THE SYNTHESIS OF

2-AZABICYCLO [2.2.1] HEPTANES

DISSERTATION

Presented in Partial Fulfillment of the
Requirements for the Degree Doctor of
Philosophy in the Graduate School of
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By

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Approved by

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To Becky
and my Parents

ACKNOWLEDGEMENTS

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The author would also like to express his appreciation to his parents who encouraged his advanced education and to his wife, Becky, who gave him happiness and understanding and made his stay here very enjoyable.

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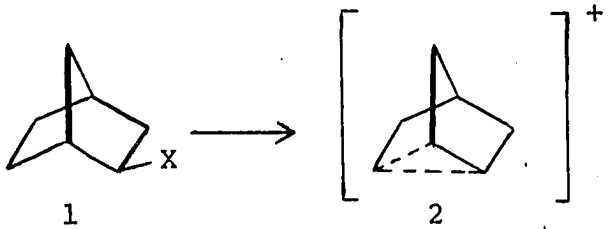
INTRODUCTION

Studies on the solvolysis of bicyclo [2.2.1] heptane derivatives (1) have led to some of the most interesting bicyclic chemistry elucidated in recent years. Winstein[1] noticed the unusual properties that characterized this bicyclic ring system when a positive charge was generated on the skeleton and suggested a non-classical ion intermediate, 2, to account for its facile rearrangements. The rigid nature of its structure and its particular stereochemistry lend themselves to this non-classical behavior and have made it a testing ground for many principles or organic chemistry.



1 2

Although the carbocyclic bicyclo [2.2.1] heptane system

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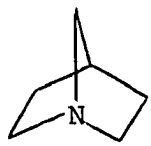
[1] S. Winstein and D. S. Trifan, J. Am. Chem. Soc., 71, 2953 (1949).

has been widely studied,[2] a similar systematic investigation of azabicyclo [2.2.1] heptanes has not been made. The synthesis and study of these azabicyclics could elucidate new principles and demonstrate new interactions unattainable in other systems.

Derivatives of all of the three basic azabicyclo [2.2.1] heptanes, 3-5, are known, but the least studied of these three types is the 2-azabicyclo [2.2.1] heptane system, 5.



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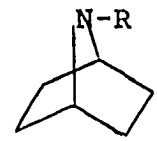

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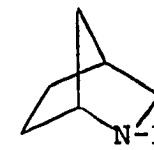

R= CH_3, CH_2CH_3

5

The first 2-azabicyclo [2.2.1] heptanes to be synthesized, 4,7,7,-trimethyl-2-azabicyclo [2.2.1] heptane-3-one (7) and its isomer, 8, were made by W. A. Noyes in 1894[3] during his investigations of camphor (6) and its derivatives.

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[2]a) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall; J. Am. Chem. Soc., 74, 1127 (1952).

b) S. Winstein and D. Trifan, J. Am. Chem. Soc., 74, 1147 (1952).

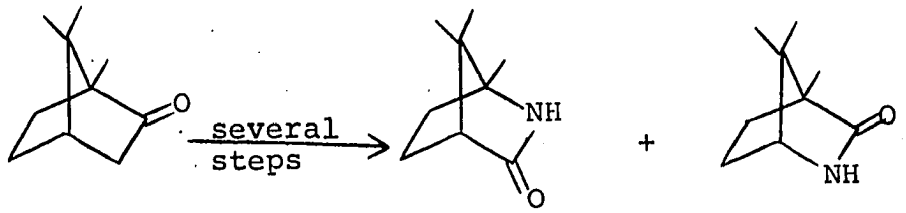
c) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr.; J. Am. Chem. Soc., 76, 4501 (1954).

d) S. Winstein and M. Shatavsky, J. Am. Chem. Soc., 77, 4183 (1955).

e) S. Winstein and E. T. Stafford, J. Am. Chem. Soc., 79, 505 (1957).

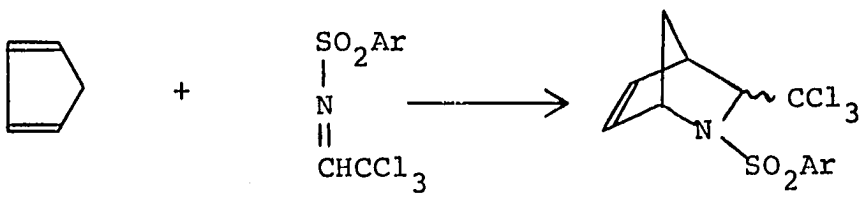
[3]W. A. Noyes, Am. Chem. Journal, 16, 500 (1894).

Very little other work was reported on these systems[4] until



6 7 8

1962 when Kresze and Albrecht[5] reported the Diels-Alder reaction[6] of 9 with 10 to give the azabicyclic 11.



9 10 11

Reports of the 1-aza and 7-azabicyclo [2.2.1] heptanes (3 and 4) are more numerous in the literature and provide possible patterns for alternate synthetic routes of the 2-aza derivative. The most reliable synthesis of cyclic amines has been via the cyclization of halomines which, in turn, can be made from the easily accessable amino alcohols. Thus

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[4]a) W. A. Noyes and L. F. Nickell, J. Am. Chem. Soc., 36, 118 (1914).

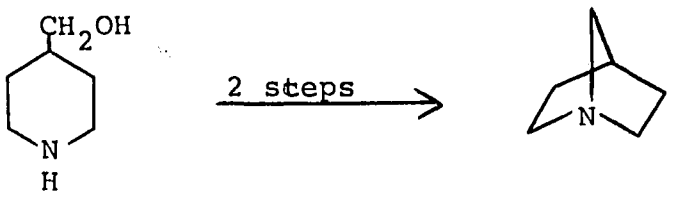
b) W. A. Noyes and J. A. Coss, J. Am. Chem. Soc., 42, 1280 (1920).

[5]a) G. Kresze and R. Albrecht, Angew. Chem., 74, 781 (1962).

b) G. Kresze and R. Albrecht, Ber., 97(2), 491 (1964).

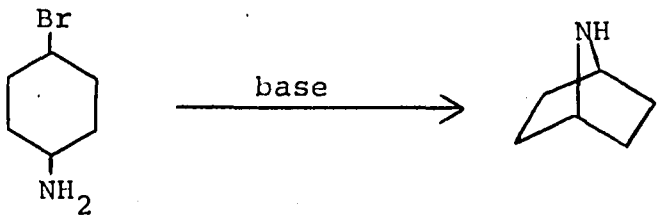
[6]O. Diels and K. Alder, Ann., 460, 98 (1928).

3 was prepared by Shickedantz[7] in 66% yield from 4-hydroxymethylpiperidine (12).



12 3

Likewise v. Braun and Schwartz[8] prepared 4 from 4-bromocyclohexylamine (13).



13 4

The Hofmann-Löffler reaction[9] also provides a means to synthesize cyclic teriary amines and has been used in the preparation of both 3[10] and 4[11] as well as other bicyclic

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[7] P. D. Schickendantz, Ph. D. Thesis, The Ohio State University (1959).

[8] J. V. Braun and K. Schwartz, Ann., 481, 56 (1930).

[9] M. E. Wolff, Chem. Rev., 63, 55 (1963).

[10] R. Lukes and M. Ferles, Coll. Czech. Chem. Comm., 20, 1227 (1955).

[11] E. J. Corey and W. R. Hertler, J. Am. Chem. Soc., 82, 1657 (1960).

amines.[12] This reaction involves heating or photolysis of an N-haloamine in sulfuric acid followed by cyclization of the generated δ or ε haloamine with aqueous base. In this manner Lukes and Ferles[10] prepared the 7-methyl derivative of 3 from N-chloro-4-ethylpiperidine (14). Similarly the 7-methyl derivative of 4 was obtained from the irradiation of N-chloro-N-methylcyclohexylamine (15).[11]

14

15

Of the three possible systems, the 2-azabicyclo [2.2.1] heptanes would be the most interesting for solvolytic studies. From the literature quoted above, four approaches to this system appear to be possible; (1) the preparation and reduction of a lactam, (2) a Diels-Alder reaction, (3) cyclization of haloamines prepared from amino alcohols, and

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[12] a) G. H. Coleman and J. J. Carnes, Proc. Iowa Acad. Sci., 49, 288 (1942).

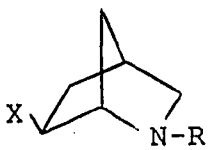
b) S. Wawzonek and P. J. Thelan, J. Am. Chem. Soc., 72, 2118 (1950).

c) S. Wawzonek, M. F. Nelson, Jr. and P. J. Thelan; J. Am. Chem. Soc., 73, 2806 (1951).

(4) the Hofmann-Löffler reaction. A more detailed survey of the literature on these four approaches to cyclic amines and their application and theoretical implications regarding the 2-aza system will be covered in the next section.

Systems like 5 which have built into them means to generate a charge on the ring analogous to the work in the carbocyclic series would be of particular interest. The most convenient way to accomplish this would be to place a good leaving group X on either the nitrogen or a carbon in the ring (16, 17, and 18).

16



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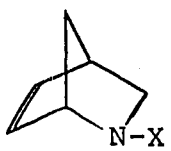

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A solvolysis of a compound of the type R_2N-X (16 and 18), where the leaving group would take both electrons to leave a positive nitrogen, would be very unusual and informative. There is evidence in the literature, however, that would support reasons to attempt this. In 1944 three Russian chemists[13] attempted to prepare the benzenesulfonate of N,N-diethylhydroxylamine (19). They found the product to be very unstable (it exploded in preparation or upon isolation if it was not kept cold) and reactive to water, alcohol, and air. The isolation of acetaldehyde and ethylamine

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[13] A. Ya. Berlin, M. N. Shchukina, and E. D. Sazonova; Zhur. Obshchei Khimii, 14, 249 (1944).

from its reaction with water and the isolation of the diethylacetal of acetaldehyde from its reaction with ethanol could be explained by the initial cleavage of the nitrogen-oxygen bond leaving the nitrogen positive (see Chart I). Loss of hydrogen then would give a Schiff base, 20, which would hydrolyze to the observed products.

Acetates[14] and benzoates[15] of N,N,-disubstituted hydroxylamines have also been prepared. Although they are relatively stable compounds, the benzoates may be able to undergo a similar solvolysis.

The rates and products of the solvolysis of exo and endo derivatives of 17 should determine whether the p-electrons on the nitrogen or the δ-electrons forming the bridgehead-to-nitrogen bond will participate in the departure of the leaving group. Similarly, solvolysis of 18 would indicate what effect the double bond had on the positive nitrogen.

Thus it appears that the investigation of the chemistry of these systems would be extremely interesting and profitable. This dissertation is a report of the synthesis of the basic systems desired for subsequent solvolytic studies.

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[14] a) G. Zinner, Angew, Chem., 69, 204 (1957).

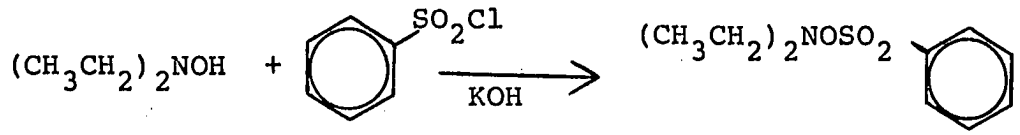
b) G. Zinner, Chem. Ber., 91, 302 (1958).

c) O. Exner and B. Kakac, Coll. Czech. Chem. Comm., 25, 2530 (1960).

d) F. Klages, R. Heinle, H. Sitz, and E. Specht; Ber., 96, 2387 (1963).

[15] D. B. Denny and D. G. Denny, J. Am. Chem. Soc., 82, 1389 (1960).

CHART I[13]



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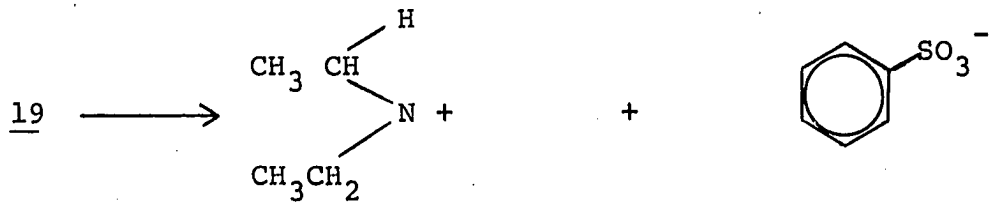

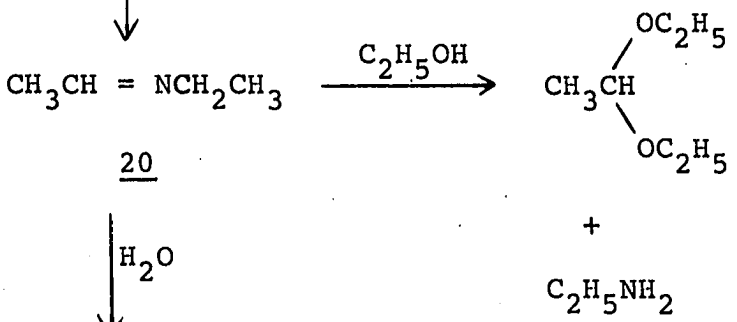

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HISTORICAL REVIEW

The first report of a synthesis of a 2-azabicyclo [2.2.1] heptane (8) appeared in a paper by W. A. Noyes in 1894[3]. In an investigation of the chemistry of camphor (6), he oxidized 6 with nitric acid to yield camphoric acid. The action of acetic anhydride on the acid gave camphoric acid anhydride (22). From this was prepared the two possible isomeric amino acids, 23 and 24 (see Chart II).

A Hofmann reaction[16] carried out on the amides gave the corresponding amino acids, 25 and 26 respectively. In an attempt to prepare the free amine 26, Noyes heated the hydrochloride with calcium oxide; the main result was decomposition, however a low yield of a lactam (7) was recovered. Attempts to repeat the reaction using barium oxide, soda-lime, and sodium methoxide were unsuccessful. The isomeric amino acid, 25, also formed a lactam (8) upon heating with calcium oxide.

The unmethylated anhydride corresponding to 22 is known[17] and would provide a suitable starting point for an analogous synthesis of the unmethylated series. The Hofmann

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[16] E. S. Wallis and J. F. Lane, Organic Reactions, Vol. III (New York: John Wiley and Sons, Inc., 1946), 267.

[17] P. G. Guha and S. K. Ranganathan, Ber., 69B, 1199 (1936).

reaction, however, is frequently unreliable, although later papers reported good yields in the camphor series.[18] The cyclization of the amino acid by Noyes did not proceed in good yield even in later papers and difficulty could be expected at this point. This method of preparation of the lactam of the unmethylated series and from thence the amine, should work, but low yields would be expected. The conversion of the unmethylated diacid to the diamine has been carried out in good yields under conditions of the Schmidt reaction,[19] so the possibility exists of stopping the reaction after the conversion of only one carboxyl group and obtaining the necessary intermediate cis-3-aminocyclopentanecarboxylic acid, known as a degradation product of the natural product amidinomycin.[20]

Two possible ways exist to prepare an azabicyclic by the Diels-Alder reaction; first, the reaction of a nitrogen containing diene with an olefin, and second, the reaction of a carbon-nitrogen double bond with a diene. Diels-Alder syntheses with tautomeric forms of pyrrole do not appear promising, although pyrrole itself will undergo the reaction with strong dienophiles to give 7-azabicyclo [2.2.1] heptanes.[21]

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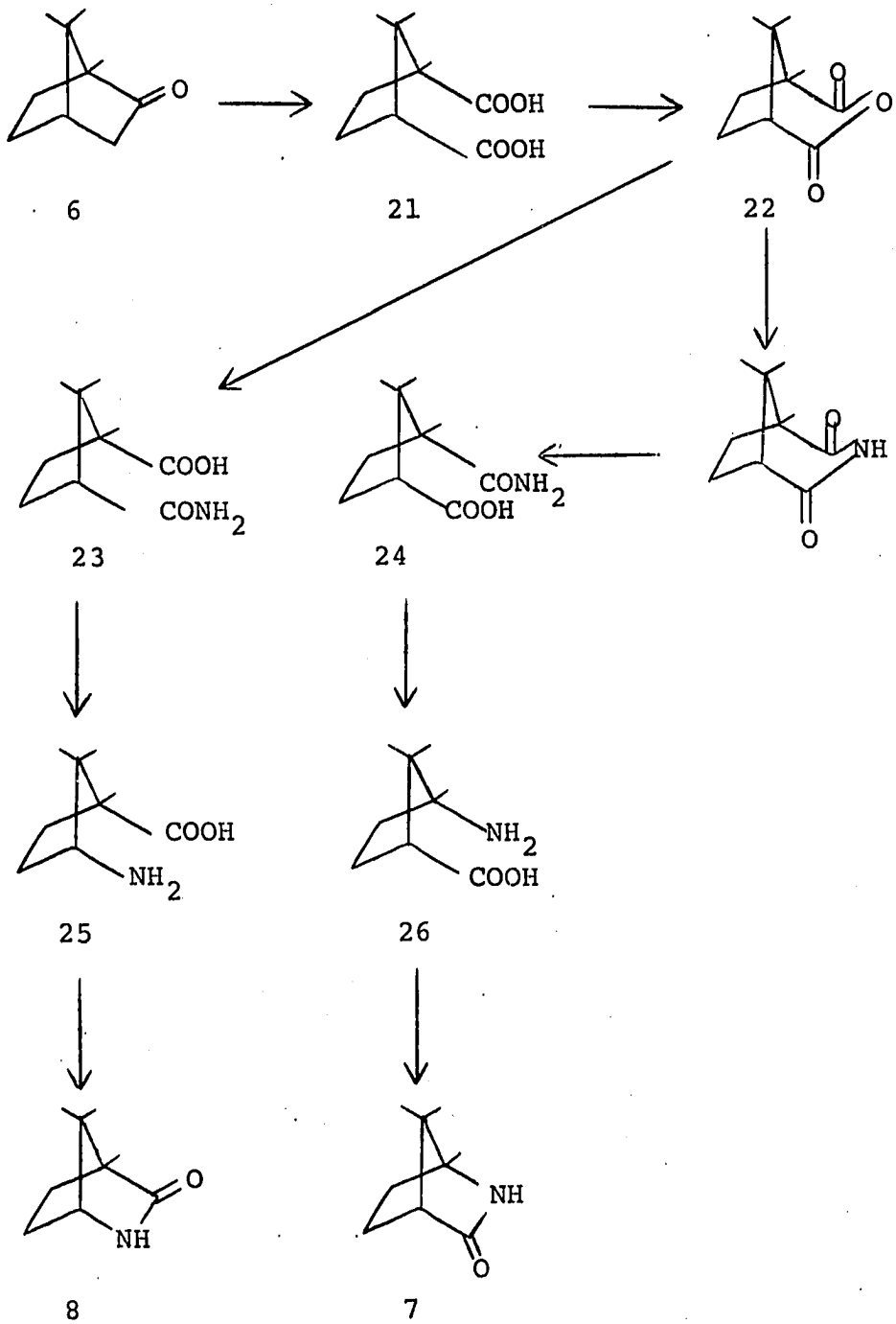
[18] For a clarification of the nomenclature of these compounds used by Noyes, see reference 4.

