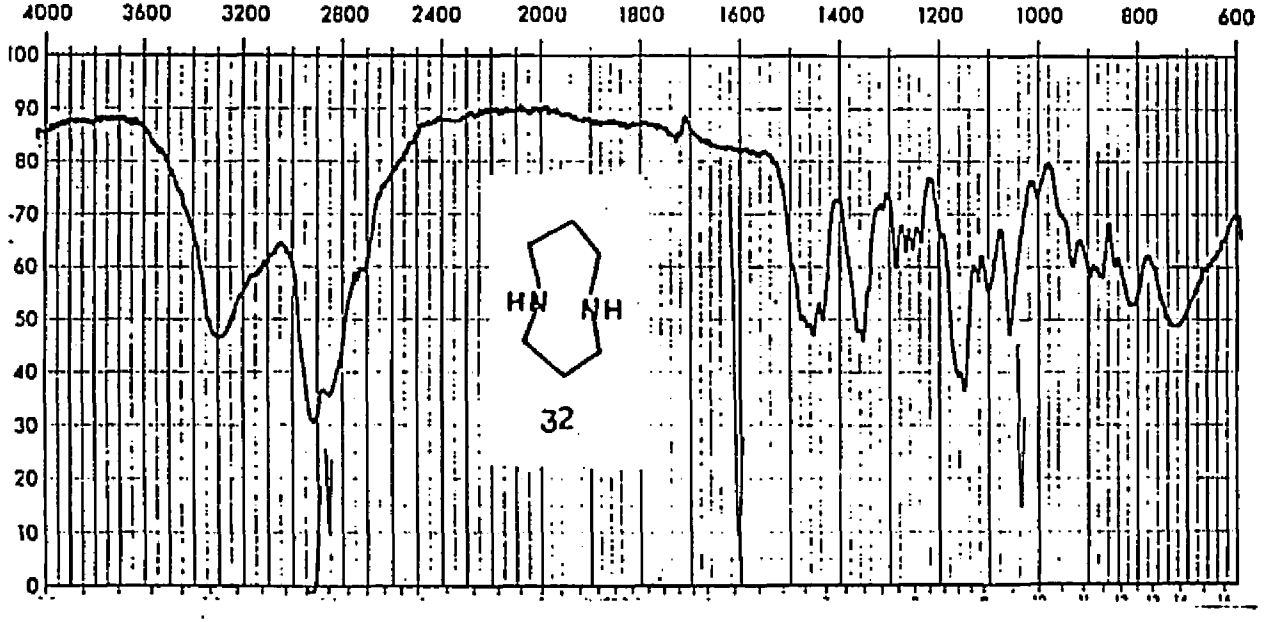
Spectrum #1: Infrared Spectrum of 11 (KBr)



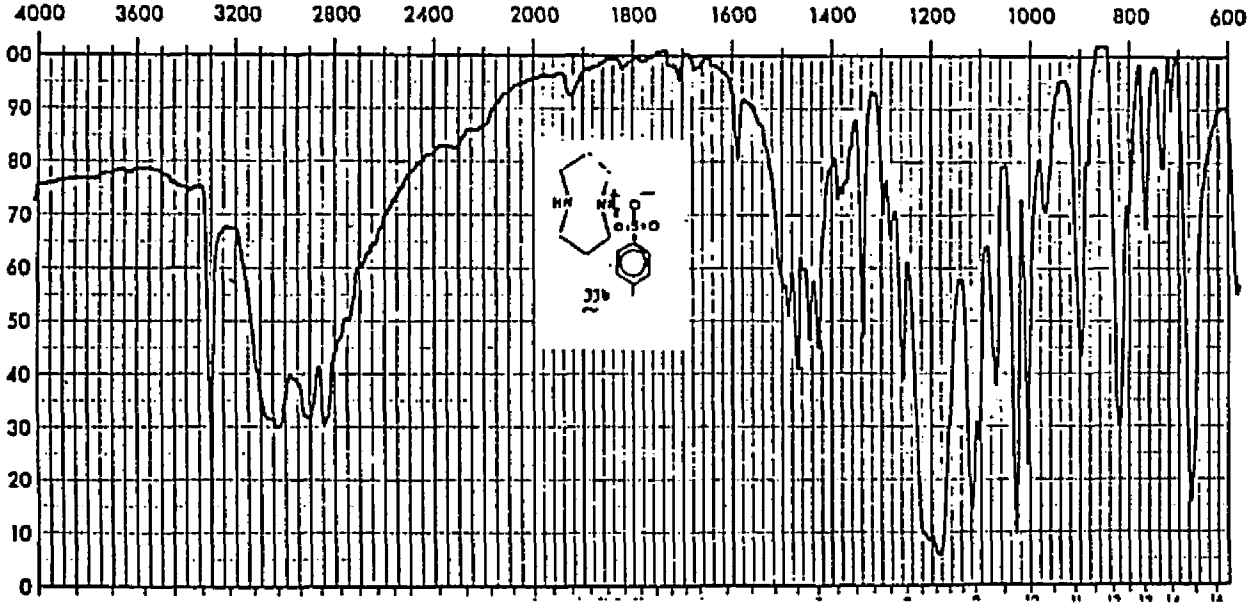
Spectrum #2: Infrared Spectrum of 12 (KBr)



