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THE SYNTHESIS OF 2-AZABICYCLO[2.2.1]HEPTANES BY THE HOFMANN-LÖFFLER-FREYTAG REACTION

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Abstract—The only tertiary amine resulting from the cyclization of N-chloro-N-ethylcyclopentylmethylamine under Hofmann-Löffler-Freytag reaction conditions was N-ethyl-2-azabicyclo[2.2.1]heptane. The structure of the 2-azabicyclo[2.2.1]heptane skeleton was proven by independent synthesis. In the course of this investigation, derivatives of the relatively unknown 6-azabicyclo[3.2.0]heptane system were also prepared.

The intrinsic preference for 1,5-hydrogen migration in the Hofmann-Löffler-Freytag reaction is discussed.

THE rearrangement of N-haloamines in strongly acidic media followed by cyclization of the resultant isomeric rearrangement products was first studied by Hofmann in 1883.[2] In 1909 Löffler reinvestigated[3,4] this reaction and discovered further examples of its utility. Since that time the reaction has become widely utilized in the synthesis of cyclic tertiary amines.[5]

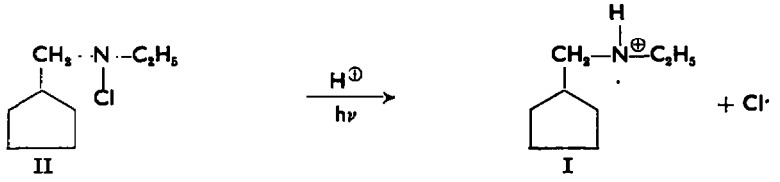
The mechanism of the Hofmann-Löffler-Freytag reaction was substantiated by Wawzonek and Culbertson,[6] who isolated the N-nitroso derivative of the δ-halo intermediate. The same research group was responsible for initially establishing the free radical nature of this reaction.[7] Corey and Hertler have recently investigated other facets of the mechanism of this useful cyclization reaction in relation to (1) stereochemistry, (2) isotope effects, (3) initiation, inhibition, and catalysis and (4) geometrical requirements.[8] These authors proposed that two factors which control the ability of the intermediate aminium radical to abstract a given hydrogen are the tendency of the hydrogen transfer to be linear and the preference for angle strain and steric repulsions to be minimized in the transition state for hydrogen transfer.

Perhaps the most interesting feature of the Hofmann–Löffler–Freytag reaction and of related radical abstractions is the unusually strong preference for attack of the δ-hydrogens. Studies of a broad spectrum of intramolecular hydrogen transfers have shown[9] that a six-membered transition state is either preferred or necessary not only in the photochemical isomerization of N-haloamines,[5,8] but also in certain

[1] National Institutes of Health Predoctoral Fellow, 1963–1965.
[2] A. W. Hofmann, *Chem. Ber.* **16**, 558, 583 (1883).
[3] K. Löffler and C. Freytag, *Chem. Ber.* **42**, 3427 (1909).
[4] K. Löffler and S. Kober, *Chem. Ber.* **42**, 3421 (1909).
[5] For a recent review see M. Wolff, *Chem. Revs.* **63**, 55 (1963).
[6] S. Wawzonek and T. P. Culbertson, *J. Amer. Chem. Soc.* **81**, 3367 (1959).
[7] S. Wawzonek and P. J. Thelan, *J. Amer. Chem. Soc.* **72**, 2118 (1950).
[8] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **82**, 1657 (1960).
[9] D. H. R. Barton and R. L. Morgan, *J. Chem. Soc.* 622 (1962).

photo-induced rearrangements of alkyl nitrites,[10] alkyl hypohalites,[11] ketones,[12] N-haloamides,[13] and pyrolysis of alkyl azides.[14]

In view of the overwhelming intrinsic preference for abstraction of the δ-hydrogens we decided to investigate a case in which the abstraction of a γ-hydrogen[15] would appear to be preferable to the abstraction of a δ-hydrogen by the intermediate aminium radical. Thus we became concerned with the specificity for hydrogen transfer exhibited by the aminium radical, (I) formed in the photo-induced homolytic cleavage of the N–Cl bond of N-chloro-N-ethylaminomethylcyclopentane (II). This cyclopentane derivative (II) is particularly interesting because of the considerable strain which