[19] H. Wolff, Organic Reactions, Vol. III (New York: John Wiley and Sons, Inc., 1946), 307.

[20] S. Nakamura, Chem. Pharm. Bull. (Japan), 9, 641 (1961).

[21] a) L. Mandell and W. A. Blanchard, J. Am. Chem. Soc., 79, 2343 (1957).
b) G. Wittig and W. Behnisch, Ber., 91, 2358 (1958).

CHART II[3]



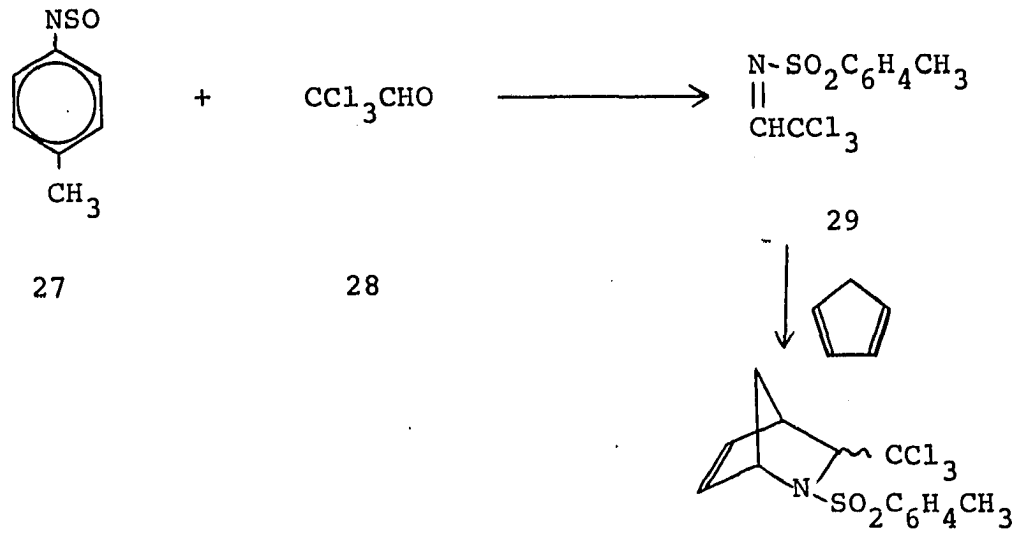
6 21 22

23 24

25 26

8 7

An adduct of cyclopentadiene and a nitrogen containing dienophile has been shown recently to provide a route to 2-p-toluenesulfonyl-3-trichloromethyl-2-azabicyclo [2.2.1] heptane-5 (30).[6] The dienophile was prepared from N-sulfinyl-p-toluenesulfonamide (27)[22] and chloral (28).



27 28 30

The intermediates in this series were difficult to purify by means other than distillation at pressures attainable only by a good mercury diffusion system (0.001mm.). Furthermore, the necessity of having strongly activating groups on the dienophile resulted in a product with unwanted substituents. Thus the utility of this synthesis for the desired investigation was not great.

Other dienophiles that contain nitrogen are available, but no report has been made of their use with cyclopentadiene. In the presence of phosphorous oxychloride, low

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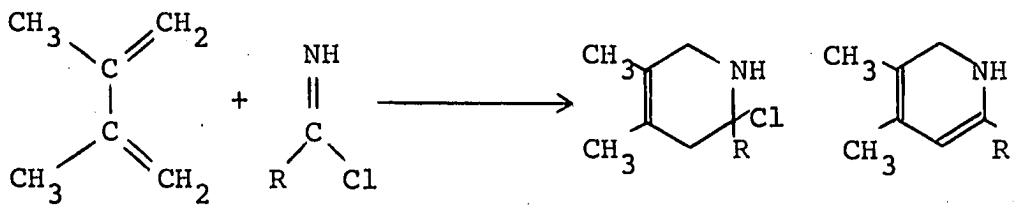
[22] G. Kresse and A. Maschke, German Patent 1,117,566 Nov 23, 1961.

molecular weight amides and oximes are converted to α-chloroimines which can act as dienophiles in the presence of an appropriate diene. In this way the 2-chloro-4,5-dimethyltetrahydro pyridine (31) has been prepared from 2,3 -dimethylbutadienes.[23] Nitriles have sometimes been used as dienophiles,[24] but the reaction is run in the gas



31

phase at 300-500° and consequently was not considered.

Merton and Müller[25] have investigated a reaction that appears to be a two-step polar addition to a diene by the ion 33. This is generated[26] by the action of boron trifluoride etherate on methylene bisurethane (32). This ion in some manner attacks the diene, and the following closure gives the cyclic product 34.

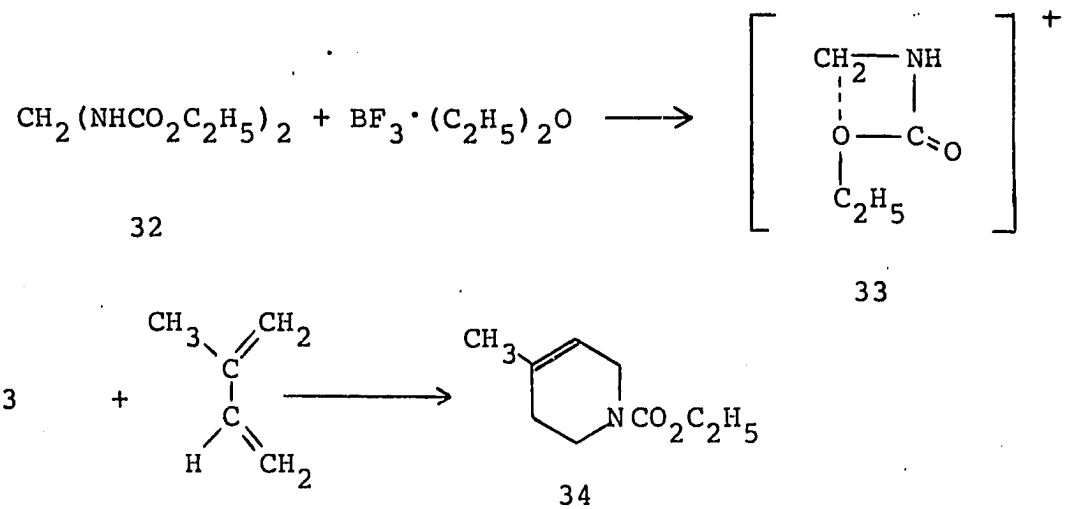
---

[23]M. Lora-Tamayo, G. G. Munoz, and R. Madronero; Bull. Soc. Chim. France, 1331 (1958).

[24]S. B. Needleman and M. C. Chang-Kuo, Chem. Rev., 62, 405 (1962).

[25]R. Merten and G. Muler, Angew. Chem., 74, 866 (1962).

[26]Houben-Weyl, Methoden Der Organishen Chemie, 4 Aufl. 7/1, (Thieme, Stuttgart Bd., 1954), 481.



Simple hydrolysis of the ester would be followed by rapid decarboxylation leaving the free amine. Cava and Wilkens[27] have succeeded in preparing isoquinuclidine derivatives in 40% yield by this procedure. This attractive method of synthesis offered a route to an unsubstituted unsaturated amine which would be most useful in preparing various derivatives.

A widely known method of preparing cyclic tertiary amines had been the Hofmann-Löffler reaction.[9] It was first discovered in 1883 by Hofmann[28] but did not become widely used until Löffler and co-workers exploited the reaction in 1909.[29] This unusual reaction involves heating or irradiation of an N-haloamine under strongly acidic conditions, usually sulfuric acid. Subsequent basification

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[27]M. P. Cava and C. K. Wilkens, Jr., Chem. and Ind., (London) 32, 1422 (1964).

[28]A. W. Hofmann, Ber., 16, 558 (1883).

[29]K. Löffler and C. Freytag, Ber., 42, 3427 (1909).

yields the cyclized product in yields reflecting the stereochemical strain in the transition state.

Wawzonek[30] and later Corey[31] investigated the mechanism of the process and proposed the mechanism which appears on Chart III. Wawzonek[32] was able to isolate the intermediate δ-haloamine, 36, from the photolysis of N-chloro-di-N-butylamine by addition of nitrous acid to form the N-nitroso derivative, 37, thus preventing cyclization.

The initial step of the reaction is the homolytic cleavage of the nitrogen-chlorine bond by light, heat, or peroxides. The unusual intermediate aminium radical, 35, intramolecularly abstracts a hydrogen from a γ- or δ-carbon, and subsequent radical recombination completes the process. The generated aminoalkyl halide is stable only in acidic media, and upon basification cyclization occurs, giving the tertiary amine.

The reaction has been used to synthesize both 1-aza[10] and 7-aza-bicyclo [2.2.1] heptanes[11] in yields ranging from 5 to 11%. The reaction will proceed in high yield if the stereochemistry of the system is favorable for the intramolecular hydrogen transfer.[33] Corey and Hertler stated that

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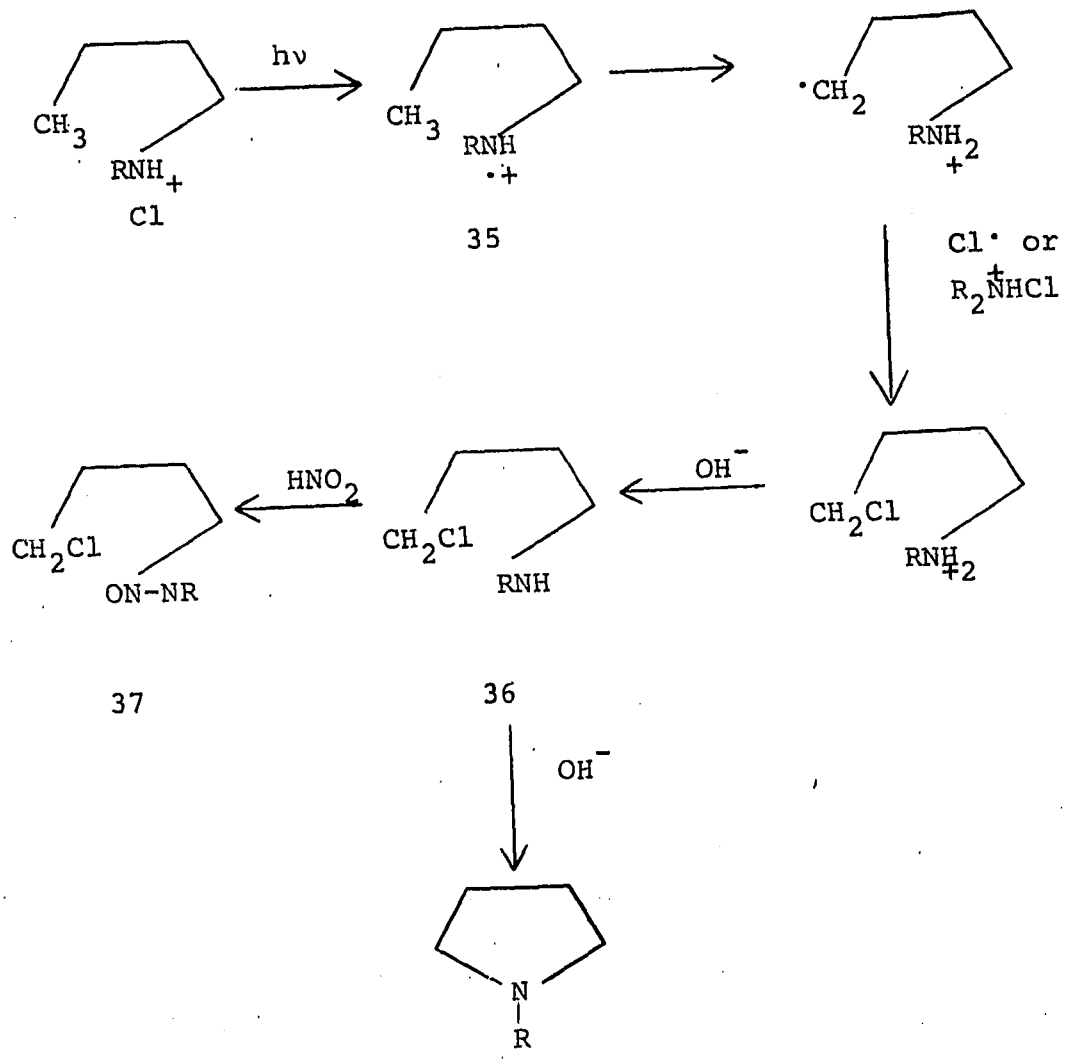
[30] S. Wawzonek and P. J. Thelan, J. Am. Chem. Soc., 72, 2118 (1950).

[31] E. J. Corey and W. R. Hertler, J. Am. Chem. Soc., 82, 1657 (1960).

[32] S. Wawzonek and T. P. Culbertson, J. Am. Chem. Soc., 81, 3367 (1959).

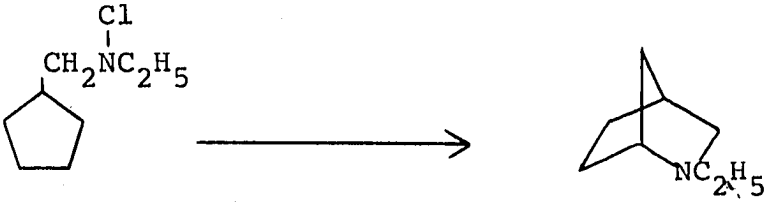
[33] W. R. Hertler and E. J. Corey, J. Org. Chem., 24, 572 (1959).

CHART III[32]


hν
CH3
RNH+
Cl
CH3
RNH
·+
35
·CH2
RNH2
+
Cl· or
R2NHCl
CH2Cl
RNH2
+
OH−
CH2Cl
RNH
HNO2
CH2Cl
ON-NR
37
36
OH−
N
R

the apparent propensity for hydrogen attack by the aminium radical is dependent upon two factors; first, the tendency of the hydrogen transfer to be linear, and second, the minimization of angle strain and steric repulsions in the transition state.[31] A third factor that is of importance, and which is related to the angle strain, is the distance within which the aminium radical can approach the available hydrogens in rigid systems. These factors clearly favor a six-membered transition state (a 1,5-hydrogen shift), giving rise to formation of pyrrolidine rings. In a few cases a 1,6-hydrogen shift is possible or even more favorable.[30,31] In an unsuccessful attempt to cyclize N-bromo-N-methyl-2-butylamine,[34] Löffler concluded that four-membered rings cannot be formed from N-haloamines.