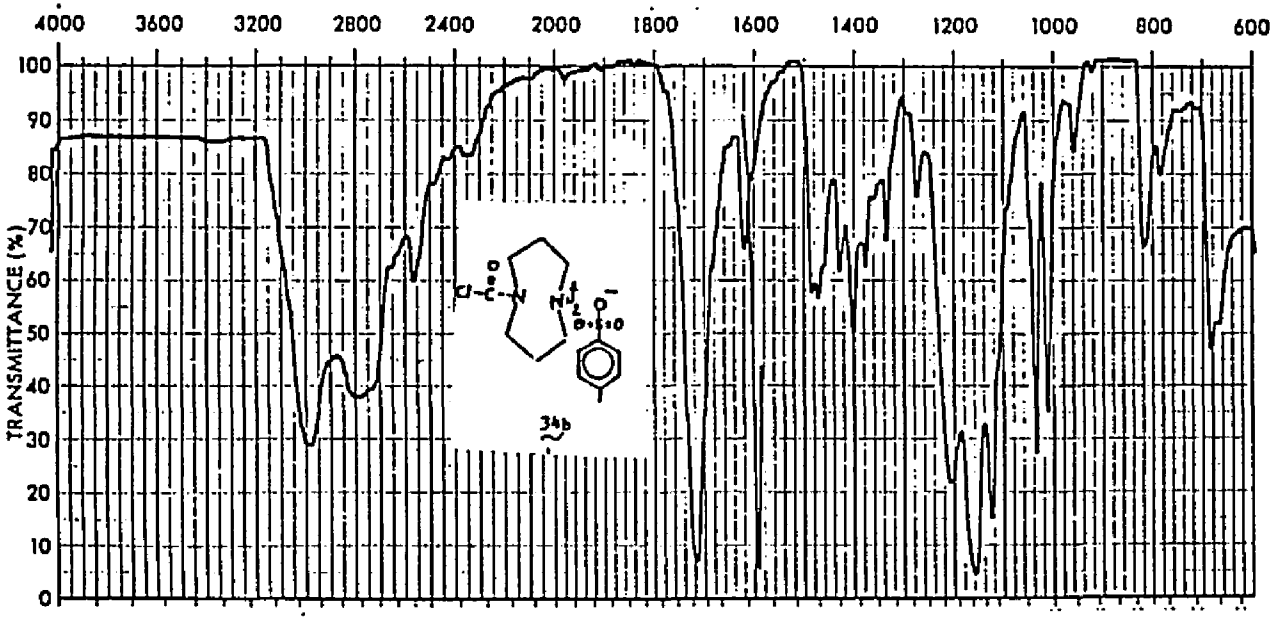
Spectrum #3: Infrared Spectrum of a Compound Proposed to be a Dimer 83 of 9 (Figure 24, KBr)