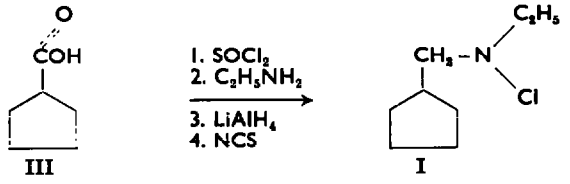


II I

would be incorporated into the molecule in bringing the nitrogen of the intermediate aminium radical into a position suitable for abstraction of the δ-hydrogen. This strain effect is easily noted from an examination of Dreiding Stereomodels of I. For a planar cyclopentane ring the interatomic distance from the nitrogen of the aminium radical to the γ- and δ-hydrogens is 1·8 Å and 3·3 Å, respectively. However the cyclopentane ring is not planar but exists in the form of an envelope or a cyclopentane half chair with the puckering rotating around the ring.[16–18] The proximity of the aminium radical to the γ-hydrogen can remain at about 1·8 Å in the envelope conformation. However the distance from the aminium radical nitrogen to the δ-hydrogen is decreased in the cyclopentane envelope. The average displacement[16] of the envelope "flap" from the plane of the ring is about 0·3 Å and the maximum displacement[19] is about 0·5 Å. In the situation where maximum flap bending has occurred the nitrogen of the aminium radical can approach within 2·2 Å, of the δ-hydrogen. This would appear to be considerably greater than the optimum interatomic distance for hydrogen abstraction. In order to shorten the interatomic distance from the nitrogen radical to the δ-hydrogen to less than 2·2 Å a large amount of strain must be incorporated into the system. This strain would result from an out-of-plane folding of the cyclopentane envelope "flap" to more than 0·5 Å. Thus on the basis of the strain incorporated into the cyclopentane ring, it would appear that γ-hydrogen abstraction would occur more readily than δ-hydrogen abstraction.

[10] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **82**, 2640 (1960).
[11] F. D. Greene, M. L. Savitz, H. H. Lau, F. D. Osterholtz and W. N. Smith, *J. Amer. Chem. Soc.* **83**, 2196 (1961); C. Walling and A. Padwa, *Ibid.* **85**, 1597 (1963).
[12] K. Schaffner, D. Arigoni and O. Jeger, *Experientia* **16**, 169 (1960).
[13] D. H. R. Barton and A. J. L. Beckwith, *Proc. Chem. Soc.* 335 (1963).
[14] G. Smolinsky and B. I. Feuer, *J. Amer. Chem. Soc.* **86**, 3085 (1964).
[15] K. Löffler, *Chem. Ber.* **43**, 2025 (1910), attempted to cyclize N-chloro-N-methyl-2-butylamine under Hofman-Löffler-Freytag reaction conditions. No cyclized product was formed. He concluded that four-membered rings could not be formed *via* abstraction of a γ-hydrogen in this reaction.
[16] J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, *J. Amer. Chem. Soc.* **69**, 2483 (1947).
[17] C. G. Le Fevre, and R. J. Le Fevre, *J. Chem. Soc.* 3549 (1956).
[18] F. V. Brutcher, Jr., T. Roberts, S. J. Barr and N. Pearson, *J. Amer. Chem. Soc.* **81**, 4915 (1959).
[19] See W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) pp. 35–36. J. Wiley, New York, N.Y. (1956).

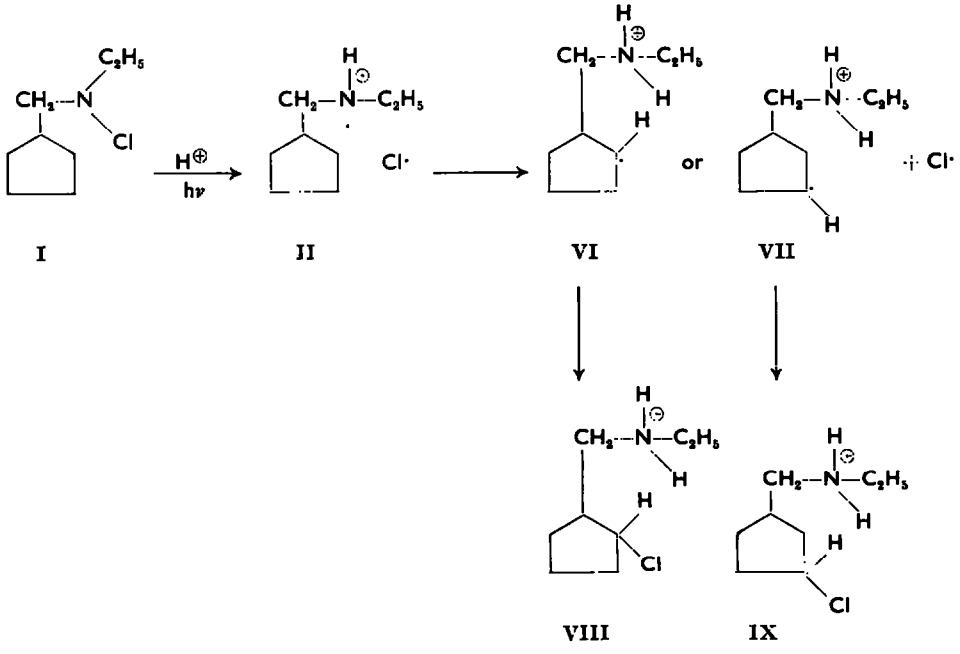
The synthesis of II was straightforward, starting with the readily available cyclopentanecarboxylic acid (III). Conversion of III into N-ethylcyclopentanecarboxamide (IV) was achieved *via* preparation of the acid chloride of III followed by reaction with ethylamine. Reduction of IV with LAH yielded the N-ethylaminomethylcyclopentane (V) which was subsequently converted into N-chloro-N-ethylaminomethylcyclopentane (I) upon reaction with N-chloro-succinimide (NCS).