The synthesis of a 2-azabicyclo [2.2.1] heptane (39) by this method would necessarily start from N-chloro-N-alkylcyclopentylmethylamine (38). It is apparent that two



38 39

positions could possibly be attacked by the generated aminium radical. It has already been stated that a 1,5-hydrogen transfer is favored; however, somewhat of a special case is

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[34] K. Löffler, Ber., 43, 2025 (1910).

presented by this molecule. Thermodynamic calculations[35] have been made which show that the cyclopentane ring has one carbon atom out of the plane of the other four. The out-of-plane displacement was calculated to be 0.3Å; however, the thermodynamic data fit the value 0.236Å better.[35] Using the larger value, this would correspond to an angle of about 17.5° for the most stable configuration of the ring. Measurements taken from Dreiding models indicate that in this configuration the aminium radical generated from 38 could approach within 2.8Å of the δ-hydrogens and within 1.7Å of the γ-hydrogens. This, however, is the value for the most stable configuration, and thermal vibrations would cause movement to both sides of this, possibly bringing this out of plane displacement to a value of 0.5Å.[36]

The angle of hydrogen transfer could not be linear in either case, being about 145° for the 1,5-shift and 120° for the 1,4-shift, but the relative importance of these competing factors was uncertain.

The convenience of this approach and its relevance to the reaction mechanism made the investigation of this reaction desirable.

The fourth general method of synthesis to be considered was the use of aminoalkyl halides. The majority of the

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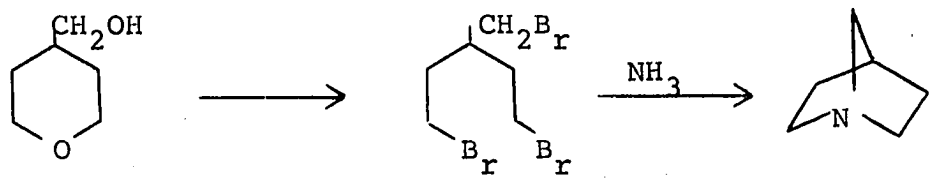
[35] J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer; J. Am. Chem. Soc., 69, 2483 (1947).

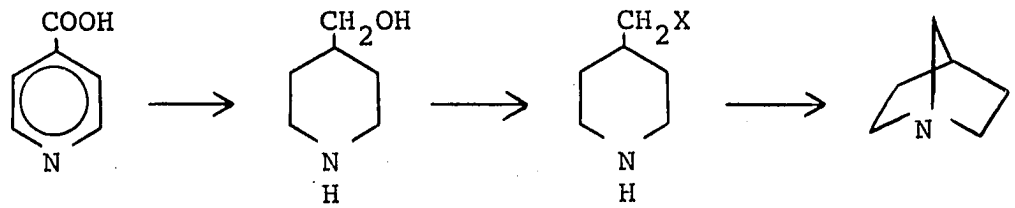
[36] M. S. Newman, Stearic Effects in Organic Chemistry, (New York: John Wiley and Sons, 1959), 36.

known azabicyclics have been prepared in this manner due to the reliability of the synthesis in preparing both small and large rings. Generally one of the rings is already intact, although both rings can be formed in the same step. Thus Prelog and Cerkovinikov[37] prepared the bicyclic 3 in one step from the tribromide derived from 4-methanolpyran (40).



40 3

Usually 3 and its derivatives have been prepared from pyridine-4-carboxylic acid (41).[37,38,39] Reduction of the aromatic ring and formation of the alkyl halide, 42, are followed by treatment with base to yield the desired product; the last step usually proceeding in good yield.



41 12 42 3

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[37]V. Prelog and E. Cerkovinikov, Ann., 525, 292 (1936).

[38]G. R. Clemo and V. Prelog., J. Chem. Soc., 400 (1938).

[39]R. Lukes, M. Ferles, and O. Strouf; Coll. Czech. Chem. Comm. 24, 212 (1959).

Similarly, derivatives of the same compound have been made from appropriately substituted pyrrolidines.[40] Derivatives of 4 are easily accessable from 4-bromocyclohexylamine in a similar fashion.[41]

The known compound 4-cyanocyclopentene[42] should provide an effective starting point for an aminoalkyl halide type synthesis of 5. Depending upon the type of reagent added to the double bond, this should also prove to be a synthetic route to the 6-substituted series, 17.

Four general methods have been outlined, and each has been shown to have its merits. Synthesis by any one of these methods should provide a relatively accessible route to 2-azabicyclo [2.2.1] heptane, and success of two routes would supply a proof of structure. To this end the research was undertaken.

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[40]Von Horst Pracejus and M. Grass, J. Prakt. Chem., 8, 232 (1959).

[41]J. V. Braun and K. Schwarz, Ann., 481, 56 (1930).

[42]N. S. Crossley, A. C. Darby, H. B. Henbest, J. J. McCullough, B. Nicholls, and M. F. Stewart; Tet. Letters, 12, 398 (1961).

DISCUSSION

A convenient way to approach the synthesis of 2-azabicyclo [2.2.1] heptane would be to parallel a known preparation of this bicyclic system. For this reason we chose to investigate the synthesis of the unmethylated lactam, 52, by an approach which was analogous to the work of Noyes.[3]

The cis-1,3-cyclopentanedicarboxylic acid (44) prepared by the ozonolysis of norbornene (43) according to the procedure of Perry,[43] was refluxed with acetyl chloride to yield the anhydride as a white crystalline product in 70-75% yield. Pure anhydride, m.p. 143-4°, was refluxed in a methanol-benzene solution for 1 - 1.5 hours and then distilled to yield the half ester, 46, a clear mobile liquid in 96% yield. Traces of acetyl chloride or hydrochloric acid in the anhydride caused the formation of up to 50% of the dimethyl ester. The action of thionyl chloride converted the half acid-half ester into the corresponding acid chloride, 47. Anhydrous ammonia was bubbled into a solution of the acid chloride in a cold ether-benzene mixture to give the half amide-half-methyl ester, 48, a white crystalline solid, in 93.5% yield.

The conversion of amides to amines by the Hofmann

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[43] R. H. Perry, J. Org. Chem., 24, 829 (1959).

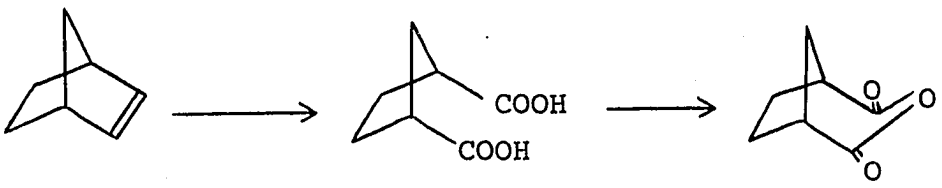
reaction similar to that carried out in aqueous solution on the trimethyl derivative, 24, was attempted on the amide, 48; however, no amino acid could be isolated. Repetition of the experiment using sodium methoxide as the base and methanol as the solvent in an attempt to form the amino acid as the urethane derivative, 49, resulted only in the recovery of a small amount of starting material.

Cis-1,3-cyclopentanedicarboximide (50) was prepared from the anhydride by the addition of ammonia followed by heating the product with acetyl chloride. The resulting colorless needles were subjected to Hofmann reaction conditions. No amino acid was isolated, but by refluxing the remaining salts in methanol with a catalytic amount of hydrochloric acid, a small amount of basic material was isolated by distillation. The product appeared by infrared analysis to be the methyl ester of the desired amino acid.

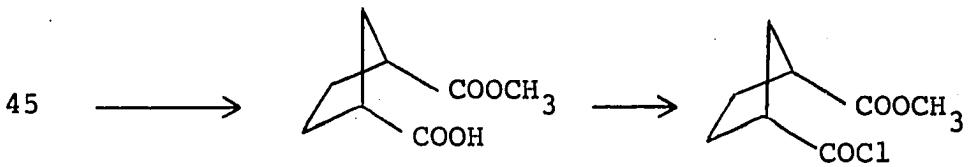
In most cases where the Hofmann reaction has failed or proceeds only in poor yield, the Schmidt reaction can be used. This reaction was tried on both the diacid, 44, and the anhydride, 45.

The Schmidt reaction run at 50° on the anhydride gave 12.3% of a white crystalline salt which appeared to be cis-3-aminocyclopentanecarboxylic acid by spectral data. The heating of this salt under 20 mm. pressure resulted in complete decomposition; similar heating of an intimate

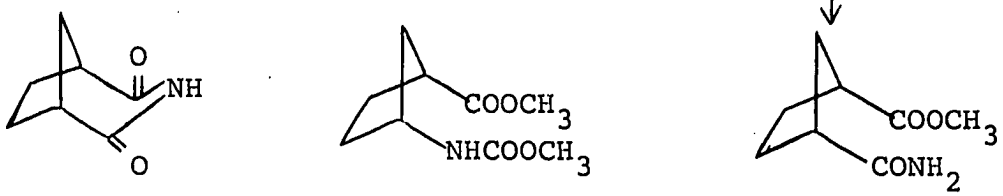
CHART IV



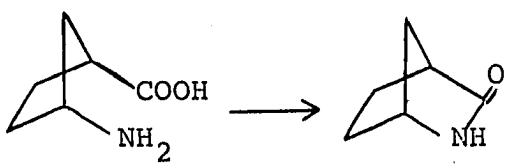
43 44 45



46 47



50 49 48



51 52

mixture of the salt with calcium oxide or barium oxide also resulted only in decomposition.

The failure of these reactions to give the amino acid in a reasonable yield may have been due either to the difficulty in isolating the product or to the inability of the molecules to rearrange under the reaction conditions. The isolation of the ester of the amino acid in only poor yields indicates that difficulty in isolation of the amino acid due to its physical properties was probably not the reason for failure. The second explanation may be plausible, since some compounds are completely inert to the Hofmann and Schmidt reactions and frequently others give only poor yields.

At this time it was apparent that the desired lactam, 52, could not be prepared in reasonable yields by this method; consequently this route was dropped from further consideration.

The Hofmann-Löffler Synthesis

The attempted synthesis of a 2-azabicyclo [2.2.1] heptane by the Hofmann-Löffler reaction entails more theoretical implications, as described in the preceeding section, than the other proposed routes and would prove to be interesting even if it failed to give the desired bicyclic amine.

The starting point for such a synthesis was cyclopentanecarboxylic acid (53) which can be prepared by the unusual oxidative ring contraction of cyclohexanone discovered

by Payne and Smith.[44] This pungent acid is converted to its corresponding acid chloride, 54, by the action of thionyl chloride. Addition of methyl or ethyl amine converted the acid chloride to the corresponding low melting amides. In the preparation of the N-ethyl derivative, ethyl amine was slowly added to a cold solution of the acid chloride in ether to yield N-ethylcyclopentanecarboxamide, 55. Reduction of the amide with lithium aluminum hydride gave a 90% yield of the corresponding amine as a clear mobile liquid. Stirring the amine for 15 hours with excess N-chlorosuccinimide in ether gave the N-chloroamine, 57, a yellow oil which decomposes on warming.

Irradiation of 57 in 80 - 85% sulfuric acid was carried out in Vycor or quartz vessels for 25 hours with a bank of ten 15 watt Sylvania "Blacklite" fluorescent lamps. The temperature was kept below 40° during the irradiation to avoid the decomposition which occurred at higher temperatures. The irradiated solution was poured onto ice, carefully made basic, and steam distilled. The amine recovered from the distillate was treated with benzenesulfonyl chloride in aqueous potassium hydroxide according to Hinsberg's method in order to separate the tertiary amine from primary and secondary amine contaminants. The isolated tertiary amine was distilled to give a colorless oil in 28 - 29% yield which was homogeneous to vapor phase chromatography. A picrate was prepared which melted at 220-1°.

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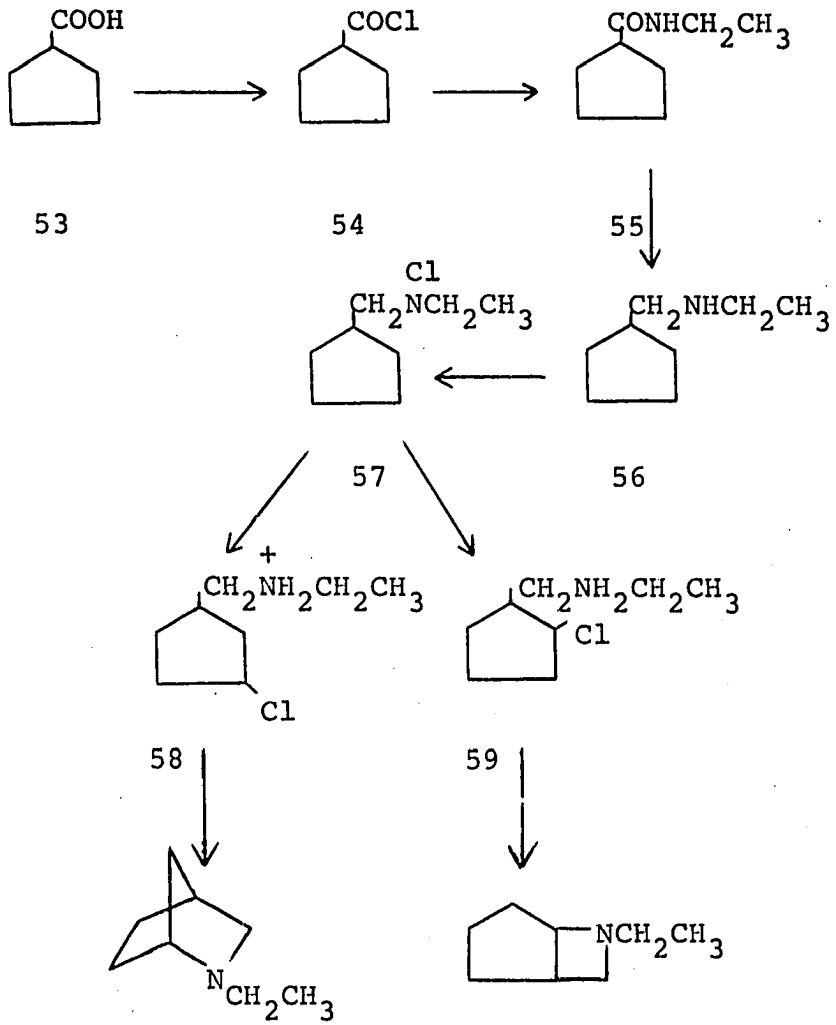
[44] G. B. Payne and C. W. Smith, J. Org. Chem., 22, 1680 (1957).

CHART V


COOH
COCl
CONHCH2CH3
53
54
55
Cl
CH2NCH2CH3
CH2NHCH2CH3
57
56
+
CH2NH2CH2CH3
Cl
CH2NH2CH2CH3
Cl
58
59
N
CH2CH3
NCH2CH3
39
60

From the foregoing experimental data it is apparent that the reaction gave only one of the two possible products, either the N-ethyl-2-azabicyclo [2.2.1] heptane (39), or the N-ethyl-6-azabicyclo [3.2.0] heptane, (60).[45] The complexity of the nuclear magnetic resonance spectrum of the compound suggested that the product was probably the former, the bicyclo [2.2.1] system. To prove this an alternate synthesis of the system was devised.

The Alternate (Haloamine) Synthesis

4-Bromocyclopentene (63) has been prepared by Bartlett and Rice[46] by the lithium aluminum hydride reduction of the product arising from the addition of one mole of bromine to cyclopentadiene. However a precaution should be noted in this preparation, since it was our experience that the hydride reduction would occasionally violently explode. A note on this hazard has been published recently.[47] The apparent cause of this explosion is the build up of the dibromide in the ice-cooled hydride reduction which will then react when the ice bath has been removed causing the reaction to become violently exothermic. This can be corrected simply by not using an ice bath and controlling the rate of

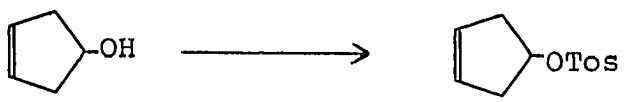
[45] This skeleton was previously prepared by C. A. Grob, Bull. Soc. Chim. France, 1360 (1960).

[46] P. D. Bartlett and M. R. Rice, J. Org. Chem., 28, 3351 (1963).

[47] C. R. Johnson and J. E. Keiser, Tet. Letters, 45, 3327 (1964).

addition of the dibromide according to the reflux rate. In order to avoid this preparation, 4-bromocyclopentene can be synthesized from Δ^3-cyclopentenol[48] by the pyridine-phosphorous tribromide method.[49]

The bromide was reacted with sodium cyanide in dimethyl sulfoxide according to the method of Friedman and Shechter[50] to give 4-cyanocyclopentene, 64. A route to 64 using the tosylate of Δ^3-cyclopentenol (62) was also attempted. The Δ^3-cyclopentenol (61) was synthesized according to the method of Allred, Sonnenberg, and Winstein[48] in 30% yield, and its tosylate, 62, was prepared according to the normal pyridine-p-toluenesulfonyl chloride method.[51] All attempts to replace the tosylate with sodium or cuprous cyanide in methanol, ethanol, dimethylformamide, or dimethyl sulfoxide at temperatures ranging from 0 - 100° failed.