Spectrum #4: Infrared Spectrum of 32



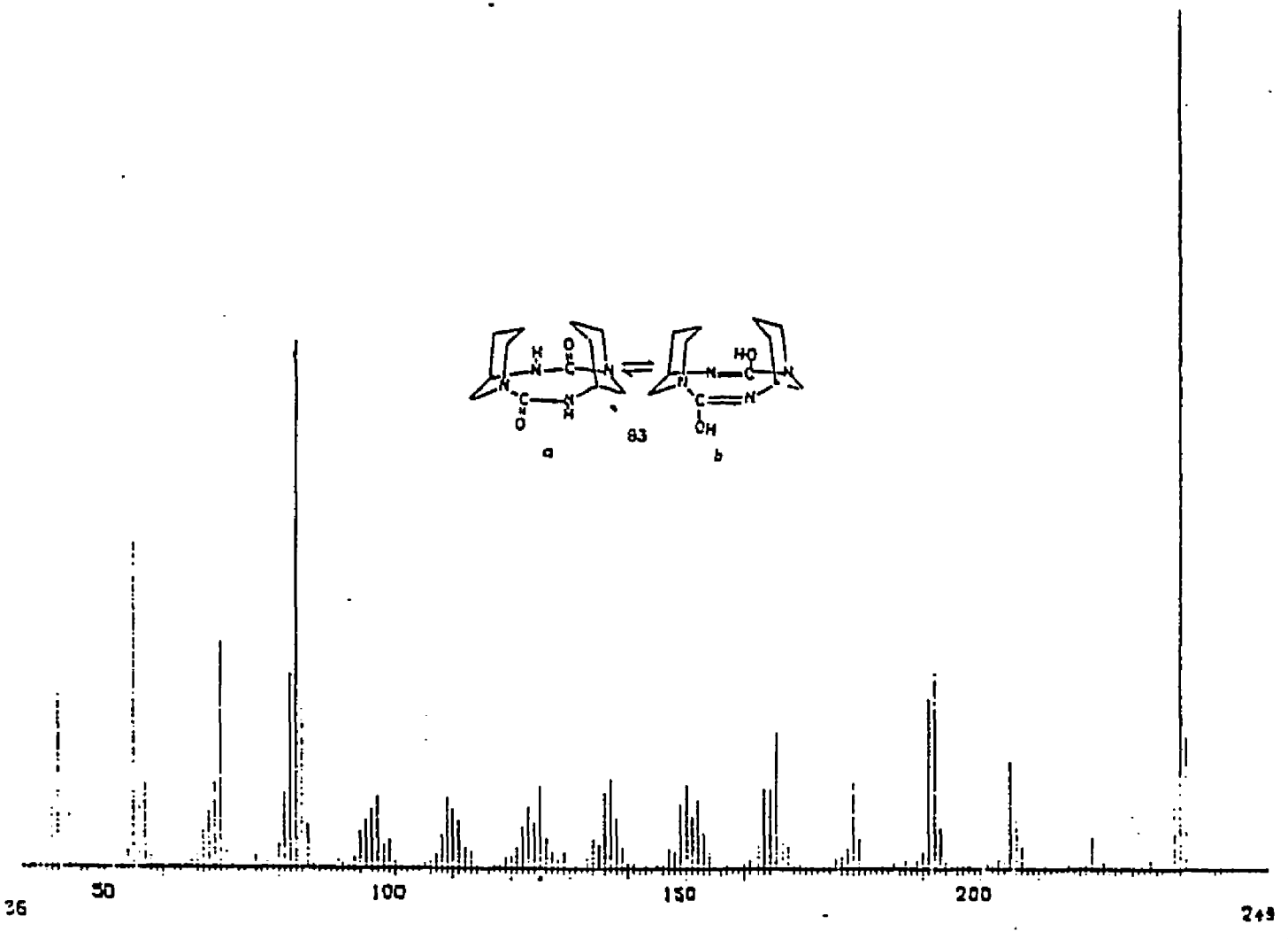
Spectrum #5: Infrared Spectrum of 33b



Spectrum #6: Infrared Spectrum of 34b (KBr)

APPENDIX C

MASS SPECTROGRAPH SPECTRA



Spectrum #1: Mass Spectrograph of a Compound Proposed to be a Dimer 83 of 9 (Figure 24)

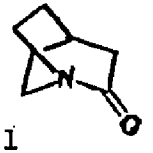
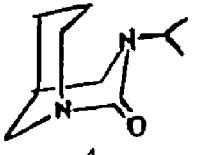
12

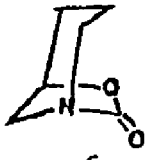
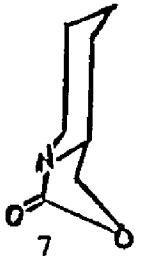
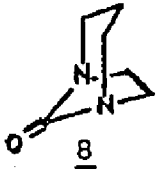
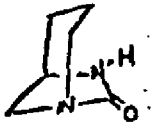
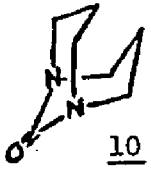
1,8-diazabicyclo[4·3·0]nonan-9-one