III I

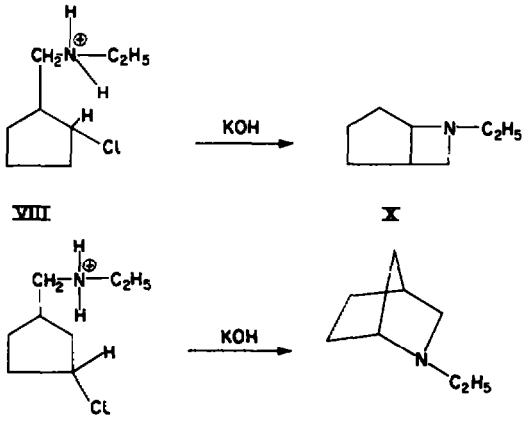
Irradiation of a solution of I in 80% sulfuric acid was achieved with a bank of ten 15 watt Sylvania "Blacklite" fluorescent lamps. After a 25 hr period of irradiation the solution was neutralized with sodium hydroxide and the isomerized γ- or δ-chloroamines were cyclized. Isolation of the basic products through steam distillation followed by removal of any primary or secondary amines by reaction with benzenesulfonyl chloride yielded a pure tertiary amine in 28–29% yield. This product was shown to be homogeneous by vapor phase chromatography.

Photolysis of the N–Cl bond in I should yield the aminium radical II. This species in turn might abstract either a γ- or δ-hydrogen to give VI or VII, respectively. Recombination of VI or VII with a chlorine radical would yield the γ-chloroamine (VIII) or



the δ-chloroamine (IX) respectively. Reaction of VIII with base would produce N-ethyl-6-azabicyclo[3.2.0]heptane (X). Similar cyclization of IX would result in the formation of N-ethyl-2-azabicyclo[2.2.1]heptane (XI). In actuality *only XI was formed.*

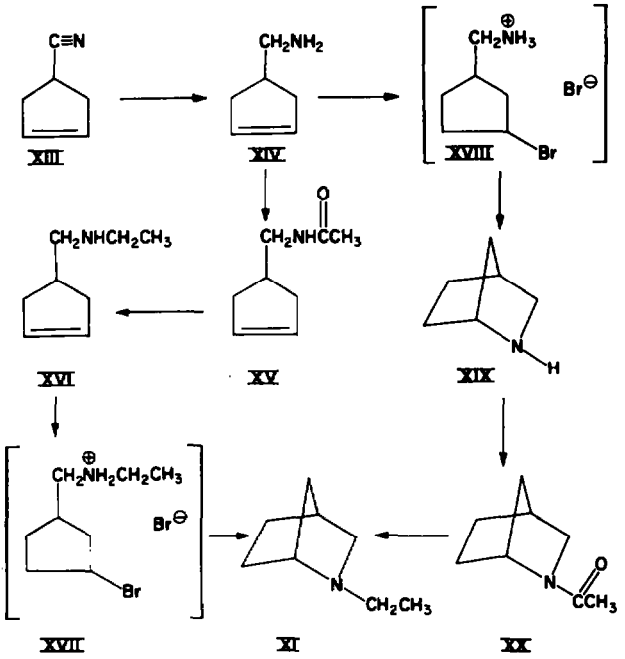
The structure of XI was established by independent synthesis. Reaction of 4-bromocyclopentene (XII)[20] with sodium cyanide in dimethylsulfoxide according to the



VIII X

IX XI

method of Shechter and Friedman[21] gave the known[22] 4-cyanocyclopentene (XIII). Reduction of XIII with LAH gave the primary amine (XIV), which on reaction with acetyl chloride yielded XV. Reduction of XV with LAH produced the unsaturated amine (XVI). Addition of anhydrous hydrogen bromide to a solution of XVI in chloroform gave XVII, which was not isolated but was immediately reacted with aqueous sodium hydroxide and steam distilled to yield a sample of XI which was identical in all



XIII XIV XVIII XVI XV XIX XVII XI XX

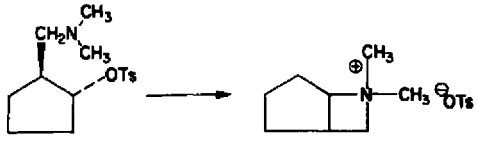
[20] P. D. Bartlett and M. R. Rice, *J. Org. Chem.* **28**, 3351 (1963).

[21] H. Shechter and L. Friedman, *J. Org. Chem.* **25**, 877 (1960).

[22] N. S. Crosley, A. C. Darby, H. B. Henbest, J. J. McCullough, B. Nicholls and M. F. Stewart, *Tetrahedron Letters* No. 12, 398 (1961).

respects to the N-ethyl compound isolated from the Hofmann-Löffler-Freytag reaction. Alternatively, XIV could be converted to XI *via* the four step sequence starting with the conversion of XIV to XVIII.

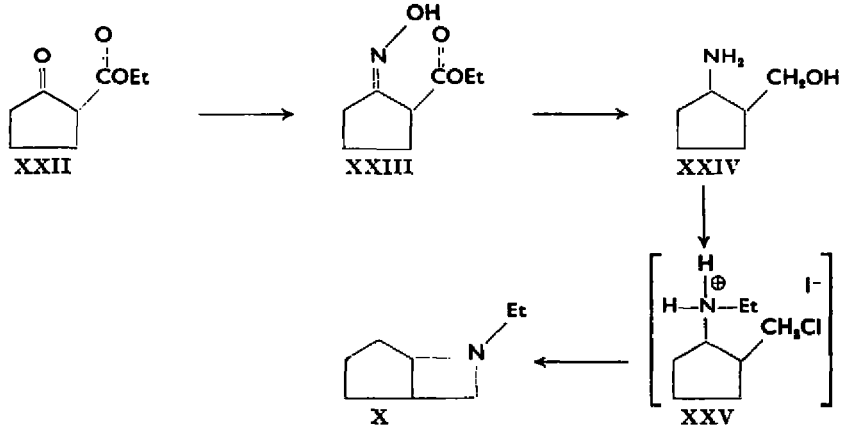
On the basis of XI being the only isolated cyclization product it would appear that hydrogen abstraction at the δ-position was quite specific. However, the possibility existed that, to some extent, hydrogen abstraction at the γ-position had occurred, but that the resulting γ-chloroamine (VIII) either did not cyclize or that the cyclized product (X) was unstable under the reaction conditions. The studies of Grob[23] on the preparation of N,N-dimethyl-6-azabicyclo[3.2.0]heptane tosylate (XXI) indicated that