61 62

A lithium aluminum hydride reduction of the cyano compound gave the unsaturated amine, 65. Addition of hydrogen

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[48] E. L. Allred, J. Sonnenberg, and S. Winstein; J. Org. Chem., 28, 3351 (1963).

[49] L. H. Smith, Organic Synthesis, Vol. 23 (New York: Wiley and Sons, Inc., 1943), 88.

[50] L. Freidman and H. Shechter, J. Org. Chem., 25, 877 (1960).

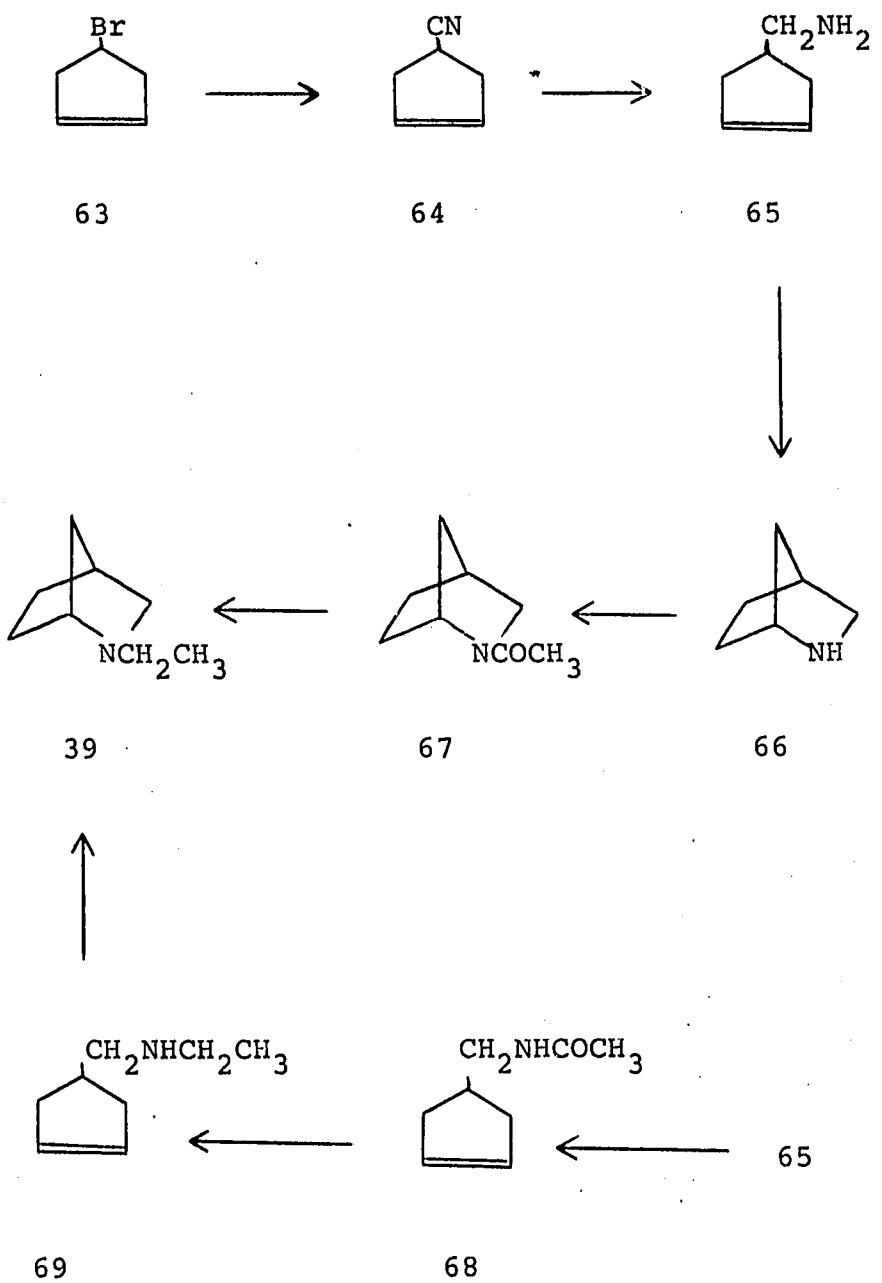
[51] R. S. Tipson and M. A. Clapp, J. Org. Chem., 18, 952 (1953).

bromide to the double bond in 65 resulted in a bromoamine which was not isolated but immediately cyclized to give the bicyclic amine, 66. Acetylation of the 2-azabicyclo [2.2.1] heptane with acetyl chloride in pyridine yielded the amide, 67. Subsequent reduction of the amide with lithium aluminum hydride gave an authentic sample of N-ethyl-2-azabicyclo [2.2.1] heptane, whose picrate melted at 220-1°. Comparison of the infrared spectrum of this product with the one arising from the Hofmann-Löffler reaction and the comparison of the melting points and mixed melting points of the two products proved them to be identical.

Difficulties in the purification of the intermediate unsubstituted 2-azabicyclo [2.2.1] heptane prompted the investigation of a second but similar approach to the desired bicyclic system. The 4-aminomethylcyclopentene was acetylated to the corresponding N-acetyl compound, (68), which was reduced by lithium aluminum hydride in ether. A chloroform solution of the resulting N-ethyl-4-aminomethylcyclopentene (69) was treated with anhydrous hydrogen bromide, adding this reagent across the double bond. Treatment with base yielded the bicyclic amine, N-ethyl-2-azabicyclo [2.2.1] heptane, whose infrared spectrum and picrate were identical to that of the amine prepared by the Hofmann-Löffler reaction.

It remained to be shown that the other possible isomer that could arise from the photolysis had not been present

CHART VI

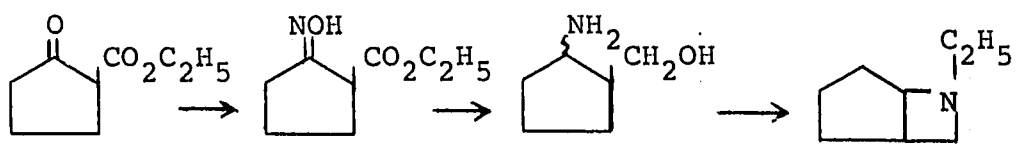

Br
CN
CH2NH2
63
64
65
NCH2CH3
NCOCH3
NH
39
67
66
CH2NHCH2CH3
CH2NHCOCH3
65
69
68

in the crude reaction mixture only to be lost or destroyed in the benzenesulfonyl chloride method of separation. Hence N-ethyl-6-azabicyclo [3.2.0] heptane (60) was also synthesized and subjected to the Hinsberg conditions.

The 6-Azabicyclo [3.2.0] Heptane Synthesis

The commercially available 2-carbethoxycyclopentanone (70) was converted to the oxime, 71, according to the method of Alder and Stein[52] and reduced with lithium aluminum hydride to yield the amino alcohol, 72, as a clear high boiling oil.

Ethyl iodide was added to 72 resulting in a yellow oil which was dissolved in aqueous sodium hydroxide and steam distilled. Purification of the distillate gave the tertiary amine, 60, identified as the picrate, m.p. 163-4°. The comparison of the infrared spectrum of this product with the one obtained from the Hofmann-Löffler reaction and the melting points and mixed melting point of the picrates of the two products showed them to be different.



70 71 72 60

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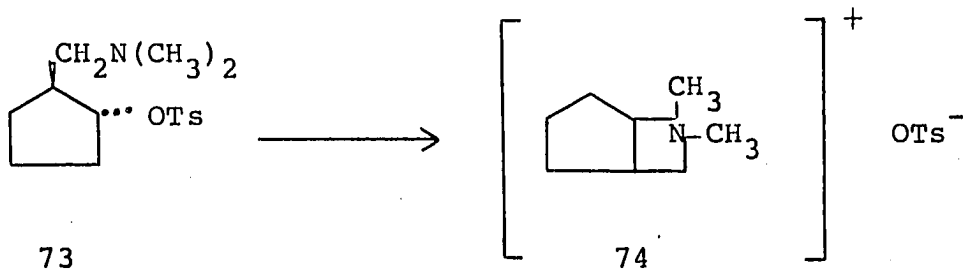
[52] K. Alder and G. Stein, Ann., 525, 218 (1936).

This evidence offered conclusive proof that 60 was not the product formed in the overall Hofmann-Löffler reaction. However, the possibility still existed that the intermediate 59 was formed and failed to cyclize to 60 or that 60 itself failed to survive the benzenesulfonyl chloride separation technique.

It is well known[53] that substituted γ-haloamines cyclize readily to give four membered rings, azetidines. That general systems similar to 59 possess no special properties in cyclizations was shown by Grob,[45] who demonstrated that 73 readily cyclized to an azetidine derivative, 74.



73 74

When an authentic sample of 60 was subjected to the Hinsberg reaction conditions, it was recovered unchanged. Thus the γ-haloamine could not have been formed in the Hofmann-Löffler reaction.

Since the transition state for the hydrogen transfer required the abstraction of a δ-hydrogen in order to form the product, it would be necessary for the carbon atom bearing the aminomethyl function to have an amplitude of out-of-plane bending greater than 0.5Å.[36] This is

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[53] E. H. Rodd, Chemistry of Carbon Compounds, Vol. 4 part A (New York: Elsevier Publishing Company, 1957), 22.

considerably beyond the normal maximum vibration from the most stable configuration. Balanced against this factor, however, is the fact that the transition state for the 1-5-hydrogen shift can attain a more closely linear configuration (145°) during the hydrogen transfer, than can the transition state for a 1,4-hydrogen shift (120°). This last factor appears to control the direction of the reaction in spite of the large internal strain necessary to attain the required transition state. In view of the yields obtained in the formation of other bicyclo [2.2.1] heptane systems by the Hofmann-Löffler reaction,[10,11] it is surprising that a yield as high as 28% could be attained through such a transition state with high internal strain and a poor angle of hydrogen transfer. This special preference for a 1,5-hydrogen shift[54] has been noticed in reactions other than the Hofmann-Löffler reaction. This 1,5-hydrogen shift has been considered either preferred or necessary in the photochemical rearrangements of alkylnitrites,[55] alkyl hypo-

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[54]This preference for a 1,5-shift and the absence of any 1,4-shift eliminates the possibility that the reaction could be intermolecular since an intermolecular shift would show no such preference for hydrogen shifts.

[55]D. H. R. Barton and J. M. Beaton, J. Am. Chem. Soc., 82, 2640 (1960).

halites,[56] certain ketones,[57] N-halomides,[58] and in the pyrolysis of alkylazides.[59]

Preparation of N-hydroxy-2-Azabicyclo [2.2.1] Heptane

It has already been stated that there would be much interest in the solvolysis of derivatives of 2-azabicyclo [2.2.1] heptanes. Of particular interest are those derivatives which could impart a positive charge to the nitrogen by the loss of a negatively charged entity from that site. N-Hydroxy-2-azabicyclo [2.2.1] heptane should be an excellent starting point for the formation of such derivatives. A Cope elimination[60] on the N-oxide of the Hofmann-Löffler product (75) should, in turn, provide a route to the desired substituted hydroxylamine.

Treatment of N-ethyl-2-azabicyclo [2.2.1] heptane (39) with hydrogen peroxide yielded the N-oxide, 75. When this product was heated under reduced pressure, elimination occurred leaving a hydroxylamine. Two possible hydroxylamines

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[56] F. D. Greene, M. L. Savita, H. H. Lau, F. D. Osterholtz, and W. N. Smith; J. Am. Chem. Soc., 83, 2196 (1961). and C. Walling and A. Padwa, J. Am. Chem. Soc., 85, 1597 (1963).

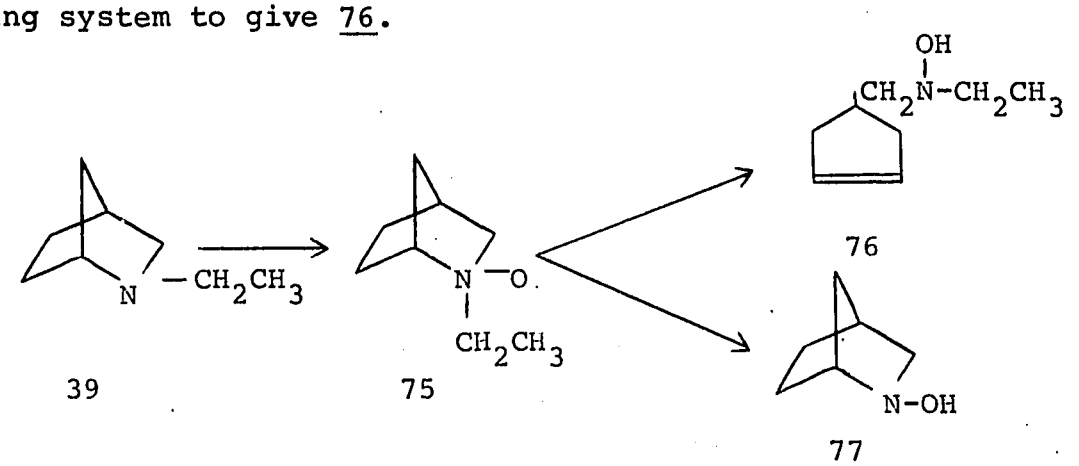
[57] K. Schaffner, D. Arigoni, and O. Jeger; Experientia, 16, 169 (1960).

[58] D. H. R. Barton and A. J. L. Beckwith, Proc. Chem. Soc., 335 (1963).

[59] G. Smolinsky and B. I. Feuer, J. Am. Chem. Soc., 86, 3085 (1964).

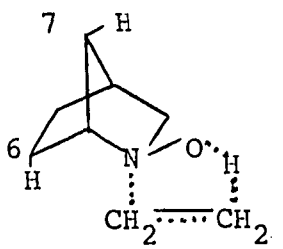
[60] A. C. Cope and E. R Trumbull in Organic Reactions, Vol. II, (NewYork: John Wiley and Sons, Inc., 1960), Chapter 5, 361.

could be visualized as the product of the reaction, one involving elimination across the ethyl group to give 77, and the other involving elimination across the bicyclic ring system to give 76.



39 75 76 77

In a Cope elinimation it is required that the five atoms involved in the transition state can become planar[61] (see structure 78).



78

Although elimination involving the 6 or 7-hydrogen would relieve strain in the system by opening the bicyclic structure, neither hydrogen could participate in a planar transition state as easily as the β-hydrogens on the ethyl group. The bicyclic hydroxylamine was thus the expected product.

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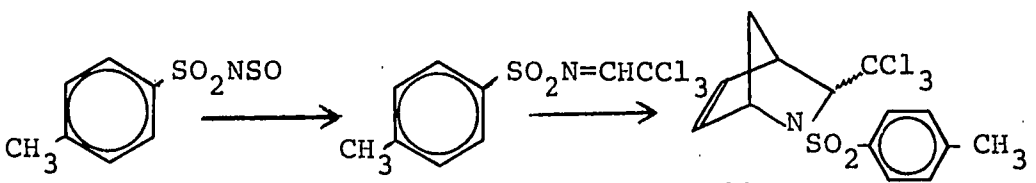
[61] A. C. Cope and N. A. Label, J. Am. Chem. Soc., 82, 4656 (1960) and J. Am. Chem. Soc., 82, 4663 (1960).

The product of the reaction was an amorphous white solid, the oxalate salt of which had an analysis corresponding to $C_8H_{13}NO_5$, indicating that ethylene had been lost. Furthermore, the nuclear magnetic resonance spectrum of the hydroxylamine showed no vinyl hydrogens substantiating the structure of the product as 77.

Diels-Alder Approaches

The use of the Diels-Alder reaction for the preparation of a 2-azabicyclo [2.2.1] heptane would be very advantageous. Investigations of this possibility were undertaken by first repeating a known synthesis of this bicyclic system.

The dienophile (29) was prepared by Kresze and Albrecht[5] by the condensation of N-sulfinyl-p-toluenesulfonamide[62] (79) and chloral.



79 29 30

The reaction of cyclopentadiene and the dienophile (29) gave the bicyclic (30). Literature yields could not be attained probably because the intermediates (79) and (29) were not distilled as they had been by Kresze and Albrecht and were difficult to purify by other means. This

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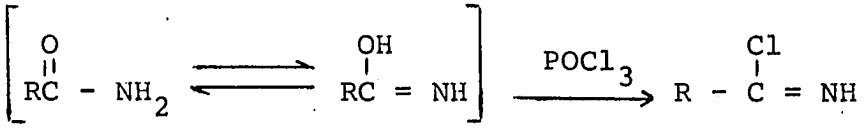
[62] R. Albrecht, G. Kresze, and B. M. Lakar; Ber., 97, 483 (1964).

difficulty was partly due to the extremely hygroscopic nature of the N-sulfinylamide (79).