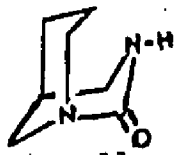
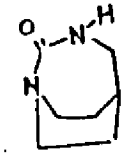
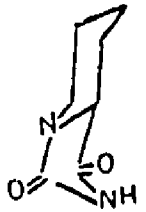
Spectrum #2: Mass Spectrum of 12

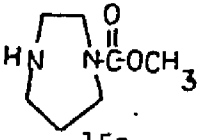
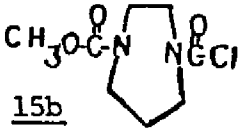
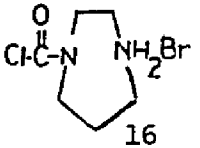
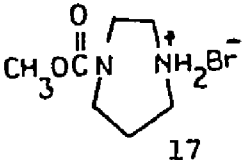
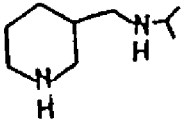
APPENDIX D

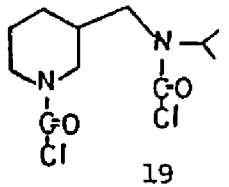
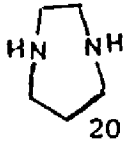
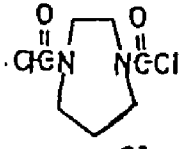
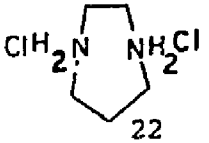
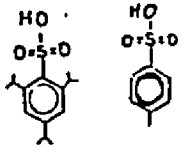
LIST OF COMPOUND NUMBERS, THEIR STRUCTURES, PAGE, FIGURE, AND APPENDIX REFERENCES

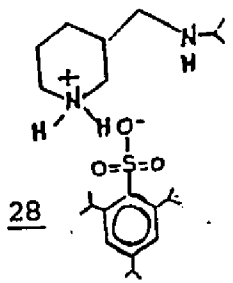
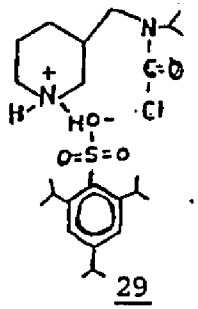
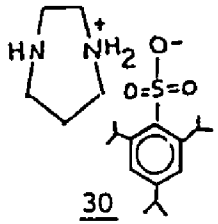
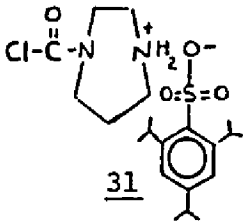
Compound #	Name	Structure	Figure	Page	Appendix	Table
1	2-Quinuclidone (1-Azabicyclo-2 2 2 octan-2-one	 1	-	1	-	-
2	1-Azabicyclo[3·3·1]nonan-2-one	 2	27	2, 54	-	-
3	1-Azabicyclo[4·3·0]nonan-9-one	 3	-	2	-	-
4	3-Isopropyl-1,3-diazabicyclo-[3·3·1]nonan-2-one	 4	2, 6, 27	3, 13, 52, 53, 96	-	-
5	1-Aza-3-oxabicyclo[3·3·1]nonan-2-one	 5	27	3, 52	-	-

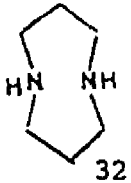
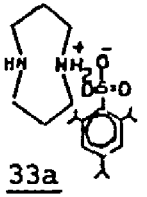
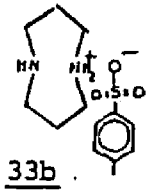
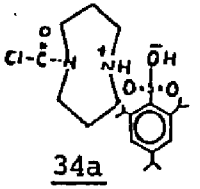
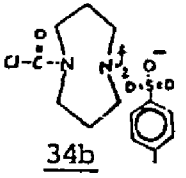
Compound #	Name	Structure	Figure	Page	Appendix	Table
6	1-Aza-6-oxabicyclo[3·2·1octan-7-one	 6	-	3	-	-
7	1-Zaz-8-oxabicyclo[4·3·0]nonan-9-one	 7	-	3	-	-
8	1,5-Diazabicyclo[3·2·1]octan-8-one	 8	3, 4, 8 11, 14, 16, 17, 19, 27	4, 14, 21, 25, 29, 32, 34, 36, 52, 99	A.1	-
9	1,6-Diazabicyclo[3·2·1]octan-7-one	 9	25, 28	4, 47, 54, 85, 90	-	-
10	1,5-Diazabicyclo[3·3·1]nonan-9-one	 10	9a, 9b, 12, 27	4, 22, 23, 26, 27, 53	-	-