XXI

the cyclization step was straightforward. It remained to be shown whether or not the 6-azabicyclo[3.2.0]heptane derivative was stable to the benzenesulfonyl chloride reaction used in the Hinsberg separation of the tertiary amines.

An authentic sample of a 6-azabicyclo[3.2.0]heptane derivative was synthesized starting with carboethoxycyclopentanone (XXII). Conversion of XXII to its oxime (XXIII) followed by reduction with LAH gave the amino alcohol (XXIV). Alkylation

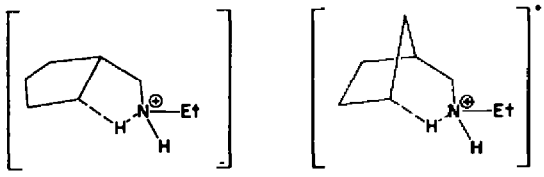


of the amine with ethyl iodide and subsequent reaction with thionyl chloride gave the quaternary salt (XXV) which was immediately cyclized through reaction with aqueous potassium hydroxide yielding N-ethyl-6-azabicyclo[3.2.0]heptane (X). When X was subjected to the conditions of the Hinsberg separation it was recovered unchanged. Thus it appears conclusive that X was not formed in the Hofmann-Löffler-Freytag reaction.

The unusual specificity observed in the formation of the 2-azabicyclo[2.2.1]heptane system under the Hofmann-Löffler-Freytag reaction conditions merits detailed consideration. As discussed above the ring strain involved in the abstraction of the δ-hydrogen should be far greater than the strain connected with a γ-hydrogen abstraction.

[23] C. A. Grob, *Bull. Soc. Chim. Fr.* 1360 (1960).

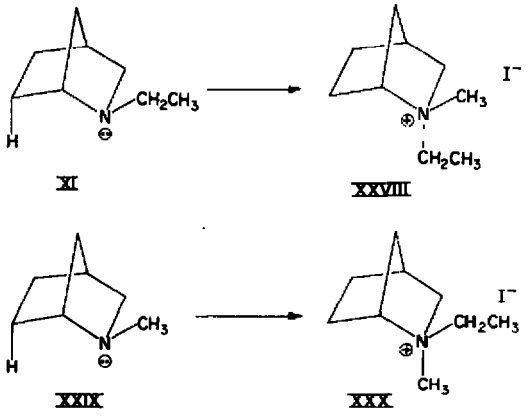
Balanced against the effect of ring strain is the preference for a linear transfer of hydrogen from carbon to nitrogen.[8] The transition states for γ- and δ-hydrogen transfer should approach the structures of 3-azabicyclo[3.3.0]octane and 2-azabicyclo[3.2.1]-octane, respectively. Such transition states are illustrated by XXVI and XXVII. The C—H—N angles[24] in XXVI and XXVII differ by about 25°, the angle in XXVI being



XXVI XXVII

about 120°, and the C—H—N angle in XXVII being approximately 145°. Since only δ-hydrogens are abstracted, it would appear that linearity of hydrogen transfer is far more important than the inhibition of hydrogen transfer due to the effect of internal strain.[25]

The alkylation of derivatives of 2-azabicyclo[2.2.1]heptane proved to be exceptionally stereospecific. Addition of methyl iodide to N-ethyl-2-azabicyclo[2.2.1]heptane (XI) yielded a single quaternary salt, m.p. 308·0–308·5°. Alkylation of N-methyl-2-



XI XXVIII

XXIX XXX

azabicyclo[2.2.1]heptane (XXIX) with ethyl iodide also produced a single quaternary, salt, m.p. 305·0–305·5°. The IR spectra of these two salts were completely different while the NMR spectra showed only slight differences in resolution and chemical shifts. Comparison of the IR spectra and m.ps of the crude and thrice recrystallized salts indicated that the attack of the alkyl iodides proceeded stereospecifically to yield epimerically pure products. Based on extrapolation of the data obtained recently by Allinger *et al.*[26] on N-alkylpiperidines it can be safely assumed the alkyl group in the N-alkyl-2-azabicyclo[2.2.1]heptane prefers the unhindered *exo* position. However, since the N-alkyl group can equilibrate rapidly between the *exo* and *endo* positions, the

[24] Bond angles were estimated from measurements on strained Dreiding Stereo-models.

[25] The possibility of intermolecular hydrogen transfer was also considered. However in an intermolecular hydrogen abstraction there should be little, if any, preference for δ- over γ-hydrogens.