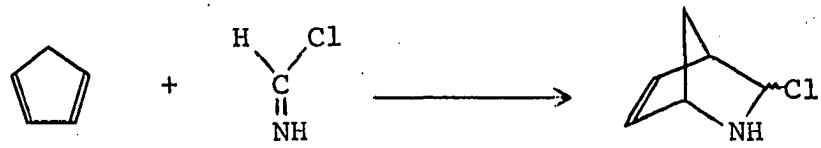
An attempt was made to remove the undesirable trichloromethyl and p-toluenesulfonyl groups from (30) by a lithium aluminum hydride reduction; however, only p-toluenesulfonamide could be isolated from the reduced material. The presence of the substituents on the azabicyclic (30) made this compound of little use for our purposes, and other approaches were investigated.

Tamayo, Munoz, and Madronero[23] have successfully used chloroamines as dienophiles with substituted butadienes. The α-chloroamine, (81) was generated in situ by the reaction of phosphorous oxychloride with an amide. This will react with a diene giving a cyclic chloroamine, e.g. 31.



80 81

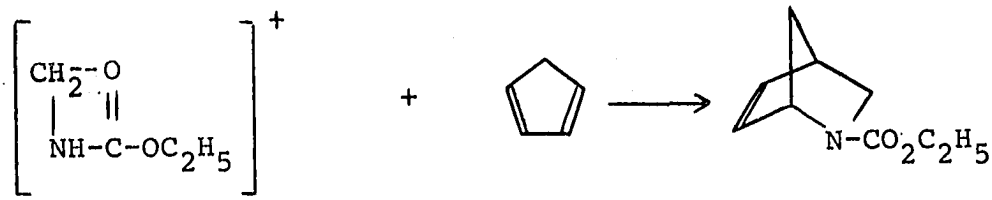
The generation of this intermediate dienophile in the presence of cyclopentadiene in an attempt to prepare (83) was complicated by decomposition and polymerization reactions. Controlling this very exothermic reaction proved to be difficult; however, a 2.1% yield of an oily basic product could be isolated. Vapor phase chromatography of a fraction (b.p. 112-112.5°) of the product showed thirteen constituents, no one of which constituted more than 15% of



9 82 83

the total yield. Since α-chloroamines are unstable and difficult to handle particularly in the presence of a double bond, this yield and the character of the product are not surprising. The nature and complexity of the product demonstrated that this reaction was not useful for preparative purposes.

A reaction has been investigated by Merten and Müller[25] which involves a 1,4-addition to a diene. This reaction led to a stable cyclic urethane as the major product. The procedure involved the addition of the carbonium ion (33) to one double bond of the diene followed by rearrangement of a 1,4-adduct. An addition of this type to cyclopentadiene should have yielded the bicyclic urethane derivative (84). Isolation of (84) followed by the basic hydrolysis



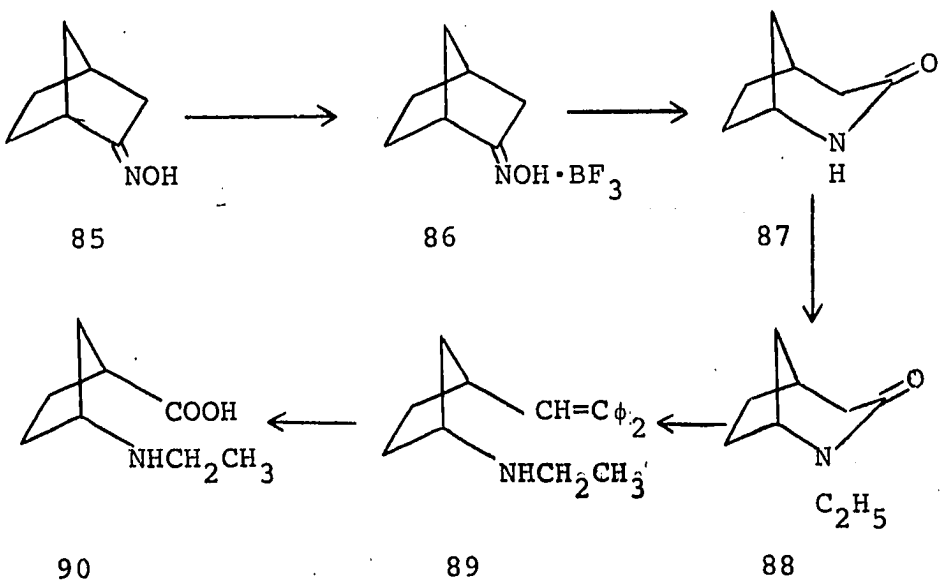
33 9 84

of the ester function would lead to an unsubstituted, unsaturated amine.

Preparation of the intermediate (33) was carried out by the action of boron trifluoride etherate on methylene bisurethane in refluxing benzene. The addition of cyclopentadiene gave a product which was hydrolyzed to a basic, water soluble oil in 20% yield. Vaphor phase chromatography of a narrow boiling fraction showed seven major peaks. Again, the low yield and complexity of the product made this reaction of little preparative value.

Alternate Lactam Approach

The easy access to 2-azabicyclo [3.2.1] octan-3-one (87) recently reported by R. T. Conley[63] renewed interest in the preparation of 2-azabicyclo [2.2.1] heptane-3-one via the cis-3-aminocyclopentanecarboxylic acid. Conley



[63] R. T. Conley, F. J. Caridi, and P. J. Balling; "Abstracts of Papers Presented at the American Chemical Society Meeting," New York, N.Y., Sept. 9-13, 1963, p. 20.

reported that the lactam, (87), could be synthesized by a rearrangement of norcamphor oxime (85) in up to 90% yield. The procedure involved making a solid boron trifluoride complex, (86), and heating it in tetrachloroethylene at 130°.

The lactam, (87), formed in this manner was ethylated with sodium hydride and ethyl iodide. Treatment of the N-ethyl derivative, 88, with phenylmagnesium bromide gave the unsaturated amine, (89). Ozonolysis of the hydrochloride of (89) in methanol followed by an oxidative work-up should provide the amino acid (90), while ozonolysis of the free amine would lead to oxidation of the amine function.[64]

The alkylation of the lactam and the addition of phenyl magnesium bromide proceeded in very poor yield, hence further attempts to prepare the bicyclic lactam (52) by this method were abandoned.

Alkylation of Bicyclic Amines

In the preparation of methyl and ethyl iodide salts of N-methyl and N-ethyl-2-azabicyclo [2.2.1] heptanes, several interesting features were noticed.

The many unsuccessful attempts that have been made to isolate isomers of tertiary amines constitute a long and

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[64] L. Horner, H. Schaefer, and W. Ludwig; Ber., 91, 75 (1958).

interesting chapter in organic chemistry.[65] The barrier to inversion about the nitrogen is, however, generally too small to allow separation of isomers, although upon quaternization the four groups are fixed. The barrier to inversion in trimethyl amine is 15 kcal. per mole,[66] a value low enough to prevent isolation of conformers of such compounds even at -80°. In cyclic and bicyclic amines, however, this barrier to inversion should be slightly larger.

Recently, dipole measurements of 4-p-chlorophenylpiperidine and substituted quinolizidines have indicated that the spacial requirements for the non-hydrogen bonded electron pair on nitrogen are less than for hydrogen,[67,68] a conclusion contrary to the work Aroney and LeFevre.[69] Investigations by Katritzky and co-workers and later Allinger and co-workers indicated that the 4-substituted piperidine was 90% in a conformation with the free electron pair in an axial position and the hydrogen in the less hindered equatorial position. Similarly, the N-methyl and N-ethyl-2-azabicyclo [2.2.1] heptanes 94 and 39 would prob-

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[65] R. L. Shriner, R. Adams, and C. S. Marvel; Organic Chemistry, An Advanced Treatise, Vol. I, Gilman, (New York: John Wiley and Sons, Inc., 1938), Chapter 3, 402.

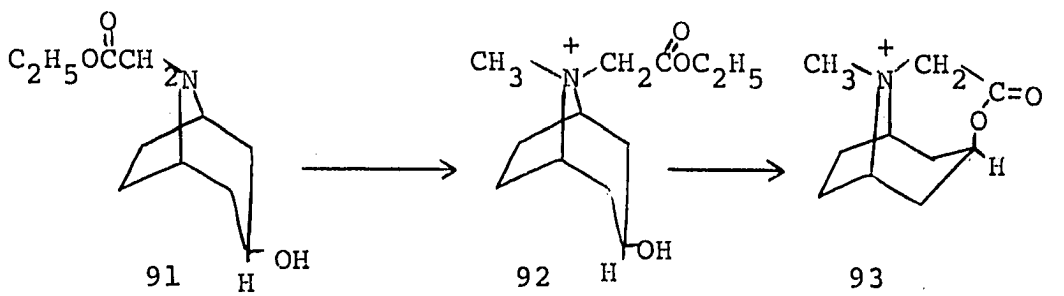
[66] J. F. Kinkaid and F. C. Henriques, Jr., J. Am. Chem. Soc., 62, 1474 (1960).

[67] a) R. J. Bishop, L. E. Sutton Dineen, R. Y. A. Jones, and A. R. Katritzky; Proc. Chem. Soc., 257 (1964).
b) K. Brown, A. R. Katritzky and A. J. Waring; Proc. Chem. Soc., 257 (1964).

[68] N. L. Allinger, J. G. D. Carpenter, and F. N. Karkowski; Tet. Letters, 45, 3345 (1964).

[69] M. Aroney and R. J. W. LeFevre, Proc. Chem. Soc., 82, (1958); and Proc. Chem. Soc., 3002 (1958).

ably exist almost entirely in conformations with the N-alkyl group in the less hindered exo position. Since the alkylation of a tertiary amine proceeds by the S_n2 displacement of the iodide by the electron pair on nitrogen, the conformation of the bicyclic amines would lead to an alkylation from the endo side. However, in studies[70] of the alkylation of a 3β-hydroxytropine derivative (91), the product was not that one indicated by the most stable configuration of 91 where the ethoxycarbonmethyl group is equatorial to the piperidine ring. The addition of methyl iodide proceeded to give the product (92) derived from attack of the alkylating agent from the least hindered side



91 92 93

of the molecule. Confirmation of this structure was obtained by demonstrating the ease of formation of the lactone (93) when the ester function was hydrolyzed.

The stereochemistry of the alkylation can be easily explained since the rates of chemical reactions are generally much less than the rates of thermal equilibrium of the conformational isomers. Hence, if the geometric requirements for the transition state are better satisfied

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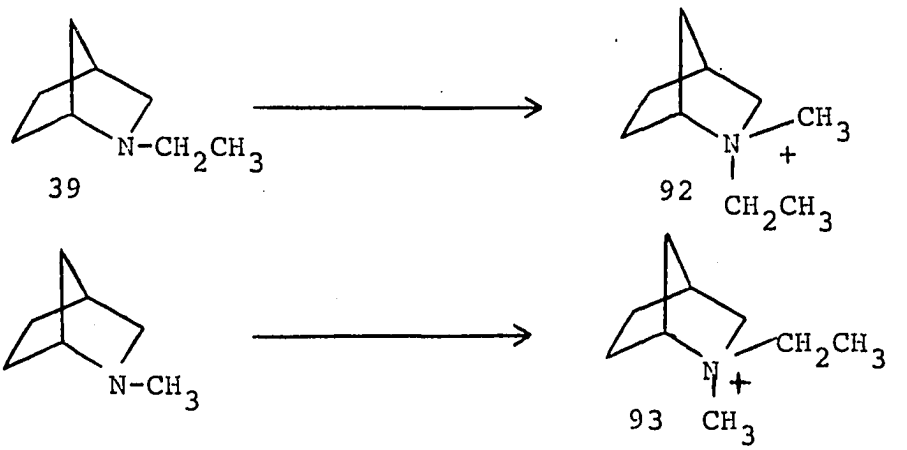
[70] G. Fodor, K. Koczka, and J. Lestyan; Magy. Kem. Foly, 59, 242 (1953); cf. G. Fudor, Tetrahendron, 1, 86 (1957).

by a less stable configuration, the reaction path may proceed through that configuration.[71]

Thus in the 2-azabicyclo [2.2.1] heptane system, the addition of methyl iodide to the N-ethylamine yielded a single quaternary salt (m.p. 308-8.5°) which was different from that derived from the addition of ethyl iodide to the N-methylamine (94) (m.p. 305-5.5°). The infrared spectra of these two salts were completely different, while the nuclear magnetic resonance spectra showed only slight differences in resolution and chemical shifts. Comparison of the infrared spectra of the crude and thrice recrystallized salts indicated that the attack of the alkyl iodides proceeded stereospecifically to yield isomerically pure



products. By analogy to the results obtained in the quaternization of the tropane alkoloids[70,72] and the great pre-

[71]L. A. Paquette, "Mass. Institute of Tech. Seminar in Organic Chemistry," Jan. 7, 1959.

[72]G. Fodor, J. Toth, and I. Vincze; J. Chem. Soc., 3504 (1955).

ference shown for exo attack to the two position of a bicyclo [2.2.1] heptane ring system,[2] the salts were assigned the structures (95) and (96).

Long Range N^{14}-H^{1} Coupling

The coupling of N^{14}-H^{1} in nuclear magnetic resonance spectra has been established in a variety of compounds. Nitrogen^{14} has a nuclear spin of one and can couple with adjacent hydrogen nuclei to give 1:1:1 triplets. In ammonia, amines, and amides, the splitting of the multiplets is generally broadened or not resolvable. This is due to hydrogen exchange processes and the fact that the nitrogen nucleus has a quadrupole moment which promotes a strong spin-lattice relaxation mechanism. The nuclei then become decoupled, resulting in collapse of the spin multiplets.[73] However, Roberts[74] and Ogg[75] have been able to demonstrate coupling of nitrogen^{14} with hydrogens attached directly to the nitrogen.

The long-range N^{14}-H^{1} coupling for β-hydrogens in quaternary ammonium salts has been noted by several work-

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[73] J. A. Pople, W. G. Schneider, and H. J. Bernstein; High Resolution Nuclear Magnetic Resonance, (New York: McGraw-Hill Book Co., Inc., 1959). 102, 227.

[74] J. D. Roberts, J. Am. Chem. Soc., 78, 4495 (1956).

[75] R. A. Ogg and J. D. Ray, J. Chem. Phys., 26, 1515 (1957).

ers.[75-81] The resolution of the multiplets resulting from the spin-spin interaction of the N^{14} nucleus on the β-hydrogen nuclei has been explained by the highly symmetrical field gradient about the quaternized nitrogen. The high symmetry of the tetrahedral charge distribution decreases the propensity for longitudinal relaxation with the surrounding molecule, and an increased relaxation time results. In tetrasubstituted ammonium salts the relaxation time is sufficiently increased that decoupling no longer occurs and the resulting multiplets can be resolved.[73]

No systematic effort has been made to investigate the effect of hybridization and substituents on the quadrupolar relaxation time and hence upon the magnitude of the N^{14}-H^1 coupling. Having a variety of quaternary ammonium salts available, we decided to investigate their nuclear magnetic resonance spectra.

From the data in Table 1 it is apparent that an increase in the number of ethyl groups on the nitrogen causes

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[76] H. G. Hertz and W. Spalthoff, Zeitschrift Fur Elektrochemie, 63, 1105 (1959).

[77] J. M. Anderson, J. D. Baldeschwieler, D. C. Dittmer, and W. D. Phillips; J. Chem. Phys., 38, 1260 (1963).

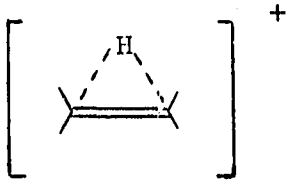
[78] E. Bullock, D. G. Tuck, and E. J. Woodhouse; J. Chem. Phys., 38, 2318 (1963).

[79] E. A. LaLancette and R. E. Benson, J. Am. Chem. Soc., 85, 2853 (1963).

[80] M. Franck-Neumann and J. M. Lehn, Mol. Phys., 7, 197 (1963).

[81] Private communication with Dr. Gideon Frankel, The Ohio State University.

a decrease in the magnitude of the splitting of the β-hydrogens. The same effect can be noticed in thallium trialkyls.[82] In the aliphatic series the substitution of from one to three ethyl groups for methyls on trimethylethyl ammonium iodide resulted in a decrease of $J_{N-\beta H}$ values of approximately 0.12 c.p.s. for each ethyl substitution. A similar decrease was noted in the cyclic series (Table 2) although the effect was not as pronounced. Substitution of the α-hydrogens with methyls in trimethylethylammonium iodide led to a decrease of 0.3 cycles for the first methyl added and 0.1 cycles for the second methyl. These decreases would lead one to generalize that electron donating groups tend to decrease the J values. However, the triethylallyl ammonium ion exhibited a large decrease in the J value, just opposite to the effect expected by the above generalization if only inductive effects are to be considered. A possible delocalization of the π-electrons into the positive nitrogen which could be considered to be similar to π-complexes of olefins (97) perhaps is the cause of this



97

unexpected result. Anilinium and pyridinium salts showed no resolvable 1:1:1 triplets, although the normal A_3X_2 triplet was broadened. The large difference in the

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[82] J. P. Maher and D. F. Evans, Proc. Chem. Soc., 208 (1961).