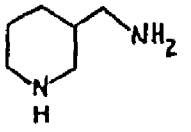
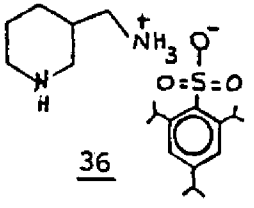
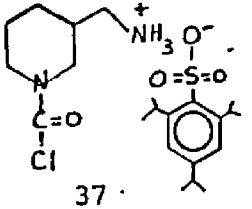
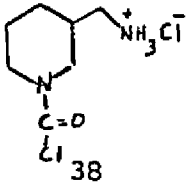
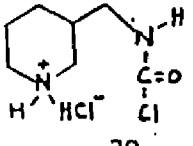
Compound #	Name	Structure	Figure	Page	Appendix	Table
11	1,3-Diazabicyclo[3·3·1]nonan-2-one	 11	7, 10, 22	4, 19, 43, 44, 52, 53, 59, 60, 61, 62, 63, 64, 66-69, 79, 80-82, 88-96, 102, 110	A.4, B.1	1, 2, 3, 5
12	1,8-Diazabicyclo[4·3·0]nonan-9-one	 12	23, 28	5, 45, 53, 54, 66, 82, 83, 90, 103, 111	A.5, B.2, C.2	4
13	1,3-Diazabicyclo[3·2·2]nonan-2-one	 13	24	5, 46, 86	-	-
14	1,8-Diazabicyclo[4·3·0]nonan-7,9-dione (a hydantoin)	 14	-	5	-	-

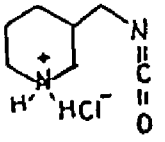
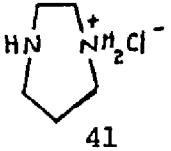
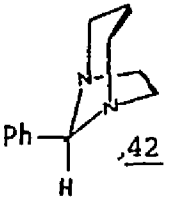
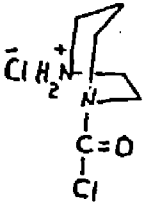
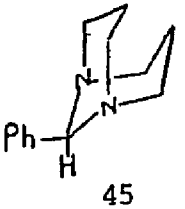
Compound #	Name	Structure	Figure	Page	Appendix	Table
15a	1-Methoxycarbonyl-1,4-diaza-cycloheptane	 15a	1	11	-	-
15b	1-Methoxycarbonyl-4-chloro-carbonyl-1,4-diazacycloheptane	 15b	3	14, 106	A.8	
16	1-Chlorocarbonyl-1,4-diaza-cycloheptan-4-hydrobromide	 16	1	11	-	-
17	1-Methoxycarbonyl-1,4-diaza-cycloheptan-4-hydrobromide	 17	1	11	-	-
18	3-Isopropylmethylaminopiperi-dine	 18	2, 6	13, 18	-	-