[26] N. L. Allinger, J. G. D. Carpenter and F. M. Karkowski, *Tetrahedron Letters* 3345 (1964); *J. Amer. Chem. Soc.* **87**, 1232 (1965).

preferred conformation probably has little, if any, effect on the stereochemistry of the resulting quaternary salts. This is in agreement with the Curtin-Hammett principle which postulates that product composition, in a reaction which yields one product from one conformational isomer and a different product when starting with a different conformational isomer of the same substrate, does not depend on the population of the ground states but only on the relative energies of the respective transition states.[27] Since the *endo* position of the 2-azabicyclo[2.2.1]heptane is considerably more hindered than the *exo* position, it would seem that the alkylation of XXIX with ethyl iodide would take place from the *exo* side of the molecule to yield XXX. If XXX has an *exo*-ethyl-*endo* methyl, XXVIII must have the epimeric stereochemistry about the nitrogen. Unfortunately this stereochemical aspect cannot be rigorously proven without an extensive investigation, possibly utilizing X-ray crystallographic techniques.

EXPERIMENTAL

Cyclopentanecarboxylic acid III. Cyclohexanone was converted into III according to the procedure of Payne and Smith.[28]

Cyclopentanecarboxylic acid chloride. To a stirred solution of 31·65 g (0·28 moles) cyclopentanecarboxylic acid in 70 ml CH_2Cl_2, 59 g (0·50 moles) $SOCl_2$ was added over a period of 0·5 hr. A drop of pyridine initiated the reaction, and the mixture was heated for 1 hr on a steam bath and 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.[28] b.p. 160–162° (atm.)].

N-*Ethylcyclopentanecarboxamide.* A solution of 68·6 g (0·52 moles) cyclopentanecarboxylic acid chloride in 400 ml benzene was cooled in an ice bath, and 400 ml ethylamine was added dropwise. The ethylamine hydrochloride was removed by vacuum filtration and washed twice with 50-ml portions of hot benzene. The solvent was removed on a rotary evaporator leaving 73·2 g (100%) of the crude amide, m.p. 57–58°. Low temp recrystallization from 35–40° pet. ether yielded a colourless crystalline product, m.p. 58·0–58·5°. (Found: C, 68·02; H, 10·77; N, 9·76. $C_8H_{15}NO$ requires: C, 68·04; H, 10·71; N, 9·92%.)

N-*Ethylaminomethylcyclopentane.* A solution of 15·0 g (0·106 moles) N-ethylcyclopentanecarboxamide in 50 ml anhydrous ether was added dropwise to 5·05 g LAH in 50 ml anhydrous ether. The mixture was stirred for 36 hr, and 20 ml water 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 a steam bath and the resulting oil distilled at red. press. yielding 13·05 g (96·7%) of the clear liquid amine, b.p. 100–101° (100 mm), n_D^{25} 1·4441. (Found: C, 75·61; H, 13·69; N, 10·89. $C_8H_{17}N$ requires: C, 75·52; H, 13·47; N, 11·01%.)

N-*Chloro*-N-*ethylaminomethylcyclopentane* (I). N-Ethylaminomethylcyclopentane, 98 g (0·77 moles), in 3 l. ether was stirred for 15 hr with 120 g (0·90 moles) N-chlorosuccinimide. One liter of 35–40° pet. ether was added and the solution decanted from the precipitated solids and the solvent removed, without warming, on a rotary evaporator until 150 ml of an oil remained. The N-chloroamine decomposed on warming or on standing and was not further purified.

N-*Ethyl*-2-*azabicyclo*[2.2.1.]*heptane* (XI). The N-chloroamine prepared above was dissolved in 400 ml cold 80% H_2SO_4, and the resulting solution irradiated for 25 hr 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 ice, made basic with cold conc. NaOH aq, 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 2 days with ether was followed by removal of the solvent from the ether extract by distillation on a steam bath. The remaining oil was added to a stirred solution of 400 g KOH in 1300 ml water at 0°. Benzenesulfonyl chloride, 400 g (2·26 moles), was added dropwise over a period of 1 hr while the reaction was cooled to 0° in an ice bath. The mixture was stirred at room temp overnight, acidified with HCl aq, and extracted with ether. The aqueous

[27] D. Y. Curtrin, *Rec. Chem. Prog.* **15**, 111 (1954). For a discussion of this principle in relation to heterocyclic systems see E. L. Eliel, N. L. Allinger, S. J. Angyl and G. A. Morrison, *Conformational Analysis* pp. 244–248. Interscience, New York (1965).

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

solution was made basic and thoroughly extracted with ether. The extract was dried over $MgSO_4$, the inorganic salts filtered off and the ether removed by fractional distillation. Distillation of the residue yielded 27·74 g (28·8%) of the tertiary amine, b.p. 92–95° (135 mm), which was 98% pure by VPC. Redistillation yielded an analytical sample of XI, b.p. 103·5–104° (167 mm), n_D^{20} 1·4639. (Found: C, 76·58; H, 12·13; N, 11·42. $C_8H_{15}N$ requires: C, 76·73; H, 12·08; N, 11·19%.)

The picrate of XI was prepared and recrystallized from EtOH, m.p. 220–221°. (Found: C, 47·28; H, 5·23; N, 15·95. $C_{14}H_{18}N_4O_7$ requires: C, 47·45; H, 5·12; N, 15·81%.)