TABLE 1

NMR Spectra of Acyclic Quaternary Ammonium Iodides

Compound[a]	J_{NH} (cps)[b]	Std. dev.	Multiplicity
$C\underline{H}_3CH_2N^+(CH_3)_3$	2.15	0.01	tripled triplet
$(C\underline{H}_3CH_2)_2N^+(CH_3)_2$	2.01	0.02	tripled triplet
$(C\underline{H}_3CH_2)_3N^+CH_3$	1.85	0.01	tripled triplet
$(C\underline{H}_3CH_2)_4N^+$	1.80	0.03	tripled triplet
$(CH_3)_3N^+CH_2C\underline{H}_3$	2.15	0.01	tripled triplet
$(CH_3)_3N^+CHC\underline{H}_3$ CH_2CH_3	1.87	0.01	tripled doublet
$(CH_3)_3N^+CH(C\underline{H}_3)_2$	1.83	0.04	tripled doublet
$(CH_3)_3N^+C(C\underline{H}_3)_3$	1.74	0.04	tripled singlet
$(C\underline{H}_3CH_2)_3N^+CH_2CH=CH_2$	1.50	0.03	tripled triplet
$(C\underline{H}_3CH_2)_3N^+CH_2CH_2CH_2CH_3$	1.80	0.02	tripled triplet
$(C\underline{H}_3CH_2)_3N^+CH_2CH_2CH_3$	1.78	0.07	tripled triplet
$(C\underline{H}_3CH_2)_3N^+CH_2C\underline{H}_3$	1.80	0.03	tripled triplet

[a] The hydrogens coupled with the nitrogen are underlined.

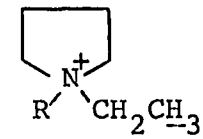
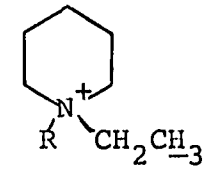
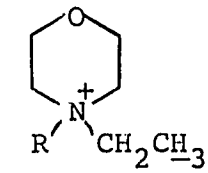
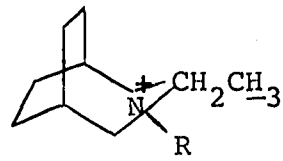
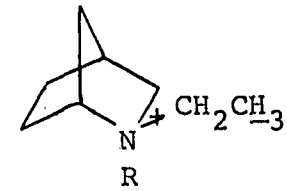
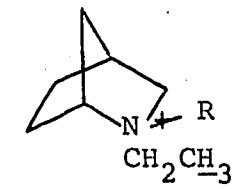
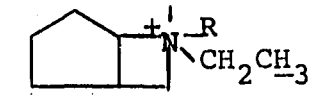
[b] Values quoted are averages of from five to nine measurements made on different days. All samples were measured in D_2O, using a Varian A-60 Nuclear Magnetic Resonance Spectrometer.

electrical properties of these substituents probably disrupted the electrical field gradient enough to allow decoupling of the nuclei. Spectra of ammonium salts in which a hydrogen or an oxygen was attached to the nitrogen consisted of sharp lines exhibiting no 1:1:1 triplets indicating that the nuclei were completely decoupled.

In the series of heterocyclic quaternary ammonium salts (Table 2), five, six, and seven membered rings showed splitting of the same general magnitude. The 1:1:1 triplets were not as well resolved in this series as in the aliphatic quaternary ammonium salts apparently due to the greater asymmetry about the nitrogen caused by the ring strain. In the methyl iodide salt of N-ethyl-6-azabicyclo [3.2.0] heptane, the nitrogen is a part of a four-membered ring. The 90^{o} angles inherent in a four-membered ring require some rehybridization of the electronic orbitals about the nitrogen. This should have the effect of reducing the symmetry of the change distribution about the nitrogen nucleus, and hence decreasing the quadrupolar relaxation time. In fact, this must have been the case as the nuclei were decoupled and no N^{14}-H^{1} splitting was observed. Several factors appear to affect the ability of N^{14} to couple with other nuclei. Dissymmetry of the electronic field gradient about the quaternized nitrogen caused either by the unequal electrical requirements of the substituents or by unfavorable spacial geometry of the groups substituted on the nitrogen can cause decoupling. An increase of electron-

TABLE 2

NMR Spectra of Cyclic Quaternary Ammonium Iodides

Compound			
	CH_3	1.90	0.04
	C_2H_5	1.88	0.04
	CH_3	1.75	0.06
	C_2H_5	1.67	0.06
	CH_3	1.75	0.03
	C_2H_5	1.69	0.06
	CH_3	1.79	0.04
	H	no spin-spin coupling[a]	
	CH_3	1.82	0.03
	C_2H_5	1.62	0.03
	CH_3	1.80	0.07
	C_2H_5	1.62	0.03
	CH_3	no spin-spin coupling	

[a]Attempts to prepare the N,N-diethyl derivative yielded the trialkylammonium hydroiodide. As noted for all other hydroiodides no splitting occurs.

donating groups about the nitrogen in the aliphatic series caused a decrease in the $J_{N-\beta H}$ values; however, other factors are involved in heterocyclic and unsaturated systems and appear to be more important in determining the magnitude of the coupling constants.

SUMMARY

Two new synthetic routes to 2-azabicyclo [2.2.1] heptanes have been developed. The first method involved the photolysis of N-chloroaminomethylcyclopentane in sulfuric acid solution (the Hofmann-Löffler reaction). Homolytic cleavage of the nitrogen-chlorine bond was followed by an intramolecular abstraction of a δ-hydrogen by the aminium radical. Chain propagating abstraction of chlorine from another molecule led to a δ-chloroamine which readily cyclized in basic media to give only N-ethyl-2-azabicyclo [2.2.1] heptane.

Dreiding models of the N-chloroamine showed that the generated aminium radical can approach the γ-hydrogen atoms more closely than the δ-hydrogens. If this were the factor that controlled product formation, an N-ethyl-6-azabicyclo [3.2.0] heptane should have resulted. Alternate synthesis via 4-bromocyclopentene and 4-aminomethylcyclopentene gave an authentic sample of N-ethyl-2-azabicyclo [2.2.1] heptane and provided a structure proof for the Hofmann-Löffler product. The possibility still remained that the 6-azabicyclo [3.2.0] heptane system had been generated only to be lost in the purification of the product by the Hinsberg reaction. N-ethyl-6-azabicyclo [3.2.0] heptane was

synthesized by the reduction, alkylation, and cyclization of the oxime of 2-carbethoxycyclopentanone and was subjected to Hinsberg's conditions. The unchanged bicyclic amine was recovered, indicating that it would have been recovered from the Hofmann-Löffler reaction had it been formed.

The failure of the Hofmann-Löffler reaction to form the azabicyclo [3.2.0] heptane system demonstrated that the important feature of the transition state is not how easily the radical can approach the available hydrogens. The controlling factor must be the linearity of hydrogen transfer, 145° for the δ-abstraction and 120° for the γ-abstraction.

Attempts to prepare the 2-azabicyclo [2.2.1] heptane system on a preparative scale by the formation of the lactam derived from cis-3-aminocyclopentanecarboxylic acid were not successful. Similar attempts of preparation of the 2-azabicyclo [2.2.1] heptane system using the Diels-Alder reaction and an addition-rearrangement reaction elucidated by Merten and Müller were also unsuccessful.

The stereochemistry of alkylation of the 2-azabicyclo [2.2.1] heptanes with methyl and ethyl iodide was studied. Stereospecific addition of the alkylating agent would lead to two different 2-ethyl-2-methyl-2-azoniabicyclo [2.2.1] heptane iodides. Addition of methyl iodide to N-ethyl-2-azabicyclo [2.2.1] heptane gave a product different from that obtained from the addition of ethyl iodide to the

N-methyl bicyclic amine. The infrared spectra of these two salts were different, but the nuclear magnetic resonance spectra were nearly identical. The configurations of the salts were assigned in accordance with the studies of alkylations of tropines and with the preference for exo attack shown by the bicyclo [2.2.1] system.

The spin-spin coupling of the N^{14} nucleus with β-hydrogens to produce a 1:1:1 triplet in the nuclear magnetic resonance spectra of quaternary salts has been known for several years. Nitrogen has a nuclear quadrupole which normally will decouple interactions with adjacent nuclei. However, the highly symmetrical field about the nitrogen in quaternary salts increases relaxation time enough to allow analysis of N^{14} coupling. Effects of substituents and geometry about the nitrogen on this coupling were investigated for a series of aliphatic and heterocyclic quaternary salts. It was found that the substitution of ethyls for methyls on trimethylethylammonium iodide led to a decrease of $J_{N-\beta H}$ of about 0.12 c.p.s. per ethyl group. Substitution of the α-hydrogens by methyls also produced a decrease in the magnitude of the splitting. The generalization that electron-donating groups decrease splittings held in general but is probably not the most important feature, since several substituents are known to deviate widely from this pattern.

EXPERIMENTAL

Lactam Approach

Norbornene (43)

The norbornene that was used was obtained from the Enjay Chemical Company and was sublimed before use.

Cis-1,3-cyclopentanedicarboxylic acid (44)

Freshly sublimed norbornene (30 g., 0.32 moles) was ozonized in methanol-petroleum ether (35 - 40°) according to the procedure of Perry.[43] The hydrogen peroxide-formic acid work up afforded 51 g. (100%) of the crude diacid, m.p. 113 - 115°. Recrystallization from a benzene-cyclohexane mixture gave white crystals of 44, m.p. 120 - 1°; (lit. m.p. 120.5 - 121.0°).[43]

Cis-1,3-cyclopentanedicarboxylic acid anhydride (45)

The cis-1,3-cyclopentanedicarboxylic acid (51 g., 0.32 moles) was dissolved in 50 ml. of benzene, and 60 ml. of acetyl chloride was added. After refluxing for 6 hr. the solution was charcoaled and filtered. The filtrate was evaporated to dryness on a rotary evaporator, and the residue was recrystallized from a benzene-cyclohexane mixture

to yield 32.5 g. (73.5%) of the anhydride, m.p. 163-4°; (lit. m.p. 161°).[83]

Methyl cis-cyclopentanecarboxylic acid-3-carboxylate (46)

Recrystallized cis-1,3-cyclopentanedicarboxylic acid anyhdride (4.95 g., 0.035 moles) was dissolved in 20 ml. of benzene and 15 ml. of methanol and refluxed for 1.3 hours. Vacuum distillation of the mixture yielded 5.84 g. (93.3%) of the half acid-half ester, b.p. 137 - 9° (2.8 mm.); [lit. b.p. 156° (4 mm.)].[83]

Methyl cis-cyclopentanecarbonyl chloride-3-carboxylate (47)

To a solution of 35.3 g. (0.225 moles) of the monomethyl ester, 46, in 25 ml. of benzene was added 27 ml. of thionyl chloride. The solution was refluxed for 6 hours, and the thionyl chloride was azeotroped off with benzene. Vacuum distillation gave 37.61 g. (96.5%) of the acid chloride, b.p. 109-114° (1.3 mm.); [lit. b.p. 109 (3 mm.)].[83]

Methyl cis-cyclopentanecarbonamide-3-carboxylate (48)

To a mixture of 200 ml. of benzene and 200 ml. of ether, 19.23 g. (0.101 moles) of the acid chloride (47) was added. Ammonia was bubbled into the solution at 0°

[83] P. G. Guha and S. K. Ranganathan, Ber., 69B, 1199 (1936).

until no further precipitate formed. The mixture was vacuum filtered, and the solids were washed with hot benzene until their weight dropped below 5.5 g. The combined filtrates were concentrated on a steam bath, cooled, and the product was allowed to crystallize yielding 93.5% of a flakey white solid, m.p. 95 - 97°. Recrystallization from ether or benzene gave pure material, m.p. 116 - 7°.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.12; H, 8.18; N, 7.65. Found: C, 55.91; H, 8.04; N, 7.91.

The Hofmann reaction on 48

A. A freshly prepared solution of sodium hypochlorite (0.06M.) and sodium hydroxide (0.06M.) (25 ml., 0.013 moles) was placed in a stirred flask with 0.015 moles of the amide, 48. The mixture was heated at 70° for 0.5 hr. then cooled. Continuous extraction of the solution with ether followed by fractionation of the extract gave two fractions neither of which showed a carbonyl absorbtion in the infrared. The same results were obtained using sodium hypobromite with varying times and temperatures.

B. A 1N. solution of sodium methoxide in methanol was prepared, 100 ml. of which was added to 8.55 g. (0.05 moles) of the amide, 48. With stirring, 8.0 g. (0.05 moles) of bromine was rapidly added, and the resulting solution was heated to 60° for one hour. The methanol was removed on a steam bath, and the remaining material was extracted with ether, benzene, acetonitrile, and cyclohexane. The

solvent was removed from the extracts leaving a yellow oil. Crystallization of the oil and attempted hydrolysis both yielded only starting material.

3-Azabicyclo [3.2.1] octan-2,4-dione (50)

Anhydrous ammonia was padded into a cooled solution of 8.59 g. of the anhydride, 44, in 300 ml. of benzene until no further precipitate formed. Vacuum filtration yielded ammonium cyclopentane-cis-1-carbonamide-3-carboxylate.[84] The white powdery salt was not purified, but was refluxed in 25 ml. of acetic anhydride for two days. Removal of the acetic anhydride followed by recrystallization of the residue from chloroform-petroleum ether (60 - 70°) yielded 6.53 g. (76.3%) of the imide as large white needles or rhombohedrons m.p. 153 - 4°; (lit. m.p. 154 - 5°).[84]

The Hofmann reaction on 50

The imide, 50, (7.0 g., 0.05 moles) was heated for 0.5 hours on a steam bath with 100 ml. of a 1.5N solution of sodium hydroxide. The solution was cooled, and 3.2 ml. (0.06 moles) of bromine was added in one portion. Warming the mixture to 50° for 0.5 hours caused it to darken. The solution was acidified and then evaporated to dryness on a rotary evaporator. Extractions with hot absolute alcohol did not yield the product amino acid hydrochloride.

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[84] R. Groit, Helv. Chim. Acta., 42, 67 (1959).

A similar reaction on 20 g. of the amide-ammonium salt precursor gave the same results, however the solid residue obtained from the reaction after evaporation was refluxed with methanol which had been acidified with hydrochloric acid. The methanol layer was dried over anhydrous magnesium sulfate and fractionally distilled to yield 150 mg. (0.1%) of a basic material which had an infrared spectrum like that expected for an amino ester. No further attempts were made to characterize the compound, since the yield was too low to be synthetically useful.

The Schmidt reaction

To a cold solution of 20 g. (0.14 moles) of cis-1,3-cyclopentanedicarboxylic acid anhydride in 140 ml. of chloroform was added 40 ml. of concentrated sulfuric acid. The mixture was maintained at 50 - 55°, and 12.4 g. (0.19 moles) of sodium azide was added in small portions over a period of 3.5 hours.

The chloroform layer was separated, and the sulfuric acid solution was poured into 200 g. of ice and neutralized with a concentrated solution of sodium hydroxide. The aqueous solution was then evaporated to dryness under reduced pressure. The remaining white salt was extracted with dioxane and then with absolute ethanol. The alcohol extract was evaporated to dryness leaving 1.91 g. (12.3%) of a white crystalline salt, m.p. 230-8° (lit. m.p. 240 - 242°).[23] The infrared spectrum was like that expected for

the amino acid. Attempts to cyclicize the amino acid to the lactam like those used by Noyes and those used for preparation of the similar isoquinuclidone resulted only in decomposition.

The Hofmann-Löffler Synthesis

Cyclopentanecarboxylic acid (53)

Cyclohexanone was converted to cyclopentanecarboxylic acid according to the procedure of Payne and Smith.[44]

Cyclopentanecarboxylic acid chloride (54)

To a stirred solution of 31.65 g. (0.28 moles) of cyclopentanecarboxylic acid in 70 ml. of dichloromethane was added 59 g. (0.50 moles) of thionyl chloride over a period of 0.5 hours. A drop of pyridine initiated the reaction. The mixture was heated for one hour on the steam bath and then allowed to stand overnight. Vacuum distillation yielded 32.14 g. (87.4%) of the slightly yellow acid chloride, b.p. 72 - 74° (50 mm.); [lit. b.p. 160 - 2° (atmos.)].[44]

N-Ethylcyclopentanecarboxamide (55)

A solution of 68.6 g. (0.52 moles) of cyclopentanecarboxylic acid chloride in 400 ml. of benzene was cooled in an ice bath, and 400 ml. of ethylamine were added dropwise. The ethylamine hydrochloride was removed by vacuum filtration and washed twice with 50 ml. portions of hot

benzene. The solvent was removed from the filtrate on the rotary evaporator leaving 73.2 g. of the crude amide, m.p. 57 - 8°. Low temperature recrystallization from 35 - 40° petroleum ether yielded a colorless crystalline product, m.p. 58.0 - 58.5°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.02; H, 10.77; N, 9.76.