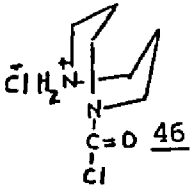
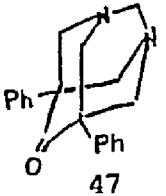
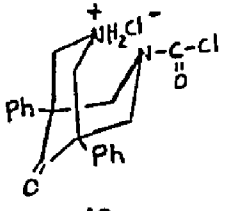
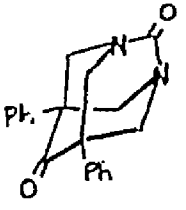
Compound #	Name	Structure	Figure	Page	Appendix	Table
19	N,N'-(Dichlorocarbonyl)-3-Isopropylmethylaminopiperidine	 19	2	13	-	-
20	1,4-Diazacycloheptane (Homopiperidine)	 20	1, 3, 7, 11, 15, 16, 17, 20	11, 14, 19, 25, 31, 32 34, 39	-	-
21	Homopiperazinebiscarbamoyl chloride	 21	3, 4	14, 15	-	-
22	Homopiperazinedihydrochloride	 22	3	15	-	-
27	(a) 2,4,6-Triisopropylbenzene-sulfonic acid and (b) p-toulene	 27a 27b	5, 6, 7, 8, 9a, 9b	17, 18, 19, 21, 22, 23	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
28	3-Isopropylaminomethylpiperidinium mono-2,4,6-triisopropylbenzenesulfonate	 28	6	18	-	-
29	N-Chlorocarbonyl-3-3-isopropylaminomethylmono-2,4,6-triisopropylbenzenesulfonate	 29	6	18	-	-
30	Homopiperidinium-2,4,6-triisopropylbenzenesulfonate	 30	8	21	-	-
31	N-Chlorocarbonyl homopiperidium-2',4',6'-triisopropylbenzenesulfonate	 31	8	21	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
32	1,5-Diazacyclooctane	 32	9a, 9b 12, 15 26, 29, 30	22, 23, 26, 31, 48, 56, 47, 113	B.4	-
33a	1,5-Diazacyclooctan-1-azonia-2',4',6'-triisopropylbenzene-sulfonate	 33a	9a	22	-	-
33b	1,5-Diazacyclooctan-1-azonia-p-toluenesulfonate	 33b	9b	23	B.5	-
34a	1-Azonia-5-chlorocarbonyl-1,5-diazacyclooctan-2',4',6'-tri-isopropylbenzenesulfonate	 34a	9a	22	-	-
34b	1-Azonia-5-chlorocarbonyl-1,5-diazacyclooctan-p-toluene-sulfonate	 34b	9b	23	B.6	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
35	3-Aminomethylpiperidine	 35	7, 10	19, 24 73	-	-
36	3-Ammoniummethylpiperidino-2',4',6'-triisopropylbenzene-sulfonate	 36	7	19	-	-
37	1-Chlorocarbonyl-3-ammonium-methylpiperidino-2',4',6'-triisopropylbenzenesulfonate	 37	7	19	-	-
38	1-Chlorocarbonyl-3-aminomethyl-piperidiniumhydrochloride	 38	10	24	-	-
39	3-(N-Chlorocarbonylamino-methyl)piperidinium hydro-chloride	 39	10	24	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
40	3=Isocyanomethylpiperidinium hydrochloride	 40	10	24	-	-
41	Homopiperidine monohydrochloride	 41	11	28	-	-
42	8-Phenyl-1,5-diazabicyclo-[3·2·1]octane	 42	11	28, 108	A.10	-
43	4-Azonia-1-chlorocarbonyl-1,5-diazacycloheptan-hydrochloride	 43	11	-	-	-
45	9-Phenyl-1,5-diazabicyclo-[3·3·1]nonane	 45	12	26, 107	A.9	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
46	5-Azonia-1-chlorocarbonyl-1,5-diazacyclooctan hydrochloride	 46	12	26	-	-
47	1,5-Diphenyl-3,7-diazaadamantan-10-one	 47	13	27	-	-
48	7-Azonia-1,5-diphenyl-9-one 3-chlorocarbonyl-3,7-diazacyclononan hydrochloride	 48	13	27	-	-
49	1,5-Diphenyl-3,7-diazaadamantan-8,9-dione	 49	13	27	-	-