The oxalate salt was also prepared and recrystallized from ethyl acetate, m.p. 159–160°. (Found: C, 55·78; H, 8·14; N, 6·37. $C_{10}H_{17}NO_4$ requires: C, 55·80; H, 7·96; N, 6·51%.)

4-Bromocyclopentene (XII). The 4-bromocyclopentene was prepared from cyclopentadiene according to the method of Bartlett and Rice.[20,29]

4-Cyanocyclopentene (XIII). To a solution of 22 g (0·49 moles) NaCN in 200 ml dimethyl sulfoxide at 100°, 44·8 g (0·30 moles) 4-bromocyclopentene was added. The solution was heated on a steam bath for 6 hr, cooled, and 200 ml water added. The resulting solution was extracted with five 100-ml portions ether, and the combined extracts dried over $MgSO_4$. The drying agent was filtered off, and the ether removed from the filtrate on a steam bath. The resulting oil was distilled at red. press. to yield 21·9 g (77·5%) of the nitrile, b.p. 93–100° (90 mm).

4-Aminomethylcyclopentene (XIV). 4-Cyanocyclopentene (3·99 g, 0·04 moles), was added dropwise to 1·64 g (0·04 moles) LAH in 100 ml anhydrous ether. The reaction was heated to reflux for 2 days, cooled to 0°, and 6 ml water added dropwise. The inorganic solids were removed by vacuum filtration, and the ether solution distilled to yield 3·17 g (76·4%) of the amine, b.p. 85–88° (127 mm). Redistillation afforded a sample of the clear liquid amine, b.p. 87–88° (134 mm). (Found: C, 74·02; H, 11·68; N, 14·21. $C_6H_{11}N$ requires: C, 74·17; H, 11·41; N, 14·42%.)

The chloroplatinate was prepared and recrystallized from EtOH containing a drop of conc. HCl aq, m.p. 190° d. (Found: C, 23·76; H, 4·09; N, 4·66; Pt, 32·53. $C_{12}H_{24}N_2PtCl_6$ requires: C, 23·85; H, 4·00; N, 4·64; Pt, 32·31%.)

N-Ethyl-2-azabicyclo[2.2.1]heptane (XI). Anhydrous HBr was bubbled into a solution of 3·46 g (0·036 moles) 4-aminomethylcyclopentene in 60 ml $CHCl_3$ for 4 hr. The solution was allowed to stand overnight and additional HBr added slowly for 2 additional hr. The $CHCl_3$ solution was extracted with three 20-ml portions water followed by two 10-ml portions 10% HCl aq. The aqueous extracts were placed in a flask equipped with a stirrer, a dropping funnel, and a distillation head. Conc. NaOH aq was added dropwise while the solution was heated to 80°. When the solution was basic, the temp was raised to distill 100 ml of liquid. The distillate was acidified, extracted with two 20-ml portions of ether, and the extracts discarded. The aqueous layer was then made basic and extracted with four 20-ml portions of ether. The combined extracts were dried over $MgSO_4$, the inorganic material filtered off, and the ether removed by distillation. The remaining oil was vacuum distilled to yield 2·77 g (77%) of an amine, b.p. 115–130°. IR analysis indicated that the product contained 30% of the unreacted unsaturated amine. Further purification by successive distillations, column chromatography, and VPC were unsuccessful.

Acetylation of the amine mixture was carried out by dissolving the above product (2·77 g, 0·03 moles) in 15 ml sat. 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 stirred overnight. The mixture was extracted with five 20-ml portions of ether, and the ether extracts washed with $NaHCO_3$ aq. The ether layer was dried over $MgSO_4$, the solids removed by filtration, and the filtrate distilled at red. press. 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) LAH in 70 ml anhydrous ether. The mixture was stirred and refluxed overnight and then hydrolyzed by the dropwise addition of 12 ml water. After 0·5 hr the inorganic salts were filtered off and the solvent removed from the filtrate on a steam bath leaving a colourless oil.

The remaining oil was added to a stirred solution of 9·0 g (0·16 moles) KOH in 26 ml water. The mixture was cooled in an ice bath, and 7 ml (0·057 moles) benzenesulfonyl chloride added dropwise. The solution was allowed to stand overnight, then acidified with conc. HCl aq, and extracted with

[29] A note of precaution on the explosive nature of the LAH reduction in the preparation of this compound should be considered before attempting its synthesis, C. R. Johnson and J. E. Keiser, *Tetrahedron Letters* No. 45, 3327 (1964). We found that slow addition of the 3,5-dibromocyclopentene to the hydride solution without cooling the reaction avoided this danger.

three 20-ml portions ether. The aqueous layer was made basic and extracted with four 50-ml portions ether. These ether extracts were dried over $MgSO_4$, the inorganic salts filtered off, and the filtrate distilled yielding 0·42 g (23·9%) of a liquid b.p. 102–105° (165 mm). The IR spectrum of the product was identical to that of XI prepared from the Hofmann-Löffler-Freytag reaction. The picrate, which was prepared in the usual fashion, had a m.p. and a mixed m.p. identical to the picrate of the Hofmann-Löffler-Freytag product (m.p. 220–221°, mixed m.p. 220–221°).