N-Methylcyclopentanecarboxamide

Anhydrous methylamine was bubbled into a cooled solution of 25.3 g. (0.21 moles) of 54 in 350 ml. of ether until no further precipitate formed. The ethereal solution was vacuum filtered, and the solids were washed with two 40-ml. portions of ether. The combined filtrates were stripped on a rotary evaporator yielding 23.4 g. (97.0%) of the crude amide, (m.p. 45 - 50°). The amide was recrystallized from 60 - 70° petroleum ether to yield colorless needles, m.p. 58 - 9°.

Anal. Calcd. for $C_7H_{13}NO$; C, 66.10; H, 10.30; N, 11.01. Found: C, 66.00; H, 10.38; N, 10.99.

N-Ethylaminomethylcyclopentane (56)

A solution of 15.0 g. (0.106 moles) of N-ethylcyclopentanecarboxamide (55) in 50 ml. of anhydrous ether was added dropwise to 5.05 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The mixture was stirred for 36 hours and 20 ml. of water was added dropwise at 0°. The

inorganic salts were removed by vacuum filtration and washed with three 30 ml. portions of ether. The solvent from the combined filtrates was removed by distillation through a Vigreaux column on the steam bath, and the resulting oil was distilled at reduced pressure yielding 13.05 g. (96.7%) of the clear liquid amine, b.p. 100 - 1° (100 mm.); n_D^{25} 1.4441.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.61; H, 13.69; N, 10.89.

N-Methylaminomethylcyclopentane

The N-methyl amine was prepared from N-methylcyclopentanecarboxamide in a manner similar to that given for the N-ethylaminomethylcyclopentene in 90.5% yield, b.p. 110-1° (240 mm.).

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.22; H, 13.33; N, 12.34.

N-Chloro-N-ethylaminomethylcyclopentane (57)

N-Ethylaminomethylcyclopentane (98 g., 0.77 moles) in 3 liters of ether was stirred for 15 hours with 120 g. (0.90 moles) of N-chlorosuccinimide. One liter of 35 - 40° petroleum either was added, and the solution was decanted from the precipitated solids, and the solvent was removed, without warming, on a rotary evaporator until 150 ml. of an oil remained. The N-chloroamine decomposed on warming or standing and was not further purified.

N-Chloro-N-methylaminomethylcyclopentane

The N-chloro-N-methylaminomethylcyclopentane was prepared in a manner similar to that above for the N-ethyl derivative.

N-Ethyl-2-azabicyclo [2.2.1] heptane (39)

The N-chloro-N-ethylamine prepared above was dissolved in 400 ml. of cold 80% sulfuric acid, and the resulting solution was irradiated for 25 hours at 35 - 40° in Vycor or quartz containers with a bank of ten - 15 watt Sylvania "Blacklite" Lamps. The dark acid solution was poured onto 1000 g. of ice, made basic with cold concentrated sodium hydroxide solution, and allowed to stand overnight. The solution was then made strongly basic and steam distilled until the distillate was no longer basic to litmus. Continuous extraction of the distillate for two days with ether was followed by the removal of the solvent from the ether extract by distillation on the steam bath. The remaining oil was added to a stirred solution of 400 g. of potassium hydroxide in 1300 ml. of water at 0°. Benzensulfonyl chloride, (400 g., 2.26 moles), was added dropwise over a period of one hour while the reaction was cooled to 0° in an ice bath. The mixture was stirred at room temperature overnight, acidified with hydrochloric acid, and extracted with ether. The extract was dried over anhydrous magnesium sulfate, the inorganic salts filtered off, and the ether removed by fractional distillation. The residue was vacuum

distilled to give 27.74 g. (28.8%) of the tertiary amine, b.p. 92 - 95° (135 mm.), which was 98% pure to vapor phase chromatography, (15% carbowax column, 70°).

Redistillation yielded an analytical sample of 39, b.p. 103.5 - 104° (167 mm.); n_D^{20} 1.4639.

Anal. Calcd. for $C_8H_{15}N$: C, 76.73; H, 12.08; N, 11.19. Found: C, 76.58; H, 12.13; N, 11.42.

The picrate of 39 was prepared and recrystallized from ethyl alcohol, m.p. 220 - 1°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47,45; H, 5.12; N, 15.81. Found: C, 47.28; H, 5.23; N, 15.95.

The oxalate of 39 was prepared and recrystallized from ethyl acetate, m.p. 159 - 60°.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.78; H, 8.14; N, 6.37.

N-Methyl-2-azabicyclo [2.2.1] heptane (91)

By the same procedure quoted above for 39, the N-methyl derivative was prepared in 26.3% yield, and was found to be 99% pure to vapor phase chromatography after one distillation, Redistillation afforded and analytical sample boiling at 82.5 - 83° (149 mm.); n_D^{20} 1.4635.

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.73; H, 11.95; N, 12.37.

The picrate of the amine was prepared and recrystallized from alcohol, m.p. 284 - 5°.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 46.15; H, 4.45; N, 16.3.

The methyl iodide salt was prepared and recrystallized from absolute ethanol as colorless cubes, m.p. 309 - 310°.

Anal. Calcd. for $C_8H_{16}NI$: C, 37.95; H, 6.38; N, 5.53. Found: C, 37.81; H, 6.69; N, 5.64.

γ-Haloamine Approach

Δ^3-Cyclopentenol (61)

Cyclopentadiene was converted to 61 by the method of Allred, Sonnenberg, and Winstein.[48]

Tosylate of Δ^3-cyclopentenol (62)

To a solution of 110 g. of p-toluenesulfonyl chloride in 480 ml. of pyridine was added 41.30 g. (0.49 moles) of the unsaturated alcohol, 61. The resulting solution was placed in the refrigerator for 16 hours, then was poured into a dilute hydrochloric acid - ice mixture with rapid stirring. The tosylate separated as a pink solid which melted just above 0°. The tosylate was removed from the slightly acidic aqueous solution by vacuum filtration. The solid material was dissolved in chloroform, decolorized with activated charcoal, and dried with anhydrous magnesium sulfate. The inorganic solids were removed by filtration, and the chloroform was removed on a rotary evaporator

leaving 115 g. (92.6%) of the tosylate, m.p. 35 - 40°. Recrystallization from Skelly C afforded white needles of the tosylate, m.p. 51 - 52°, (lit. m.p. 53.4 - 54.2°).[48]

Attempted preparation of 4-cyanocyclopentene (64)

A solution of 10 g. of the tosylate (62) in 50 ml. of methanol was added to 6 g. of sodium cyanide. The mixture was heated on a steam bath for one hour and allowed to stand for one day. Extraction with ether followed by distillation of the extracts yielded no nitrile fractions.

Further attempts were made with the following variations: (1) The temperature was varied from 25 - 100°; (2) the time was varied from one hour to two weeks; (3) the solvents, methanol, ethanol, dimethyl formamide, and dimethyl sulfoxide were used; and (4) cuprous cyanide was used in place of sodium cyanide. In no case, however, was there any significant amount of organic nitrile formed.

4-Bromocyclopentene (63)

The 4-bromocyclopentene was synthesized according to the procedure of Bartlett and Rice,[46] except that the reduction was not cooled during addition of the dibromide.[47]

4-Cyanocyclopentene[42] (64)

To a solution of 22 g. (0.49 moles) of sodium cyanide in 200 ml. of dimethyl sulfoxide at 100° was added 44.8 g.

(0.30 moles) of 4-bromocyclopentene. The solution was heated on a steam bath for 6 hours, cooled, and 200 ml. of water was added. The resulting solution was extracted with five 100 ml. portions of ether, and the combined extracts were dried over anhydrous magnesium sulfate. The drying agent was filtered off, and the ether was removed from the filtrate on a steam bath. The resulting oil was distilled at reduced pressure to yield 21.9 g. (77.5%) of the nitrile, b.p. 93 - 100° (90 mm.).

4-Aminomethylcyclopentene (65)

4-Cyanocyclopentene (3.99 g., 0.04 moles) was added dropwise to 1.64 g. (0.04 moles) of lithium aluminum hydride in 100 ml. of anhydrous ether. The reaction was heated to reflux for two days, cooled to 0°, and 6 ml. of water was added dropwise. The inorganic solids were removed by vacuum filtration, and the ether solution was distilled to yield 3.17 g. (76.4%) of the amine, b.p. 85 - 88° (127 mm.). Redistillation yielded a clear liquid b.p. 87 - 88° (134 mm.).

Anal. Calcd. for $C_6H_{11}N$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.02; H, 11.68; N, 14.21.

The chloroplatinate derivative was prepared by addition of a 25% aqueous solution of chloroplatinic acid to a small portion of the amine. The precipitate was filtered off and recrystallized from absolute ethanol containing a drop of concentrated hydrochloric acid, m.p. 190° d.

Anal. Calcd. for $C_{12}H_{24}N_2PtCl_6$: C, 23.85; H, 4.00; N, 4.64; Pt, 32.31. Found: C, 23.76; H, 4.09; N, 4.66; Pt, 32.53.

N-Ethyl-2-azabicyclo [2.2.1] heptane (66)

Anhydrous hydrogen bromide was bubbled into a solution of 3.46 g. (0.036 moles) of 4-aminomethylcyclopentene in 60 ml. of chloroform for four hours. The solution was allowed to stand overnight, then hydrogen bromide was added slowly for two additional hours. The chloroform solution was extracted with three 20-ml. portions of water followed by two 10-ml. portions of 10% hydrochloric acid. The aqueous extracts were placed in a flask equipped with a stirrer, a dropping funnel, and a distillation head. Concentrated aqueous sodium hydroxide was added dropwise while the solution was heated to 80°. When the solution was basic, the temperature was raised to distill 100 ml. of liquid. The distillate was acidified, extracted with two 20-ml. portions of ether, and the extracts were discarded. The aqueous layer was then made basic and extracted with four 20-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, the inorganic material was filtered off, and the ether was removed by distillation. The remaining oil was vacuum distilled to yield 2.77 g. (77%) of an amine, b.p. 115 - 130°. Infrared analysis indicated that the product contained 30% of the unreacted unsaturated amine. Further purification

by successive distillations, column chromatography, and vapor phase chromatography were unsuccessful.

Acetylation of the amine was carried out by dissolving the above product (2.77 g., 0.03 moles) in 15 ml. of a saturated sodium acetate solution and cooling the stirred mixture in an ice bath. Acetic anhydride (5 g., 0.05 moles) was added dropwise, and the solution was stirred overnight. The mixture was extracted with five 20-ml. portions of ether, and the ether extracts were washed with sodium bicarbonate solution. The ether layer was dried over anhydrous magnesium sulfate, the solids were removed by filtration, and the filtrate was distilled at reduced pressure to yield 3.65 g. (92.0%) of a clear high boiling liquid, b.p. 80 - 81° (0.8 mm.).

Reduction was accomplished by the dropwise addition of 1.97 g. (0.014 moles) of the amide to 3.0 g. (0.08 moles) of lithium aluminum hydride in 70 ml. of anhydrous ether. The mixture was stirred and refluxed overnight and then was hydrolized by the dropwise addition of 12 ml. of water. After 0.5 hours the inorganic salts were filtered off and the solvent was removed from the filtrate on a steam bath, leaving a colorless oil.

The remaining oil was added to a stirred solution of 9.0 g. (0.16 moles) of potassium hydroxide in 26 ml. of water. The mixture was cooled in an ice bath, and 7 ml. (0.057 moles) of benzenesulfonyl chloride was added dropwise. The solution was allowed to stir overnight, then

was made acidic with concentrated hydrochloric acid and extracted with three 20-ml. portions of ether. The aqueous layer was then made basic and extracted with four 50-ml. portions of ether. The latter ether extracts were dried over anhydrous magnesium sulfate, the inorganic salts were filtered off, and the filtrate was distilled yielding 0.42 g. of a liquid, b.p. 102-5 (165 mm.). The infrared spectrum of the product was identical to the N-ethyl-2-azabicyclo [2.2.1] heptane, prepared from the Hofmann-Löffler reaction. The picrate which was prepared in the usual fashion had a melting point and a mixed melting point identical to the picrate of the Hofmann-Löffler product (m.p. 220 - 1°, mixed m.p. 220 - 1°).

N-Acetyl-4-aminomethylcyclopentene 68

To 25 ml. of a saturated solution of sodium acetate was added 4.44 g. (0.046 moles) of 4-aminomethylcyclopentane. The solution was cooled and stirred, and 10 ml. (0.10 moles) of acetic anhydride was added dropwise. The mixture was stirred overnight and then extracted with four 20-ml. portions of ether. The ether extracts were washed with a saturated sodium bicarbonate solution until the washings were basic. The ether solution was dried over anhydrous magnesium sulfate, and the drying agent was filtered off. Distillation of the filtrate at reduced pressure yielded 4.44 g. (70.0%) of the unsaturated amide b.p. 115 -

125° (0.4 mm.). Redistillation yielded an analytical sample, b.p. 114 - 115° (0.25 mm.).

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.88; H, 9.58; N, 10.03.

N-Ethyl-4-aminomethylcyclopentene 69

To a stirred mixture of 1.91 g. (0.05 moles) of lithium aluminum hydride in 100 ml. of ether was added 1.06 g. (0.008 moles) of N-acetyl-4-aminomethylcyclopentene. The resulting solution was refluxed overnight and then was cooled and hydrolized by the dropwise addition of 4 ml. of water. The inorganic solids were filtered off and washed with three 10-ml. portions of ether. The ether was removed from the combined filtrates by distillation on a steam bath, and the remaining oil was distilled at reduced pressure yielding 0.71 g. (84.5%) of the unsaturated amine, b.p. 89 - 91°.

N-Ethyl-2-azabicyclo [2.2.1] heptane

N-Ethyl-4-aminomethylcyclopentene (0.387 g., 0.003 moles) was placed in a small erlenmeyer flask with one ml. of chloroform. Anhydrous hydrogen bromide was bubbled into the solution for 3.5 hours dissolving the first formed solid. To the solution was added 8 ml. of 6 N sodium hydroxide solution. After two hours the solution was extracted with four 20-ml. portions of ether, the extracts were dried, and the drying agent was filtered off. The ether

was carefully removed by distillation, and the remaining oil was distilled in a micro still to yield a small fraction of a clear liquid, b.p. 100 - 2° (165 mm.). Comparison of the infrared spectra showed this to be the same product, N-ethyl-2-azabicyclo [2.2.1] heptane, obtained from the Hofmann-Löffler reaction. The entire product was treated with a saturated solution of picric acid in ethanol, and the resulting crystalline picrate was removed by vacuum filtration and washed with a small portion of cold ethanol to yield 0.181 g. (13.5%) of the amine picrate, m.p. 217 - 220°. This was shown to be identical to the picrate of the Hofmann-Löffler product by a mixed melting point (219 - 220°) and by their identical infrared spectra.

N-Ethyl-6-azabicyclo [3.2.0] Heptane Synthesis

2-Carbethoxycyclopentanone (70)

The 2-carbethoxycyclopentanone used was obtained from Arapahoe Chemicals and was not further purified.

2-Carbethoxycyclopentanone oxime (71)

A solution of 16.8 g. (0.11 moles) of 2-carbethoxycyclopentanone in 30 ml. of methanol was added to a solution of 15 g. of hydroxylamine hydrochloride and 15 g. of sodium acetate in 15 ml. of water. The resulting mixture was heated on a steam bath for four hours and allowed to stand overnight. The solution was extracted with three

50-ml. portions of ether, and the ether layer was washed dilute sodium carbonate solution until the washings were basic. The ethereal solution was dried over anhydrous magnesium sulfate, and the inorganic solids were removed by filtration. Removal of the solvent followed by distillation of the residue afforded 17.59 g. (95.6%) of the oxime, b.p. 102 - 112° (0.30 mm.). Redistillation yielded a sample, b.p. 109.5 - 110° (0.30 mm.).

2-Aminocyclopentylmethanol (72)

To 9.43 g. (0.25 moles) of lithium aluminum hydride in 300 ml. of anhydrous ether was added 17.59 g. (0.10 moles) of 2-carbethoxycyclopentanone oxime over a period of one hour. The mixture was refluxed with stirring for 72 hours. The solution was cooled in an ice bath, and the excess hydride was neutralized by the dropwise addition of 30 ml. of water. The inorganic solids were filtered off and washed with three 50-ml. portions of ether. The combined filtrates were dried over anhydrous magnesium sulfate, the drying agent was removed by filtration, and the solvent was removed. Distillation of the remaining oil yielded 7.87 g. (70%) of the amino alcohol, b.p. 120 - 125° (30 mm.). Redistillation gave an analytical sample b.p. 76.5 - 77° (0.3 mm.).

Anal. Calcd. for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 63.01; H, 11.38; N, 12.27.