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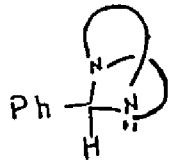
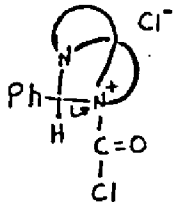
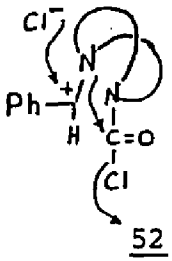
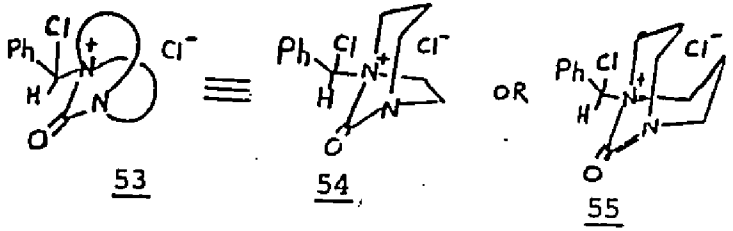
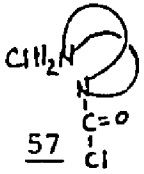
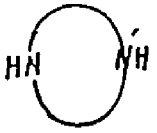
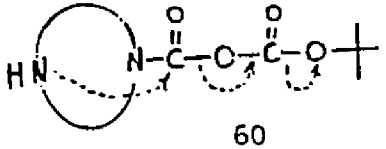
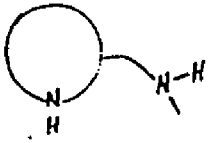
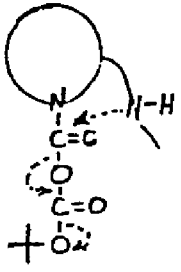
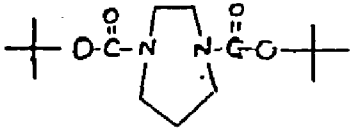
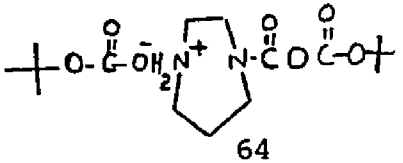
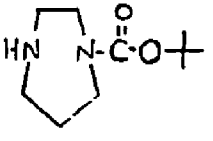
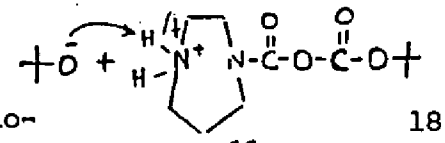
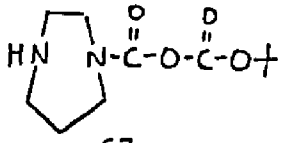
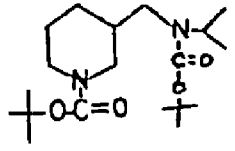
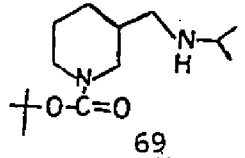
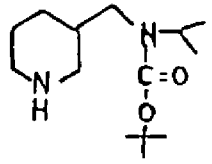
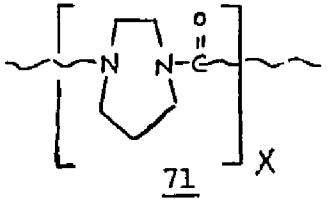
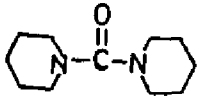
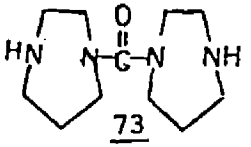
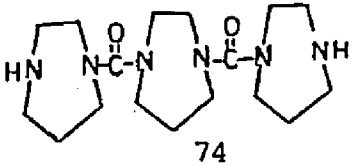
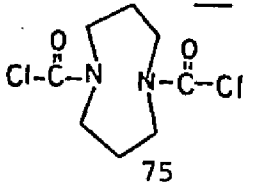
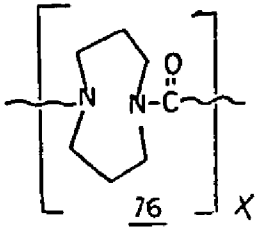
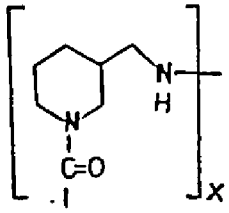
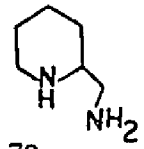
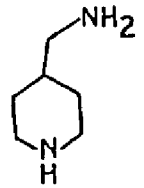
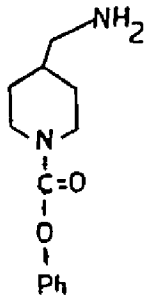
50	y-Phenyl-1,x-diazabicyclo-[z.m.1]alkane	 50	14	29	-	-
51		 51	14	29	-	-
52		 52	14	29	-	-
53		 53 ≡ 54 OR 55	14	29	-	-

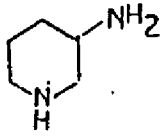
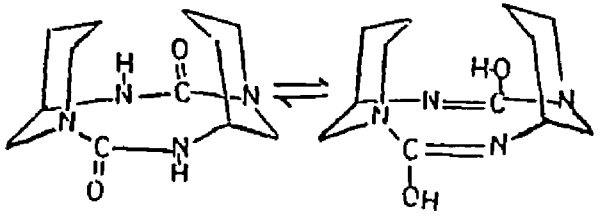
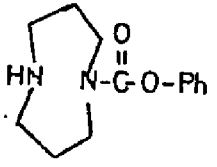
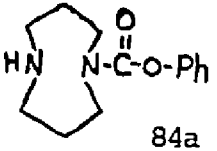
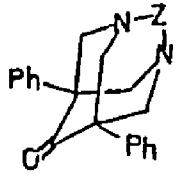
Compound #	Name	Structure	Figure	Page	Appendix	Table
54	1,5-Diazacyclooctan-8-one-1-chlorobenzylammonium chloride		14	29	-	-
55	1-Azonia[chlorobenzyl-1,5-cyclononan-9-one]chloride		14	29	-	-
56	Generalized 2 N bridgehead urea	56 = 8 or 10	14	29	-	-
57	Generalized N-chlorocarbonyl-N-ammonium chloride	 57	14	29	-	-
58	Generalized x,y-Diazacycloalkane	 58	15	31	-	-
59	Di-tertiarybutyltricarbonate	+O-C-O-C-O-C-O+	15	31, 32, 34	-	-
60	Generalized x,y-Diazacyclo alkan-N-t-butylcarbonate carbonyl	 60	15	31	-	-