N-*Acetyl-4-aminomethylcyclopentene* (XV). To 25 ml of a sat. solution of sodium acetate was added 4·44 g (0·046 moles) 4-aminomethylcyclopentene. The solution was cooled and stirred, and 10 ml (0·10 moles) acetic anhydride added dropwise. The mixture was stirred overnight and then extracted with four 20-ml portions ether. The ether extracts were washed with sat. $NaHCO_3$ aq until the washings were basic, the ether solution dried over $MgSO_4$, and the drying agent filtered off. Distillation of the filtrate at red. press. yielded 4·44 g (70·0%) unsaturated amide XV, b.p. 115–125° (0·4 mm). Redistillation yielded an analytical sample, b.p. 114–115° (0·25 mm). (Found: C, 68·88; H, 9·58; N, 10·03. $C_8H_{13}NO$ requires: C, 69·03; H, 9·41; N, 10·06%.)

N-*Ethyl-4-aminomethylcyclopentene* (XVI). To a stirred mixture of 1·91 g (0·05 moles) LAH in 100 ml anhydrous ether, 1·06 g (0·008 moles) N-acetyl-4-aminomethylcyclopentene was added. The resulting solution was refluxed overnight, cooled, and then hydrolyzed by the dropwise addition of 4 ml water. The inorganic solids were filtered off and washed with three 10-ml portions ether. The ether was removed from the combined filtrates by distillation on a steam bath, and the remaining oil distilled at red. press. yielding 0·71 g (84·5%) of the unsaturated amine (XVI), b.p. 89–91° (65 mm). (Found: C, 77·15; H, 11·91; N, 10·91. $C_8H_{15}N$ requires: C, 76·74; H, 12·08; N, 11·19%.)

N-*Ethyl-2-azabicyclo*[2.2.1]*heptane* (XI). N-Ethyl-4-aminomethylcyclopentene (0·387 g, 0·003 moles) was placed in a small Erlenmeyer flask with 1 ml $CHCl_3$. Anhydrous HBr was bubbled into the solution for 3·5 hr dissolving the initially formed solid. To the solution, 8 ml 6 N NaOH was added. After 2 hr the solution was extracted with four 20-ml portions ether, the extracts were dried, and the drying agent filtered off. The ether was carefully removed by distillation and the remaining oil distilled in a microstill to yield a small fraction of a clear liquid, b.p. 100–102° (165 mm). Comparison of the IR spectra showed this to be the same product, N-ethyl-2-azabicyclo[2.2.1]heptane, obtained from the Hofmann-Löffler-Freytag reaction. The entire product was treated with a sat. solution of picric acid in EtOH, and the resulting crystalline picrate removed by vacuum filtration and washed with a small portion of cold EtOH to yield 0·180 g (16·4%) of the amine picrate, m.p. 217–220°. Recrystallization from EtOH gave a picrate m.p. 219–220°, which was shown to be identical to the picrate of the Hofmann-Löffler-Freytag cyclization product by a mixed m.p. (219–220°) and by their identical IR spectra.

2-*Carbethoxycyclopentanone* (XXII). 2-Carbethoxycyclopentanone was obtained from the Arapahoe Chemical Co. and used without purification.

2-*Aminocyclopentylmethanol* (XXIV). A solution of 16·8 g (0·11 moles) 2-carbethoxycyclopentanone in 30 ml MeOH was added to a solution of 15 g hydroxylamine hydrochloride and 15 g sodium acetate in 15 ml water. The resulting mixture was heated on a steam bath for 4 hr and allowed to stand overnight. The solution was extracted with three 50-ml portions ether, and the ether extract washed with dil. Na_2CO_3 aq until the washings were basic. The ethereal solution was dried over $MgSO_4$, and the inorganic solids 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). This amino ester was added dropwise to a stirred suspension of 9·43 g (0·25 moles) LAH in 300 ml anhydrous ether over a 1 hr period. This mixture was refluxed with stirring for 72 hr. The solution was then cooled in an ice bath, and excess hydride neutralized by the dropwise addition of 30 ml water. The inorganic solids were filtered off and washed with three 50-ml portions ether. The combined filtrates were dried over $MgSO_4$, the drying agent removed by filtration, and the solvent 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). (Found: C, 62·29; H, 11·36; N, 12·27. $C_8H_{13}NO$ requires: C, 62·57; H, 11·38; N, 12·16%.)

N-*Ethyl-6-azabicyclo*[3.2.0]*heptane* (X). 2-Aminocyclopentylmethanol (7·08 g, 0·06 moles), was dissolved in 50 ml benzene, and 7·0 ml (0·085 moles) EtI added. The solution was refluxed for 3 hr, acidified with conc. HCl, and the solvent removed at red. press. The resulting oil was cooled in ice, and 10 ml $SOCl_2$ added. The mixture was then heated on a steam bath for 0·3 hr and the solvent stripped off under red. press. The resulting product was added to 50 ml cold 27% NaOH aq and steam distilled. The distillate was saturated with NaCl and continuously extracted with ether for

24 hr. The extract was dried over $MgSO_4$, the inorganic salts filtered off, and the filtrate distilled to yield 1·68 g (19·0%) of the tertiary amine 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. 163–164°. (Found: C, 47·18; H, 5·29; N, 15·97. $C_{16}H_{18}N_4O_7$ requires: C, 47·45; H, 5·12; N, 15·81%.)