N-Ethyl-6-azabicyclo [3.2.0] heptane (60)

2-Aminocyclopentylmethanol (7.08 g., 0.06 moles) was dissolved in 50 ml. of benzene, and 7.0 ml. (0.085 moles) of ethyl iodide was added. The solution was refluxed for three hours, acidified with concentrated hydrochloric acid, and the solvent was removed at reduced pressure. The resulting oil was cooled in ice, and 10 ml. of thionyl chloride was added dropwise. The reaction mixture was heated to 55° for one hour, and an additional 5 ml. of thionyl chloride was added. The mixture was then heated on a steam bath for 0.3 hours and then stripped under reduced pressure. The resulting product was added to 50 ml. of cold 27% sodium hydroxide solution and steam distilled. The distillate was saturated with sodium chloride and continuously extracted with ether for 24 hours. The extract was dried over anhydrous magnesium sulfate, the inorganic salts were filtered off, and the filtrate was distilled to yield 1.68 g. (19.0%) of the tertiary amine, b.p. 90 - 100° (190 mm.) and a higher boiling fraction, 3.68 g. (52%), consisting of starting material, possibly the trans isomer. Redistillation yielded a sample of the tertiary amine, b.p. 88 - 89° (105 mm.), from which a picrate was made, m.p. 163 - 4°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.18; H, 5.29; N, 15.97.

The methyl iodide salt was prepared and recrystallized from ethyl alcohol, m.p. 186 - 7°.

Anal. Calcd. for $C_9H_{18}NI$: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.25; H, 6.85; N, 5.19.

The Hinsberg separation of N-ethyl-6-azabicyclo [3.2.0] heptane

A 1.15 g. sample (0.09 moles) of the once distilled N-ethyl-6-azabicyclo [3.2.0] heptane (90% pure to vapor phase chromatography) was dissolved in a solution of 3 g. of potassium hydroxide in 10 ml. of water and cooled in a salt-ice bath. Benzene sulfonyl chloride (3 g., 0.17 moles) was added dropwise, and the solution was stirred for 6 hours. Concentrated hydrochloric acid was added until the solution was acidic, and the mixture was extracted with ether. The aqueous layer was then made basic with a concentrated sodium hydroxide solution and was extracted continuously with ether. The latter extract was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The remaining solution was distilled to yield 0.79 g. of the tertiary amine, b.p. 95 - 98° (190

mm.) An infrared spectrum showed it to be the tertiary amine.

2-Hydroxy-2-azabicyclo [2.2.1] Heptane Synthesis

N-Ethyl-2-azabicyclo [2.2.1] heptane-N-oxide (75)

N-Ethyl-2-azabicyclo [2.2.1] heptane (2.0 g., 0.16 moles) was dissolved in 10 ml. of absolute methanol and cooled to 0°. To the stirred solution was added 10 ml. of 30% hydrogen peroxide over a period of 0.3 hours. After 24 hours the solution was no longer basic to phenolphthalein, and a small amount of platinum was added to decompose the excess peroxide. The platinum was filtered off, and the solvent was removed from the filtrate leaving a colorless oil. Addition of a saturated solution of picric acid in ethanol to a small portion of the N-oxide gave the picrate. Recrystallization from ethanol yielded yellow crystals, m.p. 195° d.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.09; H, 5.10; N, 15.19.

2-Hydroxy-2-azabicyclo [2.2.1] heptane (77)

The oxide from 2.0 g. (0.16 moles) of the N-ethyl-2-azabicyclo [2.2.1] heptane was placed in a pyrolysis flask outfitted with a receiver cooled in a dry ice-acetone bath. The system was evacuated to a pressure of 20 mm., and the flask was slowly warmed over a period of one-half

hour to a maximum temperature of 180°. The distillate was dissolved in ether, dried over anhydrous magnesium sulfate, and the drying agent was filtered off. The ether solution was distilled to yield a first fraction of 0.25 g. (12.5%) of N-ethyl-2-azabicyclo [2.2.1] heptane, b.p. 92 - 95° (135 mm.). The remaining material was redistilled four times to yield 0.515 g. (28.4%) of the hydroxylamine, b.p. 107 - 110° (135 mm.). The hydroxylamine was a white amorphous solid which decomposed on standing. One sublimation, however, gave a sample of hydroxylamine m.p. 95 - 96° which appeared to be relatively stable. A portion of the product was dissolved in a saturated solution of oxalic acid in ethyl acetate. Upon standing, white crystals formed which were filtered off. The product was recrystallized from ethyl acetate to give white needles of the oxalate, m.p. 104 - 5°.

Anal. Calcd. for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.37; H, 6.51; N, 7.01.

Diels-Alder Approaches

N-Sulfinyl-p-toluenesulfonamide (77)

A solution of 50 g. (0.29 moles) of p-toluenesulfonamide in 50 ml. of benzene and 70 ml. (1.0 moles) of thionyl chloride was refluxed for three days. The resulting mixture was evaporated to dryness on a rotary evaporator to yield a yellow crystalline solid. The product was

extremely hygroscopic hence no attempts were made to characterize it.

N-Trichloroethylidine-p-toluenesulfonamide (29)

The N-sulfinyl-p-toluenesulfonamide (40 g., 0.18 moles) was dissolved in 75 ml. of benzene, and 30 g. (0.20 moles) of chloral was added. The solution was refluxed for one day and cooled. A solid, m.p. 215°, which was not the desired product, crystallized directly out of the reaction mixture and was removed by filtration. The mother liquors were stripped on the rotary evaporator leaving a yellow oil. The oil was dissolved in hot petroleum ether (95 - 100°) and filtered. Upon cooling 30.65 g. (55.5%) of a yellow solid crystallized, m.p. 118 - 120°; (lit. m.p. 113°).[5]

2-(p-Toluenesulfonyl)-3-trichloromethyl-2-azabicyclo [2.2.1] hept-5-ene (30)

A solution of 10 g. (0.03 moles) of N-trichloroethylidine-p-toluenesulfonamide and 5 ml. (0.06 moles) of cyclopentadiene in 30 ml. of benzene was refluxed for 24 hours. The solvent was removed on a rotary evaporator, and the remaining oil was dissolved in hot absolute ethanol. A yellow solid (7.7 g., 66%) crystallized out on cooling, m.p. 131-2° (lit. m.p. 133.5°).[5] A nuclear magnetic

resonance spectrum of the compound appeared reasonable for the expected structure.

Attempted Preparation of 3-Chloro-2-Azabicyclo [2.2.1] Hept-5-ene (80)

Formamide (1 mole) was dissolved in a mixture of 200 ml. of benzene and 200 ml. of chloroform, and the resulting solution was stirred and cooled in an ice bath. To the solution was added simultaneously 67 g. (0.43 moles) of phosphorus oxychloride and 66 g. (1 mole) of cyclopentadiene. After stirring for 20 hours, 84 g. (1 mole) of sodium bicarbonate in 400 ml. of water was added followed by 57 g. (1 mole) of potassium hydroxide in 200 ml. of water. The resulting mixture was steam distilled into dilute hydrochloric acid. The distillate was extracted with ether, and the extracts were discarded. The aqueous solution was then made basic and continuously extracted with ether. The ether was removed from the extract by distillation at atmospheric pressure, and the resulting oil was distilled at reduced pressure to yield 2.80 g. (2.1%) of a basic oil, b.p. 70 - 110° (atmos. -10 mm.). Redistillation yielded a sample [b.p. 61 - 64, (196 mm.)] which showed thirteen components on vapor phase chromatographic analysis.

Methylene bisurethane (32)

The methylene bisurethane used was prepared according to the procedure published in Houben-Weyl, "Methoden Der Organishen Chemie."[26]

Attempted preparation of 2-azabicyclo [2.2.1] hept-5-ene

Methylene bisurethane (98 g., 0.6 moles) was dissolved in 1.2 liters of benzene, and 40 ml. of 47% boron trifluoride etherate in 50 ml. of anhydrous ether was added. The solution was brought to reflux, and 50 ml. (0.62 moles) of freshly cracked cyclopentadiene was added dropwise. After four hours the mixture was shaken in a sepratory funnel with saturated potassium carbonate solution until the color changed from purple to red-brown. The organic layer was separated, and the benzene was distilled off. The remaining yellow viscous oil was refluxed with a mixture of 56 g. of potassium hydroxide in 200 ml. of ethylene glycol for 10 hours. The resulting solution was cooled, made acidic with hydrochloric acid, and extracted with four 100 ml. portions of ether. The extracts were discarded, and the aqueous layer was made basic and continuously extracted with ether. The ether extract from the continuous extraction was dried over anhydrous magnesium sulfate and the inorganic solids were filtered off. Distillation afforded a yellow oil (11.49 g., 20%) b.p. 50 - 140° (130-100 mm.). Triple distillation gave a sample b.p. 133-134° (82 mm.) which showed seven peaks of approximately equal size to vapor phase chromatography.

Alternate Lactam Approach

Norcamphor

The norcamphor was obtained from the Aldrich Chemical Company and was not further purified.

Norcamphor oxime (85)

In 30 ml. of water was dissolved 30 g. of sodium acetate and 30 g. (0.43 moles) of hydroxylamine hydrochloride. A solution of 48 g. (0.44 moles) of norcamphor in 60 ml. of methyl alcohol was added, and the resulting solution was allowed to stand 12 hours.

The reaction mixture was then extracted with three 100-ml. portions of ether, and the extracts were washed with dilute sodium carbonate solution. The ether layer was dried over anhydrous magnesium sulfate, and the inorganic salts were filtered off. Distillation under reduced pressure gave 50.28 g. (93.5%) of a clear viscous oil b.p. 95 - 100° (15 mm.) which crystallized on standing, m.p. 40 - 42° (lit. m.p. 45°).[63]

Norcamphor oxime-boron trifluoride complex (86)

Anhydrous boron trifluoride was bubbled into a solution of 50 g. (0.4 moles) of norcamphor oxime in 600 ml. of ether until no further precipitate formed. The white solid was removed by vacuum filtration and washed several times with

small portions of ether to yield 72.00 g. (97.2%) of the complex, m.p. 153 - 4°, (lit. m.p. 132 - 2°).[63]

2-Azabicyclo [3.2.1] octan-3-one (87)

In 120 ml. of sym-tetrachloroethane was dissolved 20 g. (0.10 moles) of norcamphor oxime-boron trifluoride complex. The solution was heated to 115 - 130° for 40 minutes in a flask fitted with a condenser, cooled, and washed with sodium carbonate solution. The remaining liquid was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The solution was distilled under reduced pressure to yield 7.71 g. (49.6%) of the lactam; b.p. 93 - 110° (0.15 mm.),[lit. b.p. 96 - 98° (0.06 mm.)].[63]

N-Ethyl-2-azabicyclo [3.2.1] octan-3-one (88)

A solution of 5.47 g. (0.044 moles) of 2-azabicyclo [3.2.1] octan-3-one in 50 ml. of toluene was cooled, and 3.24 g. (0.043 moles) of 51.6% sodium hydride dispersion was added. The solution was heated to reflux for 0.5 hr. and then cooled. Ethyl iodide, 5 ml. (0.47), was added and the solution was refluxed for one hour. The resulting mixture was vacuum filtered and fractionally distilled under reduced pressure to yield 4.97 g. (81.5%) of the N-ethyl lactam, b.p. 88 - 95° (0.1-0.3 mm.), and 0.97 g. (18%) of the unethylated lactam.

Redistillation yielded an analytical sample, b.p. 112° (3.8 mm.).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.15. Found: C, 70.47; H, 10.02; N, 8.72.

Cis-1-ethylamino-3-(2,2-diphenyl-ethenyl) cyclopentane (89)

In a dry flask was placed 50 ml. of anhydrous ether and 4.6 g. (0.19 moles) of magnesium. Methyl iodide (1 ml.) was added to initiate the Grignard reaction, and 32 ml. (0.37 moles) of bromobenzene was added slowly. When the reaction ceased, 10 g. (0.065 moles) of the N-ethyl-2-aza-bicyclo [3.2.1] octane in 20 ml. of anhydrous ether was added slowly, and the mixture was refluxed for two hours. Water (100 ml.) was added to the reaction mixture and the organic layer was separated. Vacuum distillation yielded 3.30 g. (17.5%) of the crude unsaturated amine, b.p. 135 - 140° (0.1 mm.) which solidified on cooling, and 5.99 g. (60%) of the unreacted amide. Recrystallization of the amine from petroleum ether (90 - 100°) yielded colorless rhombohedrons, m.p. 109 - 110°.

Anal. Calcd. for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.59; H, 8.60; N, 4.64.

Quaternary Salts

3-Azabicyclo [3.2.2] nonane

The 3-azabicyclo [3.2.2] nonane used was obtained from Eastman Chemical Products, Inc.,[85] and was sublimed once before use.

N-Acetyl-3-azabicyclo [3.2.2] nonane

Sublimed 3-azabicyclo [3.2.2] nonane (6 g., 0.05 moles) was dissolved in 20 ml. of pyridine and cooled to 0°. The solution was stirred, and 7 ml. (0.12 moles) of acetyl chloride was added dropwise. After stirring for two hours, the pyridine was removed under reduced pressure and the remaining material was extracted with a benzene-cyclohexane mixture. Upon cooling, 4.60 g. (57.5%) of the amide crystallized, m.p. 88.4 - 89.6°; (lit. m.p. 87 - 91°).[82]

N-Ethyl-3-azabicyclo [3.2.2] nonane

To a stirred misture of 2.25 g. (0.08 moles) of lithium aluminum hydride in 70 ml. of anhydrous ether was added 8.5 g. (0.05 moles) of the N-acetyl-3-azabicyclo [3.2.2] nonane in 80 ml. of ether. After 3 hours the excess hydride was hydrolized by the dropwise addition of 9 ml. of water. The inorganic solids were filtered off and washed with three 50 ml. portions of ether. The solvent was removed from the

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[85] Eastman Chemical Products, Inc., "3-Azabicyclo [3.2.2] nonane-Properties...Reactions", Technical Data Report, May, 1962.

combined filtrates at atmospheric pressure, and the remaining yellow oil was distilled at reduced pressure to yield 6.99 g. (90.9%) of the amine, b.p. 72 - 76° (10 mm.). Redistillation afforded an analytical sample, b.p. 71° (13 mm.).

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.40; H, 12.53; N, 9.25.

Addition of methyl iodide to the amine gave the methyl iodide salt as colorless cubes which were recrystallized from absolute ethanol, m.p. 279 - 8°.

Anal. Calcd. for $C_{11}H_{22}NI$: C, 44.75; H, 7.53; N, 4.75. Found: C, 44.65; H, 7.64; N, 4.49.

Addition of ethyl iodide to the amine gave white leaflets of a salt which was recrystallized from absolute ethanol, m.p. 248 - 9°. By nuclear magnetic resonance spectra and comparison of the infrared spectrum of this salt with the product of the addition of hydrogen iodide to the amine, it was determined to be the hydroiodide of the N-ethyl amine.

Anal. Calcd. for $C_{10}H_{20}NI$: C, 42.53; H, 7.28; N, 4.91. Found: C, 42.70; H, 7.22; N, 4.97.

Exo-2-ethyl-endo-2-methyl-2-azoniabicyclo [2.2.1] heptane iodide (93)

To a solution of 0.20 g. of N-methyl-2-azabicyclo [2.2.1] heptane in 2 ml. of ethanol was added 5 ml. of ethyl iodide, and the mixture was allowed to stand for 24

hours. Petroleum ether (35 - 40°), 10 ml., was added; and the precipitated salt was removed by vacuum filtration and dried under vacuum to yield 0.46 g. (95.7%) of the exo-ethyl-endo-methyl quaternary salt, m.p. 303 - 4°. Three recrystallations from absolute ethanol yielded colorless cubes, m.p. 305 - 5.5°. Infrared spectra of the crude salt and the recrystallized salt were identical.

Anal. Calcd. for $C_9H_{18}NI$: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.47; H, 6.78; N, 5.24.

Exo-2-methyl-endo-2-ethyl-2-azonia-bicyclo [2.2.1] heptane iodide (92)

Methyl iodide, 5 ml., was added to a solution of 0.20 g. of N-ethyl-2-azabicyclo [2.2.1] heptane in 2 ml. of ethanol, and the solution was allowed to stand for 24 hours. The salt was precipitated by the addition of 10 ml. of 35 - 40° petroleum ether and removed by vacuum filtration to yield 0.41 g. (96.3%) of the exo-methyl-endo-ethyl quaternary salt, m.p. 307 - 8°. Three recrystallizations from absolute ethanol yielded white cubes, m.p. 308 - 8.5°. The infrared spectrum of the crude salt was identical with that of the recrystallized product and different from the spectrum of the exo-ethyl-endo-methyl salt. An intimate mixture of the two salts melted at 306 - 7°.

Anal. Calcd. for $C_9H_{18}NI$: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.43; H, 6.82; N, 5.05.

2,2-Diethyl-2-azoniabicyclo [2.2.1] heptane iodide

The N,N-diethyl quaternary salt was prepared in a fashion similar to that above to yield white plates, m.p. 294.5 - 295°.

Anal. Calcd. for $C_{10}H_{20}NI$: C, 42.71; H, 7.18; N, 4.98. Found: C, 42.70; H, 7.31; 4.87.

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