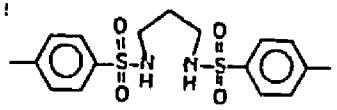
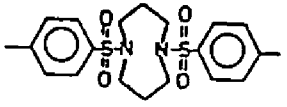
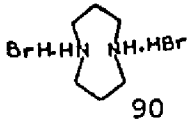
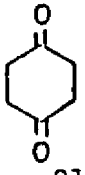
Compound #	Name	Structure	Figure	Page	Appendix	Table
61	A One-annular-N cyclic diamine	 61	15	31	-	-
62		 → 25 9,11,12, or 13 62	15	31	-	-
63	1,4-Di-t-butoxycarbonyl-1,4-diazacycloheptane	 63	16	32	-	-
64	1-Azonia-1,4-diazacyclo-heptan-4-N-carbonyldi-t-butylcarbonate	 64	16, 18	32	-	-
65	1-t-Butoxycarbonyl-1,4-diaza-cycloheptane	 65	17, 19	34, 36	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
66	1-Azonia-butoxy-1,4-diazacycloheptan-N-carbonyl-t-butylcarbonate	 66	18	35	-	-
67	1,4-Diazacycloheptan-1-carbonyl-t-butylcarbonate	 67	18, 19	35, 36	-	-
68	3-(Isopropyl-t-butoxycarbonyl)-methylamino-1-t-butoxycarbonylpiperidine	 68	-	37	-	-
69	3-Isopropylmethylamino-1-t-butoxycarbonylpiperidine	 69	-	37	-	-
70	3-(Isopropyl-t-butoxycarbonyl)-methylaminopiperidine	 70	-	37	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
71	Polyhomopiperazine urea	 71	20	39	-	-
72	Bispentamethylene urea	 72	-	40	-	-
73	Dihomopiperazine urea	 73	-	40	-	-
74	Trihomopiperazine urea	 74	-	40	-	-
75	1,5-Dichlorocarbonyl-1,5-diazacyclooctane	 75	21	41	-	-
76	Poly-1,5-Diazacyclooctane urea	 76	21	41	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
78	Poly-3-(aminomethyl)-piperidine urea	 78	22	43	-	-
79	2-Aminomethylpiperidine	 79	23	45, 74	-	-
80	4-Aminomethylpiperidine	 80	24	46	-	-
81	1-Phenoxycarbonyl-4-aminomethyl-piperidine	 81	24	46	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
82	3-Aminopiperidine	 82	25	47, 74	-	-
83		 a 83 b	25	47	A.6, B.3, C.1	-
84		 84	26	48	-	-
84a	1-Phenoxycarbonyl-1,5-diazacyclooctane	 84a	26	48	-	-
85	1,5-Diphenyl-3,7-diaza-8-thioadamantan-8,9-dione or 1,5-Diphenyl-3,7-diazacyclo-[3·3·1]nonan-9-one-3,7-sulfoxide	 85 Z = SO 86 Z = SO_2	-	51	-	-

Compound #	Name	Structure	Figure	Page	Appendix	Table
86	1,5-Diphenyl-3,7-diazabicyclo[3·3·1]nonan-9-one-3,7-sulfone					
87	Adamantene	 87	-	51	-	-
88	1,5-Ditosyl-1,5-diazaheptane	 88	29	56	A.2	-
89	1,5-Ditosyl-1,5-diazacyclooctane	 89	29	56	A.3	-
90	1,5-Diazacyclooctane-1,5-dihydrobromide	 90	29	56	-	-
91	1,4-Cyclohexane-dione	 91	30	57	-	-

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