The methyl iodide salt was prepared and recrystallized from EtOH m.p. 186–187°. (Found: C, 40·25; H, 6·85; N, 5·19. $C_9H_{18}NI$ requires; C, 40·46; H, 6·79; N, 5·24%.)

The Hinsberg test on 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 by VPC) was dissolved in a solution of 3 g KOH in 10 ml water and cooled in a salt-ice bath. Benzenesulfonyl chloride, (3 g, 0·17 moles), was added dropwise, and the solution stirred for 6 hr. Conc. HCl aq was added until the solution was acidic, and the mixture extracted with ether. The aqueous layer was then made basic with a conc. NaOH aq and continuously extracted with ether. The latter ether extract was dried over $MgSO_4$, and the drying agent removed by filtration. The remaining solution was distilled to yield 0·79 g of the tertiary amine, b.p. 95–98° (190 mm). An IR spectrum showed it to be the pure tertiary amine X.

N-*Methylcyclopentanecarboxamide.* Anhydrous methylamine was bubbled into a cooled solution of 25·3 g (0·21 moles) cyclopentanecarboxylic acid chloride in 350 ml ether until no further precipitate formed. The ethereal solution was filtered and the solid filter cake washed thoroughly with ether. The combined filtrates were stripped on a rotary evaporator to yield 23·4 g (97%) crude amide, m.p. 45–50°. Recrystallization from 60–70° pet. ether gave colourless needles, m.p. 58–59°. (Found: C, 66·00; H, 10·38; N, 10·99. $C_7H_{13}NO$ requires: C, 66·10; H, 10·30; N, 11·01%.)

N-*Methylaminomethylcyclopentane.* LAH reduction of N-methylcyclopentanecarboxamide in a manner similar to that used in the reduction of the corresponding N-ethyl compound gave pure N-methylaminomethylcyclopentane, b.p. 105° (210 mm). (Found: C, 74·22; H, 13·33; N, 12·34. $C_7H_{15}N$ requires: C, 74·27; H, 13·36; N, 12·37%.)

N-*Methyl*-2-*azabicyclo*[2.2.1]*heptane* (XXIX). Conversion of N-methylaminomethylcyclopentane to the N-chloro derivative followed by photolysis in H_2SO_4 in a manner identical to that used in the preparation of XI gave XXIX, b.p. 82·5–83·0° (149 mm), n_D^{20} 1·4635 in 26·3% yield. VPC showed this material to be 99% pure. (Found: C, 75·73; H, 11·95; N, 12·37. $C_7H_{13}N$ requires: C, 75·60; H, 11·79; N, 12·60%.)

The picrate of the amine was prepared and recrystallized from alcohol, m.p. 284–285°. (Found: C, 46·15; H, 4·56; N, 16·3. $C_{13}H_{16}N_4O_7$ requires: C, 45·88; H, 4·74; N, 16·47%.)

Exo-2-*ethyl*-endo-2-*methyl*-2-*azoniabicyclo*[2.2.1]*heptane iodide* (XXX). To a solution of 0·20 g N-methyl-2-azabicyclo[2.2.1]heptane in 2 ml EtOH, 5 ml EtI was added and the mixture allowed to stand for 24 hr. Pet. ether (10 ml, 35–40°) was added and the precipitated salt removed by vacuum filtration and dried under vacuum to yield 0·46 g (95·7%) of XXX, m.p. 303–304°. Three recrystallizations from absolute EtOH yielded colourless cubes, m.p. 305·0–305·5°. The IR spectra of the crude product and the recrystallized salt were identical. (Found: C, 40·47; H, 6·78; N, 5·24. $C_9H_{18}NI$ requires: C, 40·46; H, 6·79; N, 5·24%.)

N,N-*Diethyl*-2-*azoniabicyclo*[2.2.1]*heptane iodide.* The N,N-diethyl quaternary salt of XI was prepared in a fashion similar to that above to yield white plates, m.p. 294·5–295·0°. (Found: C, 42·70; H, 7·31; N, 4·87. $C_{10}H_{20}NI$ requires: C, 42·71; H, 7·18; N, 4·98%.)

Exo-2-*methyl*-endo-2-*ethyl*-2-*azoniabicyclo*[2.2.1]*heptane iodide* (XXVIII). MeI (5 ml) was added to a solution of 0·20 g XI in 2 ml EtOH and the solution allowed to stand at room temp for 1 day. The salt was precipitated by the addition of 10 ml 35–40° pet. ether and collected by vacuum filtration to yield 0·41 g (96·3%) of XXVIII, m.p. 307–308°. Three recrystallizations from absolute EtOH yielded white cubes, m.p. 308·0–308·5°. The IR spectrum of the crude salt was identical with that of the recrystallized material and completely different from the IR spectrum of XXX. (Found: C, 40·43: H, 6·82; N, 5·05. $C_9H_{18}NI$ requires: C, 40·46; H, 6·79; N, 5·24%.)

N,N-*Dimethyl*-2-*azoniabicyclo*[2.2.1]*heptane iodide.* The N,N-dimethyl quaternary iodide of XXIX was prepared as described for other salts above. Recrystallization from absolute EtOH gave colourless cubes, m.p. 309–310°. (Found: C, 37·81; H, 6·69; N, 5·64. $C_8H_{16}NI$ requires: C, 37·95; H, 6·38; N, 5·53%.)

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